

Contents of Volume

Number 1	
New horizons of chemistry: single molecules	1
A L Buchachenko	
Atomic resolution probe microscopy of the graphite surface	23
O V Sinitsyna, I V Yaminsky	
Modelling of the dynamic state of disperse systems	31
N B Uriev, I V Kuchin	
Crystalline water ices	57
E A Zheligovskaya, G G Malenkov	
Magnetic properties of bismuth(III) oxy compounds	77
E A Kravchenko, V G Orlov, M P Shlykov	
Number 2	
Silylium ions	95
T A Kochina, D V Vrazhnov, E N Sinotova, M G Voronkov	
Metal-mediated reactions of oximes	111
D A Garnovskii, V Yu Kukushkin	
Multisensor systems of the electronic tongue type as novel opportunities in design and application of chemical sensors	125
Yu G Vlasov, A V Legin, A M Rudnitskaya	
Polymer degradation and its role in nature and modern medical technologies	133
A Yu Bilibin, I M Zorin	
Charge transfer processes in conducting polymer films	147
V V Malev, V V Kondratiev	
Successive ionic layer deposition. The use in nanotechnology	161
V P Tolstoy	
Number 3	
Mechanochemistry and mechanical activation of solids	177
V V Boldyrev	
Chemistry of ureido carboxylic and ureylene dicarboxylic acids	191
A N Kravchenko, I E Chikunov	
Synthesis, reactions and structures of telluronium salts	207
A V Zakharov, I D Sadekov, V I Minkin	
Chiral hydroxy phosphonates: synthesis, configuration and biological properties	227
O I Kolodiazhnyi	
Pyrocatechol Violet in spectrophotometric and novel optical methods	255
V M Ivanov, G A Kochelayeva	

Number 4	
Analytical chemistry and chemical analysis Yu A Zolotov	267
Chemometrics: achievements and prospects O Y Rodionova, A L Pomerantsev	271
Prospects in analytical atomic spectrometry A A Bol'shakov, A A Ganeev, V M Nemets	289
Spatially resolved atomic absorption spectrometry A Kh Gilmutdinov, A V Voloshin, K Yu Nagulin	303
Analytical potential of Mössbauer spectroscopy V G Semenov, L N Moskvina, A A Efimov	317
Analytical chromatography. Methods, instrumentation and applications Ya I Yashin, A Ya Yashin	329
Organic reagents in spectrophotometric methods of analysis S B Savvin, S N Shtykov, A V Mikhailova	341
Number 5	
Principal trends in the chemistry of amidinate complexes of main-group and transition elements D A Kissounko, M V Zabalov, G P Brusova, D A Lemenovskii	351
The chemistry of peroxyxynitrite. Reaction mechanisms and kinetics V L Lobachev, E S Rudakov	375
Piezoelectric immunosensors: analytical potentials and outlooks T N Ermolaeva, E N Kalmykova	397
Mesoporous titanium silicates as catalysts for the liquid-phase selective oxidation of organic compounds O A Kholdeeva, N N Trukhan	411
Molecular assemblies of polymethine dyes B I Shapiro	433
Number 6	
Molecular and crystal design of nonlinear optical organic materials K Yu Saponitsky, T V Timofeeva, M Yu Antipin	457
Nuclear magnetic resonance studies of translational diffusion in thermotropic liquid crystals S V Dvinskikh, I Furó	497
Metal derivatives of tetrazoles P N Gaponik, S V Voitekhovich, O A Ivashkevich	507
Chemical modification of oxide surfaces with organophosphorus(V) acids and their esters P G Mingalyov, G V Lisichkin	541
Number 7	
Chemical design of high spin polynuclear manganese(II) and iron(II) carboxylates M A Kiskin, I L Eremenko	559

The chemistry of 3-cyanopyridine-2(1<i>H</i>)-chalcogenones V P Litvinov	577
Features of solid-phase transformations induced by shock compression S S Batsanov	601
Phase equilibria in the W–C system and tungsten carbides A S Kurllov, A I Gusev	617
Number 8	
Discreteness of nanostructures and critical dimensions of nanoclusters I P Suzdalev, P I Suzdalev	637
Methods of synthesis of Group 4–9 transition metal imido complexes D N Zarubin, N A Ustynyuk	671
Organolithium and organomagnesium compounds of the naphthalene series in organic synthesis A F Pozharskii, O V Ryabtsova	709
Optically active supramolecular systems based on porphyrins V V Borovkov, N Zh Mamardashvili, Y Inoue	737
Number 9	
A new class of compounds with unusual magnetic behaviour: quasi-one-dimensional complex oxides of the $A_{3n+3m}A'_nB_{3m+n}O_{9m+6n}$ family G V Bazuev	749
Energetics of bimolecular nucleophilic reactions in solution V M Vlasov	765
Oximes as reagents A I Mikhaleva, A B Zaitsev, B A Trofimov	797
Enediyne antibiotics and their models: new potential of acetylene chemistry I A Maretina, B A Trofimov	825
Number 10	
New materials for SRS lasers T T Basiev, V V Osiko	847
From the Gomberg radical to organic magnets N M Shishlov	863
Formazans and their metal complexes G I Sigeikin, G N Lipunova, I G Pervova	885
Molecularly imprinted materials: synthesis, properties, applications G V Lisichkin, Yu A Krutyakov	901
Topological structure and relaxation properties of branched polymers V I Irzhak	919
Number 11	
Oleg Matveevich Nefedov	-1

Theoretical studies on [3+2]-cycloaddition reactions M L Kuznetsov	935
Molecular similarity concept and its use for predicting the properties of chemical compounds M I Skvortsova, I V Stankevich, V A Palyulin, N S Zefirov	961
Regularities in the molecular structures of stable fullerenes V I Kovalenko, A R Khamatgalimov	981
Light-created chemiluminescence R F Vasil'ev, Yu B Tsaplev	989
Application of metal–carbon catalysts in conversions of lower aliphatic alcohols M A Ryashentseva, E V Egorova, A I Trusov, E R Nougmanov, S N Antonyuk	1003
Number 12	
Thiophene 1,1-dioxides as unique building blocks in modern organic synthesis and materials chemistry A M Moiseev, E S Balenkova, V G Nenajdenko	1015
Certain aspects of the reactivity of carotenoids. Redox processes and complexation N E Polyakov, T V Leshina	1049
Inorganic nanofluorides and related nanocomposites S V Kuznetsov, V V Osiko, E A Tkatchenko, P P Fedorov	1065
The kinetic ordering and growth dissymmetrisation in crystalline solid solutions A G Shtukenberg, Yu O Punin, O V Frank-Kamenetskaya	1083

New horizons of chemistry: single molecules

A L Buchachenko

Contents

I. Single molecules as investigation subjects	1
II. Luminescence of single molecules	1
III. Scanning tunnelling spectroscopy	7
IV. A single high-spin molecule as a nanomagnet	12
V. Raman spectroscopy of single molecules	14
VI. Electrical conductivity of single molecules	15
VII. Mechanics and mechanochemistry of single molecules	17
VIII. Conclusion	20

Abstract. The chemistry has reached its upper boundary, *i.e.*, the ability to detect, fix in space and identify a single molecule, measure almost any of its properties and observe its chemical transformations and functioning. At this frontier, procedures for manipulating single molecules are developed and the element base for nanooptics, nanomechanics and nanoelectronics is created. This is the prologue for a new technological civilisation, *viz.*, to molecular electronics which operates with electric voltages of the order of millivolts and electric currents of the order of nanoamperes. The bibliography includes 101 references.

I. Single molecules as investigation subjects

At the boundary of the 20 and 21 centuries, a quiet revolution almost unnoticed by the broad scientific community took place in chemistry and molecular physics, namely, a breakthrough in the experimental techniques for detection and identification of single molecules and manipulation of them. Luminescence, electrical conductivity, magnetism, non-linear optics, electron paramagnetic and nuclear magnetic resonances, atomic vibration frequencies, elasticity and strength, *i.e.*, all the parameters and properties that have been measured previously only for large ensembles of molecules are now measured also for a single molecule.

This review gives analysis of the key ideas and concepts in the chemistry, physics and mechanics of single molecules. Their significance for chemistry is formulated.

First, detection of a single molecule corresponds to the limit of detection in analytical chemistry. For 'readout' of one molecule on a $1\ \mu\text{m}^2$ surface from a $1\ \mu\text{m}$ -thick layer (nowadays, this is the normal 'operating' condition), the concentration detection limit is $10^{15}\ \text{litre}^{-1}$ or $10^{-9}\ \text{mol litre}^{-1}$. This boundary is meant in the design of detectors of single molecules and highest-sensitivity sensors.

Second, it becomes possible to establish the individual, 'personal' properties of a single molecule rather than averaged or

'hidden' in a large ensemble of similar molecules. Any spectroscopy of large ensembles exhibits non-uniform broadening of spectral lines, which are superpositions of a multitude of lines (differing in widths and frequencies) from the multitude of molecules occurring in different environments. 'Extracting' the spectrum of an individual molecule from the superposition of lines is a complicated and ambiguous task. The spectroscopy of single molecules normally does not face this problem. The spectrum of a single molecule is a reliable and sensitive test of its local environment (molecular site), *i.e.*, the place occupied by the molecule and its near surrounding.

Third, it is now possible to observe functioning of a single molecule and answer the question of how it works, either continuously or with 'rest' periods, in a time-correlated mode or its functioning is random, whether or not it retains the 'memory' of the preceding events of its 'life.' Actually, this is a new field of molecular knowledge which we are only starting to enter.

Fourth, while developing the techniques for manipulation of single molecules (their migration, joining, insertion and combination to form specified molecular ensembles), researchers acquire the experience in designing elements of nanoelectronics, nanomechanics, nanooptics — the future high technology. This is not just a declaration; this is real work on the route of research and discoveries.¹

II. Luminescence of single molecules

The principle of optical detection of single molecules is simple: laser irradiation of a surface containing luminescent molecules excites their luminescence and they can be detected as molecular 'glow-worms'. In Fig. 1a one can see signals from 'luminous' rhodamine B molecules dispersed on the surface of a poly(methyl methacrylate) film;² the site from which the radiation is collected is $4.5 \times 4.5\ \mu\text{m}$. Figure 1b shows the signals from single molecules of the enzyme cholesterol oxidase embedded into an agarose gel film.³ Flavin adenine dinucleotide is the emitter in the enzyme molecule. Light is collected from a $8 \times 8\ \mu\text{m}$ area which accommodates only several molecules. The flickering glow of one cholesterol oxidase molecule is shown in Fig. 1c.³

Since the first observations of the luminescence of single molecules (the late 1980s),⁴ the techniques and technology of optical detection have substantially progressed as regards both sensitivity and reliability.^{5,6} Scanning optical microscopes, high-sensitivity photoelectric detectors, and near-field microscopy

A L Buchachenko Institute of Problems of Chemical Physics, Russian Academy of Sciences, 142432 Chernogolovka, Moscow Region, Russian Federation. Fax (7-496) 524 96 76, tel. (7-495) 939 71 28, e-mail: spinchem@chph.ras.ru, abuchach@chph.ras.ru

Received 25 March 2005

Uspekhi Khimii 75 (1) 3–26 (2006); translated by Z P Bobkova

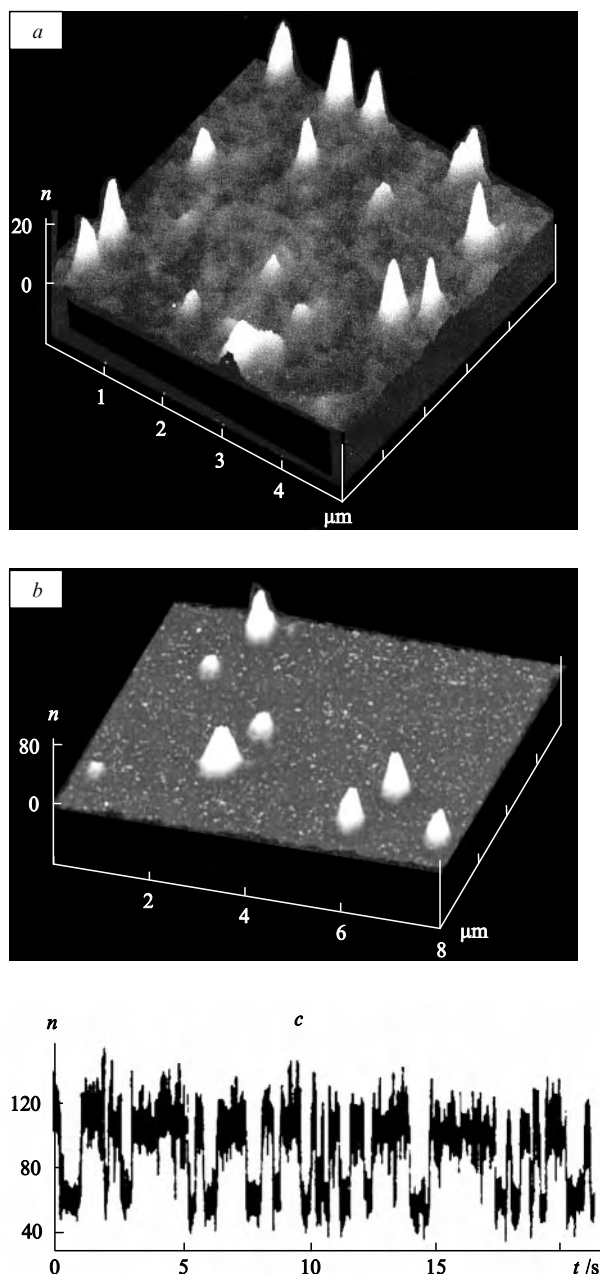


Figure 1. Image of the luminescence of single molecules: (a) rhodamine B on poly(methyl methacrylate) (the drawing was taken from Ref. 2); (b) cholesterol oxidase in the agarose gel (the drawing was taken from Ref. 3); (c) ‘flickering’ of one cholesterol oxidase molecule with time (n is the number of photons emitted per unit time).

opened up the access to detection of luminescent molecules and luminescent labels in solids and liquids, on surfaces and at interfaces, in monolayers and Langmuir–Blodgett films, in liquid crystals and gels, emulsions and porous media, membranes, proteins, nucleic acids, enzymes, chromosomes and molecular motors.^{7,8} A procedure has been developed for detecting luminescent molecules in microcapillaries and microdrops (hanging or dropping), during electrophoresis and in the tunnelling microscope cavity in which luminescence is excited by the tunnelling current.⁹ The range of luminophores (emitters having a high photostability and a great quantum yield) used for attachment to biomacromolecules as luminescent labels and suitable for being placed into any medium has been markedly extended.⁷

A two-quantum luminescence excitation process has been developed. In this case, a molecule is excited by a long-wavelength

radiation, the emission being detected in the short-wave region; this sharply decreases the scattered optical background in the luminescence band and increases the signal-to-noise ratio and, hence, the sensitivity.

Now we consider what new information useful for chemistry is provided by the optical detection of single molecules.

1. Testing of molecular sites

From classical luminescence measurements, one can derive information on averaged properties and interactions of a large ensemble of molecules (even when these are identical). The spectroscopy of a single molecule rules out the averaging. The data obtained by detecting a set of single molecules are much more valuable. The frequency, intensity, line width and polarisation of the luminescence of a single molecule depend on its local environment (local compression, crystal density, vacancies, the presence of quenchers) and on its interaction with the environment (through acoustic phonons and local vibrations). Actually, a single molecule is a ‘reporter’ providing information on the molecular site occupied by the molecule and on the events taking place in this site. An example of this ‘running commentary’ is shown in Fig. 2.¹⁰ Figure 2a shows a series of the fluorescence spectra of pentacene in a *p*-terphenyl crystal at 1.5 K; each spectrum was recorded for 2.5 s (at 0.25 s intervals). It can be seen that the radiation frequency of pentacene varies randomly and unpredictably (every time fluorescence is excited at a different laser frequency; the variation of this frequency is laid-off along the abscissa axis). This means that the energy state of the reporter molecule also varies randomly. The wandering of the molecule over its energy

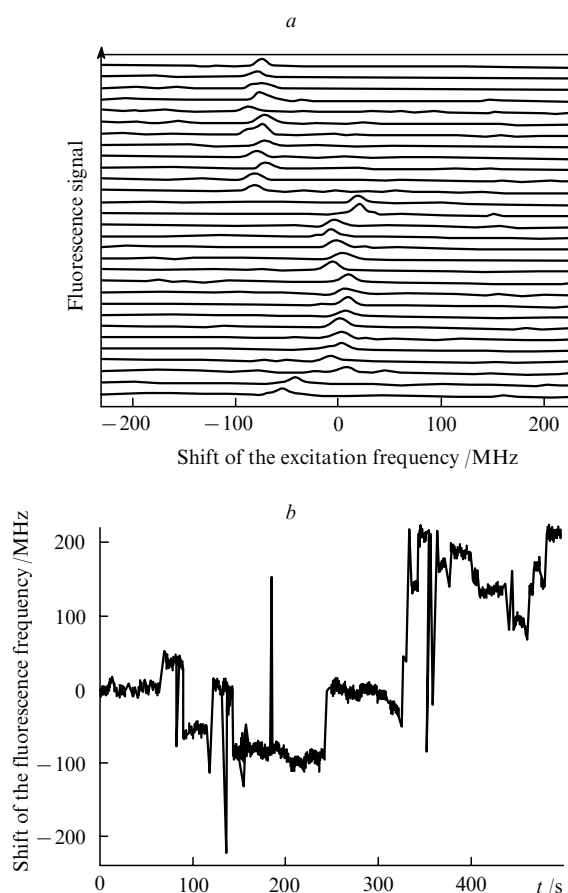


Figure 2. Spectral diffusion of pentacene in *p*-terphenyl at 1.5 K. (a) successive fluorescence records showing random shifts of the excitation frequency (recording duration 2.5 s, spacing between the records 0.25 s); (b) path of the variation of the fluorescence frequency during the detection of the spectra (500 s).¹⁰

states (*i.e.*, over the luminescence spectrum) can be regarded as a random diffusion process, spectral diffusion.

Figure 2*b* presents the path of spectral diffusion. It can be seen from this path how the fluorescence spectral shift (it was taken from Fig. 2*a*) fluctuates with time.¹⁰ This is an example demonstrating how the environment influences a single reporter molecule. Note high resolution of the ‘running commentary’: at a luminescence wavelength of 592.546 nm (this corresponds to a zero in the abscissa axis in Fig. 2*a*), the molecule reports about energy changes of about 10 MHz; this corresponds to an energy resolution of 10^{-7} – 10^{-8} . A single molecule is the most sensitive sensor.

The spectral diffusion of a single terylene molecule in polyethylene at 0.03 K has been studied.¹¹ In this case, the excited molecule discharges the energy to high-energy phonons, which are partly used for reorganisation of the molecule environment. In turn, this reorganisation changes the orientation of the molecule, which is thus gets into a new environment. Thus, a single molecule is simultaneously a phonon generator and the detector of changes made by these phonons. Actually, we are dealing with spectral self-diffusion. The frequency of self-diffusion events (the probability of spectral jumps N) depends on the amplitude of energy jumps (Fig. 3): the greater the jump amplitude, the lower the probability. For example, a molecule experiences a 20 MHz jump 16 times, and a 40 MHz jump is made only once.

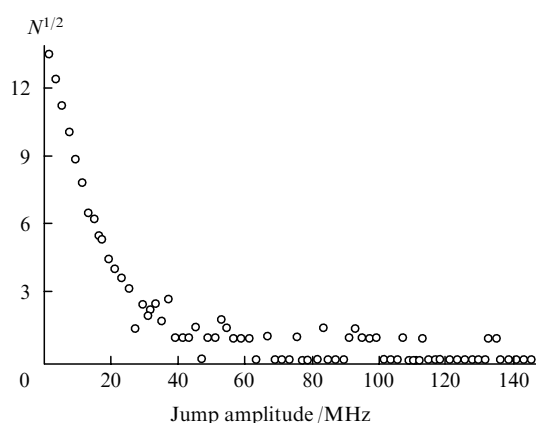


Figure 3. Probability (N) of the diffuse jumps over the spectrum as a function of the jump amplitude.¹¹

The spectral self-diffusion theory provides quantitative characteristics of host–guest interactions, namely the interaction constants and spectral self-diffusion coefficients. For example, the activation energy for the phonon interaction between a single luminescent molecule of dibenzanthanthrene (DBATT)[†] and a naphthalene crystal has been measured.¹² It was found to be 40 cm^{-1} , which corresponds to the local vibration mode in the environment of the guest molecule.

The sensitivity of the molecular sensor is so high that it is possible to measure the external pressure applied to the crystal from the shift of luminescence lines;¹³ this shift is directly proportional to the pressure, but the proportionality coefficients are different for different probe molecules. The linearity with respect to pressure describes the local compressibility of the matrix, different coefficients being indicative of the ‘individuality’ of the probe molecule with respect to the external pressure ‘violence’.

Using molecular sensors, one can reliably measure the linear and quadratic Stark effects (line shift in an electric field) even for

centrosymmetric molecules. Due to local defects in the molecular environment, the symmetry of the molecule is partially violated; as a result, an induced electric dipole equal to several millidebyes appears on the molecule;[‡] even this minor dipole moment on a single molecule suffices for detecting the Stark shift.¹⁴

A cubic Stark effect, indicative of substantial distortion of the geometry of the DBATT molecule in the n-hexadecane crystal, has been recently observed.¹⁵

2. Molecular dynamics

Procedures for direct observation of the migration of single luminescent molecules based on total internal reflection microscopy have been developed. Figure 4 shows the result of this observation for a single rhodamine 6G molecule in the polyacrylamide gel.¹⁶ Analysis of the path of the molecule may give a diffusion step, the distance distribution of the steps, the diffusion coefficient — actually, this is the visualisation of the Brownian motion of the single molecule.

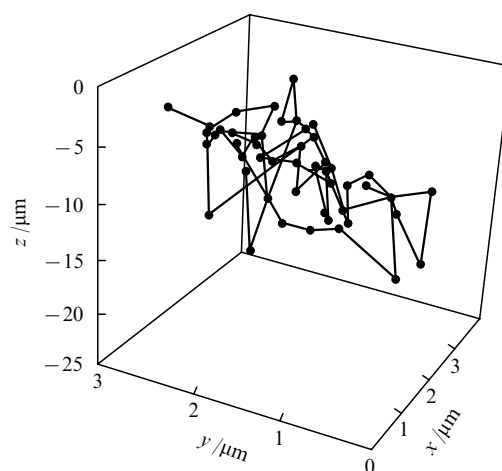


Figure 4. Three-dimensional path of the diffusion walk of a single rhodamine 6G molecule at 20 °C. The gap between the points is 0.1 s.

In some cases, this motion is unexpected and even non-Brownian (non-isotropic). For example, diffusion of rhodamine 6G in a thin polyvinylbutyral film is non-uniform: some molecules remain still, while the other move randomly and isotropically, and some other move highly anisotropically and almost unidimensionally.¹⁷ These features can be attributed to different structures of the polymer local regions (molecular sites) in which the molecule is observed: each dictates the motion of its molecule. However, averaging of the independent paths of 97 molecules has shown¹⁷ that the averaged motion is simultaneously Brownian and isotropic with a diffusion coefficient of $2.6 \times 10^{-15}\text{ cm}^2\text{ s}^{-1}$.

Testing of the surface and surface regions at the level of single molecules is a promising line of research providing a lot of information. The dynamic probing of molecular sites is a complicated task; however the first steps have already been made. For instance, tetramethylrhodamine attached covalently through a flexible chain of atoms to a glass surface and immersed into ethylene glycol can occur in different conformation states — in some of them it moves freely, while in other it contacts with the surface. By measuring the luminescence intensity of single molecules as a function of time (in the nanosecond range and in the mode of single photon counting with time correlation analysis), it

[†] According to the IUPAC nomenclature, tetraceno[2,1,12,11-*opqra*]-tetracene.

[‡] In glasses, due to the chaos in the arrangement of host molecules around the guest, the induced dipole on the guest molecule may be as high as 1 D.

was found that the contact of the luminophore with the surface restricts the lifetime of the excited molecule; the presence of a quencher, an azulene molecule, also shortens this time.

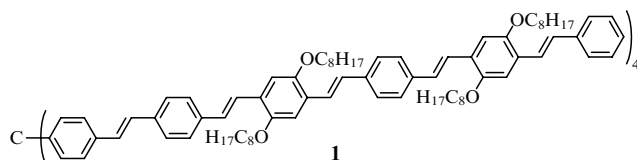
The distribution of single molecules (for arrays composed of 300–500 molecules) over the fluorescence times has been obtained. It was found that fluorescence times are different in the absence and in the presence of the quencher. A theory needed for the analysis of a complicated motion dynamics modulated by conformational transitions has been developed.¹⁸

Optical methods are especially attractive for investigating fluorescence-labelled lipids and their motion in lipid layers and on the surface of cells. The motion of molecular motors along protein threads (for example, myosin along actin) and the unidimensional motion of RNA polymerase bound non-specifically to DNA were visualised at the single molecule level. Thus the motion of tetramethylrhodamine-labelled kinesin along a protein nanotube labelled by the same luminophore at the cysteine groups has been traced. The motion takes place only in the presence of adenosine triphosphate and is physiologically ‘native’. In this case, as in the case of myosin on actin, the motion of the luminescent biomolecule along the luminescent protein nanotube resembles movement of a car with switched-on headlights along a night highway with a chain of lights (if this movement is observed from above).¹⁹

For detecting the rotational dynamics of single molecules, luminescence is excited by polarised light; after this, emission of the polarised quanta accompanied by the loss of polarisation due to reorientation of the molecule is observed. Actually each molecule is excited many times and every time its emission is readout as an elementary event. Then the time distribution of these events is determined and the characteristic time of reorientation of the molecule is found by averaging over the events.

In solutions, reorientation times of the molecule occur in the picosecond region. By rigidly linking the luminophore to a large molecule, one can study the slow orientational dynamics of these molecules. By observing the depolarisation of the fluorescence of the fluorophore-labelled lipid molecule, the fluidity of the lipid membrane was measured.²⁰ This technique is of special interest for investigating the motion of the molecular-biological motors. In particular, it was shown that myosin reorientation on actin occurs jumpwise rather than as continuous rotation.²¹ In some cases, motion of the fluorescent label itself is studied. The label is connected with the ‘principal’ molecule by a flexible bridge. This method was used to study the rotation of Texas Red attached to a DNA molecule *via* a (CH₂)₆ chain.²²

If the molecule contains several freely jointed fluorescent fragments, one can study its intramolecular dynamics. As an example, consider molecule **1** in which four fluorescent fragments, namely, chains of phenylenevinylene groups, are attached to a carbon atom. Luminescence depolarisation for these four chains (arms) allows one to measure the frequency at which the molecule ‘swings its arms’ and to determine the resting time.²³



The rotation dynamics of the rhodamine 6G molecule in supercooled *o*-terphenyl was measured based on luminescence dichroism. Rotation was detected by two sensors located at right angle to each other.²⁴ Each molecule was characterised by the same time of the Brownian rotation motion τ_c ; however, after 10–100 rotation periods, the τ_c values sharply changed. These jumps of the molecule over τ_c are indicative of its motion. The characteristic time for the position change by the molecule (τ_{ex}) is on average 15 times longer than τ_c , although the temperature dependences of τ_c and τ_{ex} are the same. This means that both the rotation and the local rearrangement are motions of the same

type, their temperature dependences being described by the Debye–Stokes–Einstein theory.²⁴

We have already mentioned that the main function of single molecules is the reporter function. It is significant that reporter molecules (luminophores) be characterised by high quantum yields of radiation and high photostability; the latter ensures a long ‘reporter’ lifetime. Rhodamine 6G, Nile Red and terylene-diimine are most popular in the optics of single molecules, and green fluorescent protein GFP (see below), flavin adenine dinucleotide, *etc.* are used most widely in biology. Since recently, dendrimers have been used as luminophores.⁸

The problems of photostability of single molecules, in particular, their lifetime as a function of luminescence excitation intensity have been discussed.²⁵ The lifetime of the molecule and the number of photons it emits were found to sharply increase at low excitation intensities; the sensitivity of the method decreases but its information content increases.

The luminescence of single molecules has already found practical application; in particular, the single-molecule optics has been used to study the influence of the moisture content and swelling of polymers on their physicochemical properties and molecular dynamics.²⁶

3. Electronic spectroscopy of single molecules

Fluorescence detection in the photon counting mode (with high time and wavelength resolutions) underlies the electronic spectroscopy of single molecules. The spectra of single molecules differ from each other in signal position (frequency shift) and width, and often also in luminescence times. This indicates that molecules occur in different environments and experience the action of different local force fields (*i.e.*, they occupy different molecular sites). As a rule, the lines in the emission spectra of single molecules are less broadened than those in usual spectra, which is indicative of the lack of non-uniform broadening caused by superposition of the spectra of various molecules; in other words, the spectrum of a single molecule rather than spectral distribution is recorded — this is a great benefit of single-molecule spectroscopy. Of particular interest is the near-field optical spectroscopy in which the emission from a molecule is collected by an optical-fibre probe.⁶

The high resolution of single-molecule spectroscopy opens up the way to direct detection of the transfer of the electron excitation energy between single donor and acceptor. The transfer efficiency is a function of the distance, the environment and the overlap of the spectra in the donor–acceptor pair; these functional dependences can be directly measured. Examples of such spectroscopic studies have been reported.^{5,8} Of particular interest is the spectroscopy of biological molecules, which provides data on the conformation, complex formation, enzyme–substrate interactions, functioning of cell elements, *etc.*

High resolution (about 10^{-4} cm⁻¹, or 10^{-8} in absolute frequency units) in the electronic spectra of single molecules can be obtained using the two-laser procedure; one laser saturates the electronic-vibrational transitions of a specified molecule, while the other (probing) one records the spectrum thus eliminating the saturation. This technique was used to detect four terylene molecules placed into a deuterionaphthalene crystal at 1.4 K.²⁷ The frequencies of the two lower vibration levels and the homogeneous (true) line width of the electronic-vibrational transition were measured. The measurements showed that spectra of the molecules are not identical, as the molecules occupy different positions in the host crystal.

The exciton fluorescence of a single poly(diacetylene) macromolecule in the host monomer crystal was measured at temperatures of about 6 and 60 K.²⁸ The macromolecule adequately simulates the semiconducting organic quantum wire. In the crystal, the fraction of the polymer chains was less than 10^{-8} and excitation was performed in the vibronic band at 501.7 nm. Both light absorption and luminescence were highly polarised

along the axis of the molecule (the linear dichroism was about 600).

A single macromolecule was represented by a single Lorentzian emission line at 2.282 eV with a half-width of 350 μeV . The line shifted somewhat to higher energies and the line width increased linearly with temperature due to the exciton–phonon interaction. The characteristic time of the loss of phase coherence by the exciton was about 2 ps. It was found that upon excitation of only one part of the macromolecule, both its parts emit, although the second part is spaced by a 10 μm distance. This means that exciton moves rather fast along the molecule by distance of $\sim 10 \mu\text{m}$ over a time period shorter than its lifetime (~ 110 ps). The mechanism of exciton movement has not been unambiguously established; however, irrespective of the mechanism (ballistic transport or diffusion migration), the motion velocity is high, $\sim 10^7 \text{ cm s}^{-1}$ for the former mechanism or $10^4 \text{ cm}^2 \text{ s}^{-1}$ for the latter.²⁸

Spectroscopy of single macromolecules has been applied to study the structure and properties of conductive polymers²⁹ and to study functioning of the single light-storing complex LH2.³⁰ The complex contains 27 bacteriochlorophyll *a* molecules and 18 carotenoids. Analysis of the luminescence spectra and their dependence on polarisation of the exciting light demonstrated that excitation is concentrated on a limited number (1–3) of bacteriochlorophyll molecules.³⁰

4. Quantum and non-linear optics

The key goal of quantum optics is to generate single photons ‘by request’. The optical detection of single molecules in a specified mode contributes to achieving this goal. A source of photons can serve as the main unit in cryptography and communication systems and in computer systems. A highly luminescent photostable single molecule in the crystal (for example, a terylene molecule in the *p*-terphenyl crystal) may be a new candidate for this role. The possibility of using such systems in quantum optics is under active discussion.⁸

The luminescence of single molecules is closely related to the non-linear optics of single molecules, *i.e.*, non-linear interaction of the molecules with the electromagnetic field of a light wave where optical properties are functions of the light intensity. A large number of non-linear effects known for large ensembles of molecules have already been detected and studied for single molecules, for example, optical saturation, four-wave mixing, photon echo.³¹

5. Functioning of single molecules

In order to answer the question of how one molecule functions, we will consider decomposition of hydrogen peroxide induced by oxidoreductase in the presence of hydrogen donors.³²

Horseshoe peroxidase is an enzyme containing protoporphyrin IX as the key structural element. The iron ion incorporated in protoporphyrin IX participates in the redox cycle that initiates decomposition of the H_2O_2 molecule and reduction of donor molecules. Dihydrorhodamine 6G was used as the hydrogen donor; this compound does not fluoresce itself but the product of its oxidation, rhodamine 6G, is a bright luminophore.

To monitor the functioning of a single enzyme molecule, the biotinylated enzyme was immobilised on streptavidin-modified glass and placed into a buffer solution of calcium phosphate containing dihydrorhodamine 6G and H_2O_2 ; after that, enzyme single molecules were exposed to laser radiation. Enzyme functioning resulted in generation of rhodamine 6G, whose luminescence was detected. According to experimental conditions, free rhodamine 6G molecules quickly departed from the laser-irradiated environment of the enzyme, so that the major contribution to the luminescence was made by the molecules that had no time to leave the enzyme where they had been formed.³²

Figure 5 shows the records of counting of the photons emitted by rhodamine 6G molecules resulting from functioning of three enzyme molecules (curves 1–3, respectively). It can be seen that

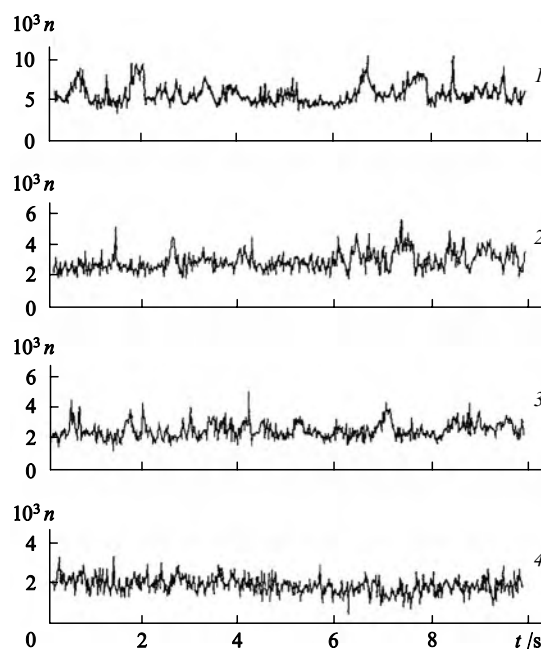


Figure 5. Number of photons n emitted by rhodamine 6G synthesised by three single horseradish peroxidase molecules as a function of the functioning time of these molecules (curves 1–3). Curve 4 is the luminescence background from the region containing no enzyme molecule.³²

over the observation period (10 s), the product yield varies, *i.e.*, periods of intensive functioning of the enzyme alternate with resting periods; moreover, the enzyme molecules ‘flicker’ in different ways, which is indicative of different activities of the three enzyme molecules. This difference is detected only in the case of short observation periods but disappears for longer periods. This means that the enzyme molecules behave as ergodic steady-state systems, for which time averaging is equivalent to ensemble averaging. The flickering (fluctuating) activity of the enzyme was attributed³² (and this was convincingly proved) to different conformational states of the molecule. The conformational conversions of the enzyme change its activity and, hence, the product yield.

The energy transfer between two luminophores has been used to study the conformational dynamics of the molecule of staphylococcal nuclease, a small globular enzyme.³³ Each enzyme molecule was labelled by two luminophores: tetramethylrhodamine acting as the energy donor (it was specifically attached to the cysteine residue in the 28-position) and the cyanine dye Cy5, which was the energy acceptor (it was attached to an amino group of the protein).

Laser irradiation of single enzyme molecules induced alternating flickering luminescence of both luminophores: when one luminophore was active, the other was at rest. The flickering frequency corresponded to the frequencies of the conformational transitions in the protein that were accompanied by luminophore movement either towards or away from each other. It is noteworthy that in the presence of an inhibitor (deoxythymidine phosphate), which is bound by the nuclease active site, the conformational dynamics greatly changes. This opens up an additional source of information about the enzyme active sites.³³

The same method was used to study the conformational behavior of α -tropomyosin in an aqueous solution.³⁴ This protein is a dimer composed of twisted identical chains. In both chains, luminophores were grafted on cysteine-190, in particular, Cy3-maleimide (energy donor) on one chain and Cy5-maleimide (energy acceptor) on the other chain. When two α -tropomyosin chains occurred in the twisted state, only the acceptor luminesced, while in the untwisted (denatured) state, only the donor exhibited

luminescence. The alternating flickering of the donor and acceptor luminescence observed for one α -tropomyosin molecule indicates that the two chains of this protein get twisted or untwisted at intervals. Obviously, this 'single-molecule' strategy can be used to study the association–dissociation dynamics of other biomolecules and their complexes.

The folding dynamics of the GCN4 peptide dimer has also been studied based on the label luminescence.³⁵ In the folded state, the peptide is a two-stranded helix. The researchers attached fluorescent labels to one ends of the strands: rhodamine 6G (energy donor) to one strand and Texas Red (energy acceptor) to the other. By the other ends (negatively charged glutamic acid residues), the dimer was immobilised, through electrostatic interaction, on the surface of glass modified by the aminopropylsiloxane groups.

In the folded dimer, both luminophores (the donor and the acceptor) are located close to each other. Therefore, on laser irradiation of the dimer and excitation of the donor, the excitation energy is transferred to the acceptor. Rhodamine 6G is thus quenched, while the Texas Red 'glows'. In the unfolded state where the donor and the acceptor are separated in space, no energy transfer from the donor to the acceptor takes place, and rhodamine 6G 'glows', while the Texas Red is quenched.

The peptide transitions from the folded to the unfolded conformation and back are detected as periodic switching-on of either donor or acceptor luminescence, which takes place in opposite phases: luminescence of one luminophore is inevitably accompanied by quenching of the other — this is clearly seen in Fig. 6. This approach is becoming popular as a general method for the study of proteins at the level of single molecules and complexes.

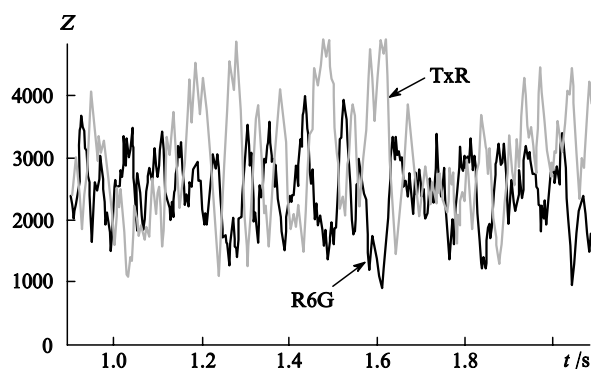


Figure 6. Luminescence, in opposite phase, of two luminophores, Texas Red (TxR) and rhodamine 6G (R6G), at functioning of a single peptide GCN4 dimer molecule.

Z is the counting rate of the emitted photons.³⁵

Enzymes are not always ergodic. The two-stranded oligonucleotide, 217 bp long, labelled by tetramethylrhodamine at one end and modified by biotin at the other end, was immobilised on a streptavidin-modified glass surface due to biotin binding to streptavidin. The DNA molecule fixed in this way fluctuated between two conformational states, in one of which the label occurred near guanosine and did not luminesce (being quenched by guanosine) and in the other, the label and guanosine were separated in space; therefore, the label luminesced. The residence periods of the molecule in these two states are 0.16 and 0.03 s.³⁶

Remarkably, on averaging the oscillation frequency over the time of observation of a single molecule (the lifetime of the luminophore label, which is determined by its photochemical stability), the oscillation frequencies of the light and dark periods did not depend on time, *i.e.*, each of the 37 DNA molecules studied was a time-ergodic system (this is called homogeneous ergodicity). However, the behaviour of each molecule is individual and, in this

sense, the ensemble of molecules is a non-ergodic system (heterogeneous ergodicity); thus, time average is not equivalent to ensemble averaging. The reason for the non-ergodicity is the individual character of every DNA position on the glass surface. A similar heterogeneous non-ergodicity was found in a study of the catalytic activity of a single molecule of lactate dehydrogenase.³⁷

Green fluorescent protein (GFP) is widely known in the molecular and cell biology;³⁸ it is used as a gene expression indicator and as a fluorescence label for proteins. A small (238 amino acid residues) GFP isolated from jellyfish contains, at the centre of the molecule, a strongly absorbing and luminescent chromophore, which is formed spontaneously from three amino acid residues in the presence of oxygen. The luminescence of a single GFP molecule is unique: it flickers spontaneously. The luminophore emission is excited at 488 nm and lasts for 0.4 s at low laser pumping powers. The higher the power, the shorter the emission, *i.e.*, luminescence is not only excited but also quenched by light. The dark state is stable for several minutes and returns spontaneously into the initial state capable of luminescence. Flickering is caused by the conformational transitions in the protein. The nature of flickering is still obscure; it is only known that it does not depend on the pH and is not related to GFP protonation.⁸

Single-molecule spectroscopy actively enters analytical biochemistry. The first example of the use of this method dates back to 1997.³⁹ The researchers obtained a chameleon protein complex consisting of the CFP and YFP proteins (CFP and YFP are mutants of the GFP with cyan and yellow fluorescence, respectively), combined by a calmodulin molecule (Ca^{2+} -binding protein).

In the absence of Ca^{2+} ions, calmodulin molecule occurs in the unfolded state; therefore, the CFP and YFP are remote from each other. Laser irradiation of CFP at a wavelength of 442 nm induces luminescence at 480 nm. After the addition of four Ca^{2+} ions, the calmodulin molecule becomes folded; as a result, the two luminophores, CFP and YFP, approach each other, and energy transfer from CFP to YFP takes place. In this case, irradiation of CFP results in YFP emission at about 530 nm. Actually, the protein complex is a highly sensitive sensor for Ca^{2+} ions: switching of the cyan fluorescence to yellow is a precise indicator for Ca^{2+} ions. Similar indicators for H^{+} ions have already been developed (single-molecule pH-meter). The good prospects of this line of research for highly sensitive analytical and ecological chemistry are quite obvious.

An important problem in the molecular biology (in particular, neurochemistry) is the mechanism of operation of molecular motors, which ensure substance and microbody transport in the living cells. Single-molecule optics helps to answer this question. For instance, it has been used to study the movement of the protein kinesin along the microtubules composed of tubulin. Kinesin functions as a molecular motor, thus carrying various cell 'goods'. For example, it delivers the vesicle with neuromediators from the Golgi apparatus to presynaptic membranes, collects the 'containers' (*i.e.*, vesicle lipids) after liberation of neuromediators and return them to the initial 'loading' site.⁸ The transport of this motor by a 8 nm distance requires hydrolysing one ATP molecule ($\text{ATP} \rightarrow \text{ADP}$). However, neither X-ray nor electronic spectroscopy could answer the question how two ends of the kinesin molecule can extend for 8 nm.

In order to answer this question, it is necessary to study the orientational mobility of a single kinesin molecule. A kinesin mutant was prepared, in which two cysteine groups were located at a fixed distance; a reporter molecule, rhodamine, was rigidly attached to these groups (a bifunctional iodoacetamide rhodamine derivative was used for this purpose). By exciting the rigidly fixed luminescent label by polarised light and detecting luminescence polarisation of a single kinesin molecule, one can draw conclusions concerning its behaviour: whether the molecule

rotates and whether the orientation of the optical dipole changes upon kinesin functioning.

The result was unusual. It was found that polarisation of the luminescence of ADP-bound kinesin does not depend on the polarisation of the exciting light. This means that the optical dipole of a single kinesin molecule is dynamically disordered on the time scale of polarisation measurements (0.1 s), *i.e.*, the molecule (motor) executes motion averaging the optical dipole orientations. At the same time, kinesin remains bound to the microtubule through both ends. This brings about the idea of a new type of motion, *viz.*, ‘rolling’ of kinesin along the microtubule; the details of this motion are unknown as yet.⁴⁰

Interestingly, this type of motion is characteristic only of kinesin bound to ADP, whereas ATP-bound kinesin is rigidly oriented and remains still. Thus, every ATP → ADP cycle is accompanied by movement of the ‘motor’ by a 8 nm distance. Undoubtedly, single-molecule optics is a brilliant tool for investigating the functioning of molecular motors.

III. Scanning tunnelling spectroscopy

The discovery of the scanning tunnelling microscopy has become a great breakthrough in the science of the nanoworld. Direct monitoring of the atomic and molecular relief of the surface has opened up the way to nanotechnology. The tip of the tunnelling microscope has become the tool for diverse operations with single atoms and molecules. The possibility of controlling tunnelling currents and atom migrations in molecules with high accuracy (0.1 Å across the surface and 0.01 Å along the height) ensures the reliability of manipulation with atoms and molecules.

Moreover, the control systems ensure a special mode of operation of the tunnelling microscope in which the tip hangs above a single atom or molecule for an arbitrarily long period.⁴¹ This fact has immediately transformed the tunnelling microscopy into tunnelling spectroscopy of single molecules, which provided the way to their electronic-vibrational spectra and to their relaxation and chemical dynamics.

1. Visualisation of molecules and their movements

The visualisation of molecules, their ‘pushing’ or ‘dragging’ by the tunnelling tip and combination of atoms and molecules into ensembles of a specified architecture is a well-developed field of science (nanoengineering).⁴² However, for chemistry, it is important to visualise chemical events (transformations and migrations of the reacting molecules and products) and monitor their evolution.

A vivid example is the discrete rotation of the O₂ molecule on the Pt(111) surface.⁴³ Figure 7*a* shows the topographic view of the O₂ molecule. The ‘pear-like’ shape of the molecule is due to the fact that one oxygen atom ‘sits’ on the Pt atom; it is ‘buried’ and, hence, the tunnelling current from this atom is low, and it ‘glows’ weakly. The other atom is somewhat elevated, being located closer to the tip; the tunnelling current from this atom is greater, and the atom ‘glows’ more brightly.

If the tip of a tunnelling microscope is mounted above an O₂ molecule and a voltage of 0.15 V is applied to the tip, a jumpwise, counter-clockwise rotation of the molecule by 120° will take place after 20 s (Fig. 7*b*); at the same instant, the tunnelling current will sharply diminish (Fig. 7*d*). This indicates that the oxygen atom partly ‘moves away’ from under the tip. A new voltage application is accompanied by a new rotation of the molecule by 120° (Fig. 7*c*), *etc.* This hindered oscillating rotation of the O₂ molecule between three equivalent positions on the Pt(111) surface[§] is induced by a low-voltage tunnelling current, the rotation velocity being proportional to the tunnelling current and the rotation

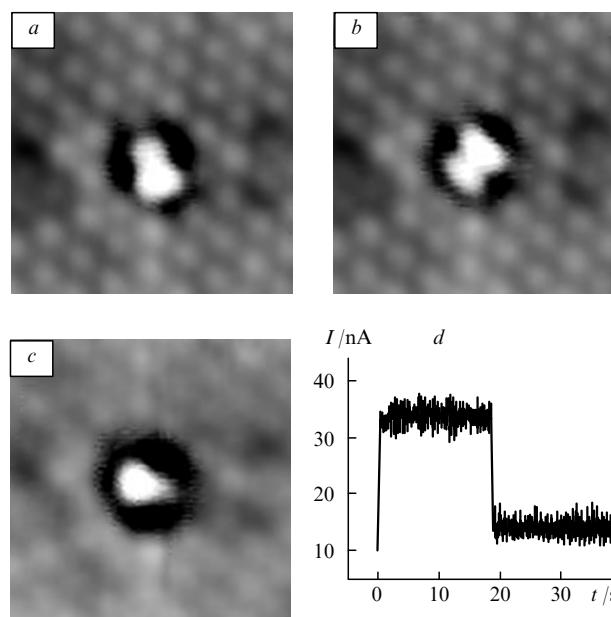


Figure 7. Topographic images of the O₂ molecule on the surface of the Pt(111) crystal during its successive angular rotations by 120° (*a, b, c*); (*d*) is the jumpwise decrease in the tunnelling current at the instant of rotation.⁴³

barrier being between 0.15 and 0.175 eV (at 8 K).⁴³ Note that O₂ molecules not subjected to the tunnelling current remain still.

Yet another example is the rotation of an acetylene molecule on the Cu(100) surface. An acetylene molecule placed on the Cu(100) atomic surface [$l(\text{Cu} - \text{Cu}) = 2.55$ Å] can occupy two equivalent orthogonal positions in which the centers of the two C–H bonds fall on neighbouring Cu atoms, *i.e.*, the acetylene molecule ‘lies’ on two Cu atoms (Fig. 8*a, b*).⁴⁴ When the tip to which the voltage is applied is located above one end of the C₂H₂ molecule (nearly above the C–H bond lying on the Cu atom), the tunnelling current jumps in a random mode between two values (Fig. 8*c*). The jumps correspond to the instants the C₂H₂ mole-

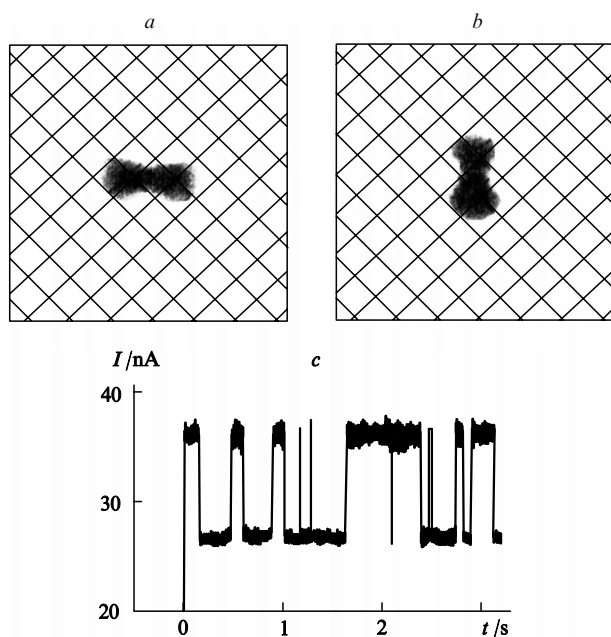


Figure 8. Topographic images of the C₂H₂ molecule in two orthogonal sites on the Cu(100) surface (*a, b*); (*c*) time dependence of the tunnelling current.⁴⁴

§ Three potential wells for the O₂ molecule on the Pt(111) surface shifted by 120° with respect to the centre are determined by the hexagonal symmetry of the arrangement of Pt atoms.

cule hops between two orthogonal positions identical in energy. This can be clearly seen when looking at the images of the C_2H_2 molecule before and after the rotation (see Fig. 8*a,b*) or from reversible fluctuations of the tunnelling current (see Fig. 8*c*).

The rotation frequency of the acetylene molecule depends on the tip position (it is maximum when the tip is located above the C–H bond) and on the tunnelling current. The latter dependence is linear. The dependence of the rotation frequency on the voltage on the tip is not monotonic, showing a sharp maximum at the voltage where the energy of the tunnelling electrons coincides with the energy of the vibrational excitation of the C–H bond. For example, the rotation frequency of the acetylene molecule increases by an order of magnitude at a voltage of 358 mV (the frequency of C–H stretching vibrations).[†] In the case of the C_2D_2 molecule, a sharp increase in the rotation frequency (by almost two orders of magnitude) takes place at a voltage of 266 mV, which corresponds to the C–D stretching frequency.

These data indicate that the first event caused by the tunnelling current is the excitation of the C–H (or C–D for C_2D_2) bond; this is followed by the intramolecular energy transfer from the C–H stretching vibrations to bending vibrations and to vibrations of the molecule as a whole, or directly to the complex vibrations composed of the bending and rotation frequencies. The final outcome is the molecule jump from one position to the other (orthogonal). The quantitative estimates are consistent with this pattern: the probability of the orientational jump of the C_2H_2 molecule per passing (tunnelling) electron is constant and equals $\sim 10^{-10}$. Since approximately every hundredth electron excites a stretching vibration, we obtain that the probability of transformation of the stretching excitation into the rotation of the molecule as a whole is $\sim 10^{-8}$. Note that all this information — topographic images, jump frequencies, stretching vibration frequencies and the probabilities of excitation of various types of vibrations — has been gained from a single molecule.

Unlike the O_2 and C_2H_2 molecules, which rotate on the crystal surface, while remaining on the spot, an ethylene molecule migrates chaotically over the Ni(110) surface.⁴⁵ Figure 9*a* shows that the C_2H_4 molecule jumps by arbitrary distances in an arbitrary direction in different atomic planes of the nickel single crystal, short jumps being most probable. Most of the points in Fig. 9*a* are grouped at the centre, near the starting position of the molecule, which is designated by zero displacement. Figure 9*b* shows the histogram of the number of jumps as a function of the jumps distance; most (almost 90%) of 112 events fall in the distance range of 0.1–2.0 Å.

The jumps of the ethylene molecule over the surface are in line with jumps of the tunnelling current: when the molecule moves away from under the tip, the tunnelling current sharply drops; when the molecule returns, the tunnelling current increases jumpwise to the initial value. The return of the molecule is not a rare event. Indeed, during the pulse of the tip voltage (10 s), the tunnelling current ‘switches on’ many times, *i.e.*, the molecule has time to move away and return back to the start hundreds of times.

The histogram of the time intervals during which the molecule is waiting for a jump from under the tip is exponential (the histograms were constructed based on observation of 300–1300 events with their subsequent averaging over 8–16 single molecules⁴⁵). Using these histograms, the rate constants for the ‘departure’ of a molecule from under the tip were determined. The constants were found to depend markedly on the mass of the isotopes that form the molecule, being equal to 196, 204, 42, 24, and 15 s^{-1} for $CH_2=CH_2$, *trans*-CHD=CHD, *cis*-CHD=CHD, $CD_2=CD_2$, and $CH_2=CD_2$, respectively. It should be noted, however, that this dependence is not regular: the *trans*-CHD=CHD molecule jumps faster than *cis*-CHD=CHD and much faster than $CH_2=CD_2$ having the same mass. It has been

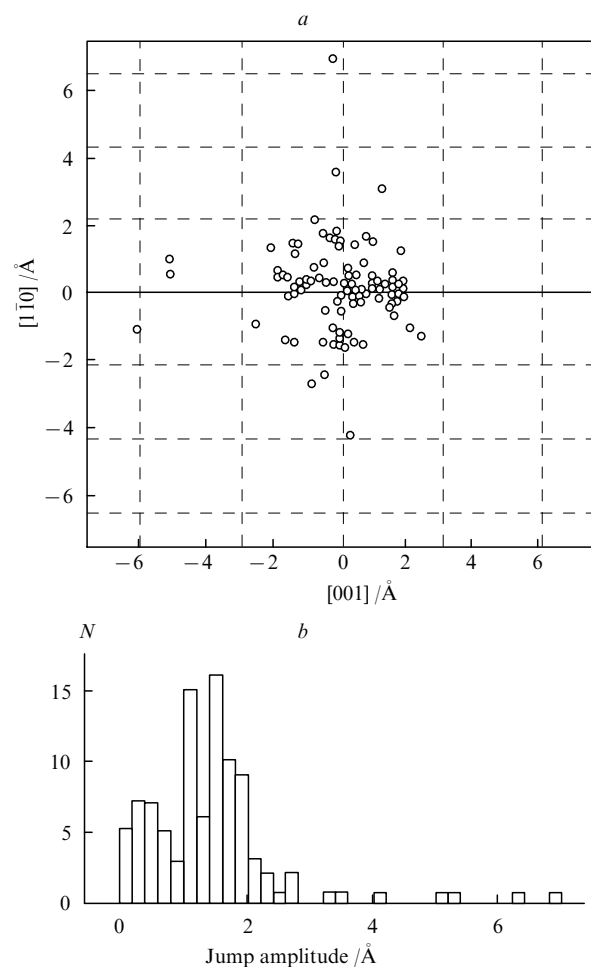


Figure 9. Distribution of the jump amplitudes of single ethylene molecules on the Ni(110) surface (*a*) and column diagram of the jumps (*b*) (N is the number of jumps with a given amplitude).⁴⁵

noted⁴⁵ that for stimulation of vibrations of the molecule as a whole by the tunnelling current, it is important whether the geometric centre of the molecule (to which the tunnelling current is directed from the tip) coincides with its centre of mass. This has a crucial influence on the efficiency of pumping of the vibrational energy of the molecule by tunnelling electrons.

The rate constants for the return of the ethylene molecule under the tip were measured in a similar way. For the same series of isotope-substituted ethylene molecules, they were 74, 65, 22, 21 and 6 s^{-1} . It is clear that lower constants correspond to weaker tunnelling currents. The dependence of the jump frequency on the mass of the molecule attests unambiguously to an inelastic interaction of the tunnelling electrons with the molecule, *i.e.*, to the vibrational excitation of the adsorbed molecule.

Note that the dynamic behaviour of each molecule is unique and is detected independently. There is no need to describe it by the rate constant. This value is useful only for the statistical, probabilistic characteristics of the molecule and is obtained by time averaging (over the number of migration events for one molecule) and ensemble averaging (averaging of these events over 8–16 individual molecules).

The migrations of the C_{60} molecule chemisorbed on silicon are also induced by the tunnelling current of about 1 nA at a voltage of 2–3 V.⁴⁶ It is remarkable that in this case, it is possible both to push and to pull the molecule, *i.e.*, the tip interaction with C_{60} takes place at both types of potential, namely, attraction and repulsion. The C_{60} molecule moves by steps, the step length being equal to two silicon lattice spacings. In the case where C_{60}

[†] 1 mV corresponds to 8.0655 cm^{-1} .

chemisorption implies the formation of the C–Si bond, the migration of the C_{60} molecule can be regarded as rolling conjugated with valence migration.

The conformational dynamics of individual pyrrolidine and deuterated pyrrolidine molecules on the Cu(001) surface at 9 K has been studied.⁴⁷ These molecules are attached fairly strongly to the crystal surface due to the nitrogen lone pair and occupy two positions, being arranged either at right angle to the crystal surface (position I in Fig. 10a) or parallel to the surface (position II in Fig. 10a). The tip mounted at a constant height above the molecule records two levels of the tunnelling current, high (0.15 nA) and low (0.03 nA) (see Fig. 10b), which correspond to these two positions. The random current ‘flickerings’ mark precisely the reversible jumps of the molecule, while the position of the molecule on the surface remains fixed (this follows from the topographic images of the molecule).

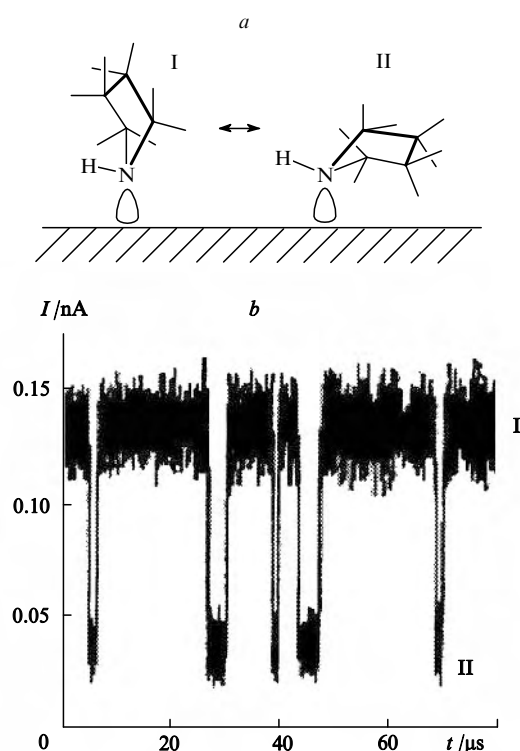


Figure 10. Arrangement of a single pyrrolidine molecule on the Cu(001) surface in two conformations I and II (a) and jumps of the tunnelling current upon the $I \leftrightarrow II$ conformation transitions (b).⁴⁷

By comparing the durations of two currents, one can estimate the populations of the two positions (orientations), *i.e.*, their statistical weight. Both the populations and the rate of transitions between the ‘standing’ and ‘lying’ positions (*i.e.*, the frequency of current flickering) depend on the tip voltage. It is clear that the populations are not thermodynamically equilibrated, as the molecule is exposed to the tunnelling current, which stimulates the orientational transitions.

When the transition rate is low, both orientations can be seen (see Fig. 10b), while in the case of fast transitions, the tunnelling current between them is averaged. This is observed at a tip potential of 376 mV for pyrrolidine and at 283 mV for d_8 -pyrrolidine. These potentials correspond to the excitation of the vibrational levels of the CH_2 and CD_2 fragments, respectively. The vibrational excitation induces fast transitions between two conformations and levelling of their populations. When the tip moves away from these resonance potentials, the slow orientation dynamics is again restored.

Two states of rigid molecules, thiophene and pyrrole, can also be clearly detected in their topographic images: in one state, molecules ‘lie’ on the Cu(001) surface (adsorption through the π -orbitals of the aromatic ring), while in the other one, they are arranged perpendicular to the surface (‘stand’), being strongly attached to the Cu atoms by the S or N lone electron pair, respectively. Conversely, the furan molecule is weakly bound to the Cu atom; it is too labile to stay under the tunnelling current.⁴⁸ It is of interest that tetrahydrothiophene similar in structure to pyrrolidine did not show any orientational transitions under the tip current; the topographic images of tetrahydrothiophene indicate that the molecule ‘stands’ on the Cu atom.⁴⁸

A special type of migration of single molecules is the controlled transfer from the surface to the tip and back; it is attained by variations of the voltage and tunnelling currents.⁴⁹ Thus the transfer of ethylene molecules is accomplished in the following way. A tungsten tip is mounted above the C_2H_4 molecule located on the Ag(110) surface. For a tunnelling current of 0.1 nA, a voltage of +70 mV is applied to the tip. While the current is maintained constant, the voltage is changed jumpwise by –70 mV and then brought gradually to –140 mV. The tunnelling current thus increases from 0.1 to 10 nA and the C_2H_4 molecule is transferred on the tip end. The back transfer takes place when the tip bearing the C_2H_4 molecule is mounted above the Ag atom and a +390 mV voltage is applied.⁴⁹ The reversible transfer of CO occurs in a similar way but at different tip potentials. Note that the physical mechanism of the transfer under these conditions is not entirely clear.

More definite considerations on the mechanism of molecular transfer were reported in another study⁵⁰ where high voltage was used to transfer the CO molecule from the Cu(111) surface to a Cu tip. When the voltage was > 2 V and the distance between the tip and the surface was ~ 7 Å, the current was several nanoamperes. The transfer of a CO molecule to the tip mounted above this molecule or along the surface took place at a voltage exceeding the threshold value of 2.4 V. In this case, the derivative dI/dV increased. This increase coincided with the occupation of the excited $2\pi^*$ -state of the CO molecule (this was determined by two-photon photoemission spectroscopy). The relaxation time of this electronically excited state was found to be very short (0.5–5.0 fs). The fast energy relaxation from the antibonding π^* -orbital of the CO molecule was the reason for the low quantum yield of carbon monoxide desorption (2.7×10^{-11} at 2.7 V or 3.0×10^{-11} at 3.0 V) and for its transfer to a new position (including the tip).

The average residence time of the CO molecule after voltage application (*i.e.*, the transfer waiting time) depended on the voltage and the current. The transfer rate (the reciprocal of the residence time) is proportional to the tunnelling current; this means that the transfer of the molecule is a single-electron process.

The isotope effect in the transfer rate has also been measured:⁵⁰ the heavy $^{13}C^{18}O$ molecules jumped to a new position under current 2.7 times more rarely than the light $^{12}C^{16}O$ molecules. The isotope effect attests to a key role of the relaxation of the electronic excitation to vibrations of the molecule as a whole. Quantitative analysis of the effect lead to an important conclusion: only 0.5% of all the tunnelling electrons excite the CO molecule to the $2\pi^*$ state and, hence, the probability of the ‘jump’ per excitation event is $\sim 5 \times 10^{-9}$. This is a low value but it is consistent with the low probability of electron energy relaxation to low-frequency vibrations of the molecule as a whole.

2. Tunnelling spectroscopy

The topographic images of the atomic-and-molecular surface relief are formed due to the elastic interaction of the tunnelling electrons with the surface atoms. However, probing of the energy levels of the surface atoms and molecules requires inelastic electron interaction; only inelastic interaction does involve the exchange of energy between the tunnelling electrons and surface particles. The presence of energy exchange (inelastic tunnelling)

can be detected from the current–voltage dependences the study of which constitutes the subject of tunnelling spectroscopy.

In chemistry, two versions of tunnelling spectroscopy are used most efficiently: threshold spectroscopy and resonance spectroscopy. The former was mainly developed by Ho and co-workers⁵¹ and the latter, by Dalidchik and co-workers.^{52,53}

The threshold spectroscopy uses low potentials $V \ll \varphi$ (φ is the electron work function in the tip–surface nanocontact). The scheme of tunnelling transitions for this case is shown in Fig. 11.

The inelastic tunnelling channel opens only at a voltage exceeding the critical (threshold) value, which corresponds to the energy level of the molecule in the nanocontact. At lower voltages, the inelastic tunnelling is forbidden, as an electron cannot lose energy by sinking below the Fermi level where all electronic states are occupied and there is no room for new electrons.

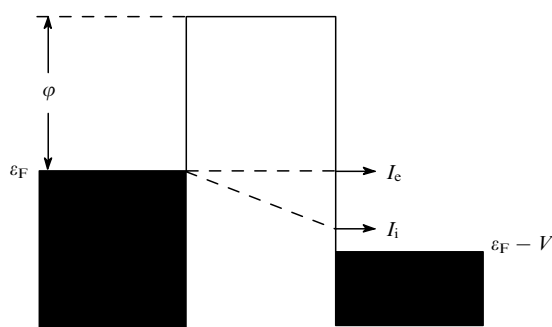


Figure 11. Scheme of tunnelling in a nanocontact at voltages $V \ll \varphi$. ε_F is the Fermi level, φ is the electron work function, I_e and I_i are elastic and inelastic tunnelling.

The threshold voltage V at which an additional inelastic tunnelling appears is recorded based on the jump in the tunnelling current $I(V)$. On excitation of the vibration frequencies of the molecule, the probability (cross-section) of the inelastic process is very low, because the probability of energy exchange between the ‘light’ electron and vibrations of ‘heavy’ atoms is low. In order to detect the vibration frequencies of single molecules based on small current $I(V)$ jumps, Ho and co-workers⁵¹ have developed highly sensitive equipment in which they attained a high stability of the tip position above the selected molecule (the tip could stay for hours); during this period, the potential on the tip varied periodically from $-V$ to $+V$, passing a multitude (hundreds or even thousands) of times the threshold value where the jump of the tunnelling current took place. The smoothly varying and controlled voltage on the tip was modulated at a frequency of hundreds of Herz, so that the current jump was detected based on the second derivative d^2I/dV^2 ; the peak position in the d^2I/dV^2 vs. voltage V dependence corresponds to the potential V_k , which is equal to a frequency in the vibrational spectrum of the molecule.⁴⁸

An example of such dependences for single C_2H_2 and C_2D_2 molecules on the Cu(110) surface is shown in Fig. 12. For the C_2H_2 molecule, the peak is clearly seen at 358 mV, while for C_2D_2 , the peak is at 266 mV. On an energy scale, these peaks coincide with the C–H and C–D stretching frequencies, respectively. Thus, the isotope shift in the potentials corresponds to a shift in the C–H and C–D vibration frequency.^{44, 51}

Threshold spectroscopy was used to obtain the spectra of diverse molecules: the $^{12}C^{16}O$ and $^{13}C^{18}O$ isotope forms,⁴⁹ ethylene and its isotope forms,⁴⁵ pyridine, benzene,⁵⁴ pyrrole, pyrrolidine, thiophene, tetrahydrothiophene and their deuterated analogues.⁴⁸ Recording of the vibrational spectrum of molecules, especially ‘light ones’ (for example, the spectrum of the O_2 molecule on the silver surface⁴⁹) is far from being always possible. This is due to the fact that molecules ‘run away’ from under the tip earlier than a relatively reliable spectrum can be accumulated from the d^2I/dV^2 vs. V dependence. Possible physical reasons are

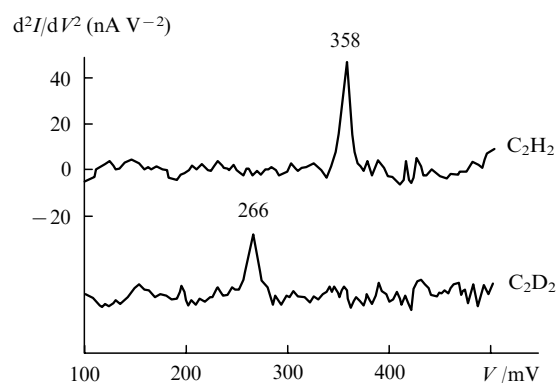


Figure 12. Second derivative of the current with respect to the voltage as a function of voltage for single C_2H_2 and C_2D_2 molecules. The voltages of 358 mV and 266 mV correspond to C–H and C–D vibration frequencies, respectively.⁴⁴

either direct pumping, by tunnelling electrons, of the low-frequency vibrations of the molecule as a whole or the transfer of the vibrational energy from the stretching vibrations excited by inelastically tunnelling electrons to the vibrations of the whole molecule.

The resonance tunnelling spectroscopy of single molecules developed by Dalidchik *et al.*^{52,53} operates in the field-emission mode, *i.e.*, at tip voltages exceeding the electron work function. Under these conditions, the tunnelling electrons overcome two barriers, while leaving the tip and while entering the surface (Fig. 13); therefore, they become ‘captured’ in the space between the tip and the molecule for about 10^{-13} – 10^{-14} s. The space between the tip and the surface functions as a ‘nano-scale resonator’ in which stationary waves (field-emission resonances) are established at a certain value of energy. Since the energy of the resonances depends on the tip potential, the tunnelling current as a function of the voltage applied has clear-cut peaks corresponding to the electronic-vibrational (resonance) levels of the adsorbed molecule, which interacts with the electron captured by the resonator. This is a manifestation of the fundamental quantum effect, *i.e.*, the resonance clearing of the double potential barriers, which become absolutely transparent when the energy of the tunnelling electrons coincides with the vibration energies. At these resonance potentials, the tunnelling current sharply increases, thus recording the vibrational spectrum of the molecule under the tip (this is shown schematically in Fig. 13).

The resonance tunnelling spectroscopy is being actively developed by Dalidchik and co-workers since 1997.^{52,53,55,56} An example of the vibrational spectra of single H_2O and D_2O

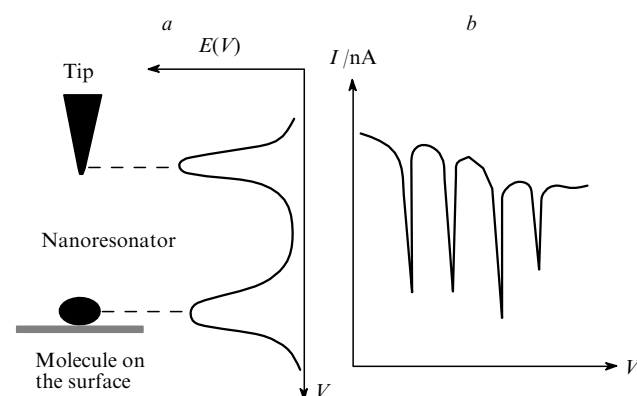


Figure 13. Scheme of a nanoresonator confined by two barriers (a) and schematic dependence of the tunnelling current on the voltage (b).

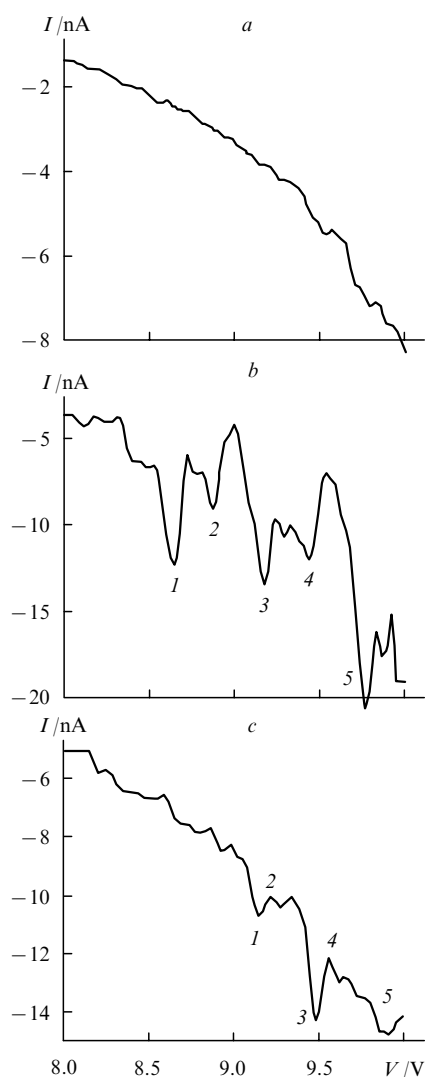


Figure 14. Tunnelling current vs. voltage for a clean oxidised titanium surface (a) and for single H_2O (b) and D_2O (c) molecules adsorbed on the oxidised titanium surface. Resonance lines (1–5) correspond to the vibration frequencies of the molecule (see the text).^{53, 56}

molecules adsorbed on oxidised titanium is shown in Fig. 14. Here one can see the following resonance lines: $\omega_1 = e(V_3 - V_1) = 0.5$ eV and $\omega_2 = e(V_2 - V_1) = 0.2$ eV (one-quantum stretching and bending vibrations), $\omega_3 = e(V_5 - V_1) = 2\omega_1$ (two-quantum stretching vibrations) and $\omega_4 = e(V_4 - V_1) = \omega_1 + \omega_2$ (complex vibrations), where the subscripts n correspond to the numbers of resonance lines shown in Fig. 14 (V_n are the corresponding voltages).^{53, 56} For the D_2O molecule, ω_1 and ω_2 are 0.35 and 0.15 eV, *i.e.*, the isotope shift corresponds almost exactly to the isotope frequency ratio $[\omega(\text{H}_2\text{O})/\omega(\text{D}_2\text{O}) \approx \sqrt{2}]$.⁵⁶

Figure 15 presents the vibrational spectra of molecular oxygen adsorbed on different sections of the iron oxide surface.⁵⁷ Note that the scope of resonance tunnelling spectroscopy is unlimited. This method can be used to detect and measure the frequencies of individual vibrations and their combinations; measure the vibrational relaxation rates by controlling the tunnelling current (*i.e.*, the vibrational pumping rate). The difficulties and limitations of the resonance spectroscopy are also evident: it is far from being always possible to interpret the spectrum and assign the peaks in the tunnelling current to definite vibrations; interpretation of the spectra is a difficult task, especially for polyatomic molecules. In the interpretation, it is expedient to use related molecules, isotope forms, *etc.*

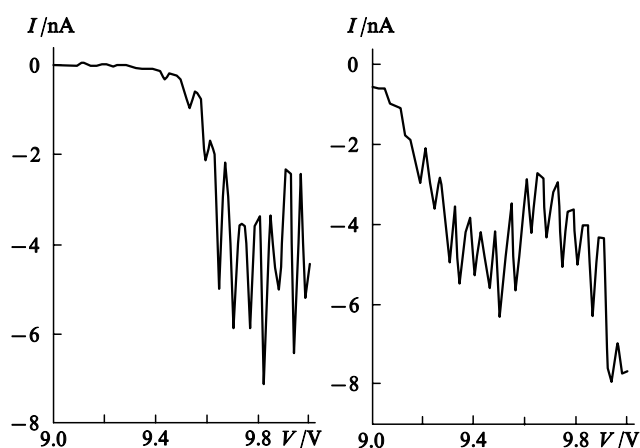


Figure 15. Vibrational spectra of oxygen molecules on different (non-identified) Fe_xO_y sites.⁵⁷

3. The chemistry of single molecules

The inelastic interaction of the tunnelling electrons with a molecule is accompanied by pumping the molecule with vibrational energy, which stimulates its chemical transformations. These events are detected based on the images of the reactant and product, on the tunnelling current jump at the instant of reaction and on the vibrational spectra of the reactant and the products.

The simplest example is the dissociation of the O_2 molecule, physically adsorbed on the Pt(111) surface, at 40–150 K.⁵⁸ When the voltage on the tip is 0.3 V and the tunnelling current is 22 nA, dissociation of the O_2 molecule into atoms takes place in 30 s, the atoms being dispersed by three Pt(111) lattice spacings. Simultaneously, atom images and a tunnelling current jump at the instant of the reaction are observed. The rate constant for dissociation measured by statistical averaging over many molecules increases with current according to the power law I^n , where the power exponent n depends on the voltage, being equal to 0.8, 1.8 or 2.9 for voltages of 0.4, 0.3 or 0.2 V, respectively. It is of interest that the behaviour of the O_2 molecules depends on their position on the surface of a Pt crystal, in particular, they only dissociate on a *fcc* face, desorb without dissociation on the terrace steps and both dissociate and desorb on the transition bridges. It is clear that the energy pumping to the inner (reaction) vibrations competes with that to the outer vibrations of the molecule as a whole.

Yet another example is the dissociation of the C_2H_2 and C_2D_2 molecules to C_2H and C_2D on the Cu(001) surface at potentials of 2.8 and 3.9 V, respectively.⁵⁹ The resulting C_2H and C_2D species then dissociate to C_2 at potentials of 2.1 and 2.7 V, respectively. The great isotope effects are due to not only isotopy of the C–H and C–D bonds but rather by the difference in the cross-sections of excitation of the isotope molecules by tunnelling electrons. As noted above, the excitation cross-section is determined by the probability of energy transfer (inelastic process) from the ‘light’ electron to the ‘heavy’ molecule. This probability is usually very low and proportional to $(a_0/R_0)^{2\Delta v}$, where a_0 is the amplitude of the zero-point vibrations of the molecule (or atoms in it), R_0 is the equilibrium position of the oscillator simulating the vibrational subsystem, Δv is the change in the vibrational quantum number upon excitation. Thus the large isotope effect in the excitation cross-section is obvious.

The whole sequence of reactions of the single C_2H_2 and C_2D_2 molecules is reliably recorded based on images (topographic), the tunnelling current (it changes jumpwise at the instant of $\text{C}_2\text{H}_2 \rightarrow \text{C}_2\text{H} \rightarrow \text{C}_2$ transformations), vibrational spectra and isotope frequency shifts.⁵⁹

The dehydrogenation of five isotope forms of ethylenes on the Ni(110) surface (they were considered in Section III.1) to acetylene by the tunnelling current has been studied. The process was

monitored by images and vibrational spectra of the reactant and the product. The dehydrogenation started at voltages exceeding the threshold values, the threshold voltages being different for each isotope molecule.⁴⁵ In this case, as in the case of acetylene (see above), the isotope effect is the result of competition between the energetic pumping on the internal and external vibrations of the molecule.

The single-molecule chemistry of pyridine and benzene (and their deuterated analogues) on the Cu(001) surface has been studied by spectroscopy and topography.⁶⁰ The main reaction is the dissociation of the C_5H_5N and C_6H_6 molecules to C_5H_4N and C_6H_4 , respectively. For pyridine, the dissociation threshold amounts to 3.0 V; for the deuterio analogue, this is 3.2 V. The data on the molecule topography are ambiguous; only a tentative conclusion has been drawn according to which benzene 'lies' on the crystal surface, while the dissociation product, the C_6H_4 molecule, stands on the edge.⁶⁰

The transformation of two iodobenzene molecules into biphenyl on the Cu(111) surface includes their dissociation, removal of the iodine atoms and coming together of the phenyl radicals until they are combined to form biphenyl. Each step of this process was controlled topographically and induced by the tunnelling current of the tip.⁶¹

Recently, Japanese researchers have published a reliable and convincing study dealing with dehydrogenation of *trans*-but-2-ene on Pd(110).⁶² First, they obtained topographic images of the initial molecules (Fig. 16a) and the dehydrogenation product, buta-1,3-diene (Fig. 16b): the former looked like dumb-bells (the methyl groups at the ends of the molecule are elevated and provide a substantial elevation of the tip), while the latter looked like ellipses with their principal axes parallel to the row of Pd atoms. The arrangement of the *trans*- C_4H_8 and C_4H_6 molecules relative to the lattice Pd atoms is shown in Fig. 16c,d.

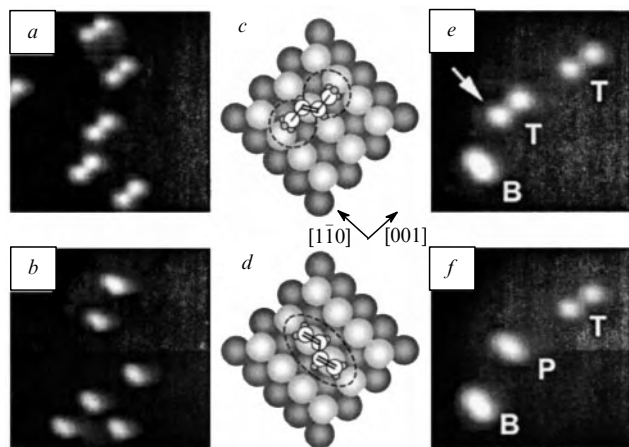


Figure 16. Topographic images of single *trans*-but-2-ene (a) and buta-1,3-diene (b) molecules, their arrangement on Pd(110) (c, d) and images of the *trans*-but-2-ene (T) molecule before the reaction (e) and after its transformation into buta-1,3-diene (P) (f). B is the initial buta-1,3-diene molecule.

Figure 16e shows the initial state of the surface on which two *trans*-but-2-ene molecules (T) and one buta-1,3-diene molecule (B) are co-adsorbed. The tip of the tunnelling microscope was mounted above one of the *trans*-butene molecules (designated by the arrow in Fig. 16e). At a 7 nA current and a 450 mV voltage, this molecule is converted after 1 s into the product molecule (P), which is identical to the initial buta-1,3-diene molecule (B, Fig. 16f). Thus, the researchers were able to observe how *trans*-butene is dehydrogenated under the action of the tunnelling current. Probably, the hydrogen atoms are removed non-simultaneously from the methyl groups of *trans*-butene, but the inter-

mediate structure with one removed hydrogen atom is unstable and gives off the second hydrogen atom so rapidly that its image cannot be recorded.

Spectroscopic evidence for dehydrogenation of *trans*-butene and its deuterated analogue has been derived from analysis of the $I(V)$ dependence: the second derivative d^2I/dV^2 has maxima corresponding to the C–H vibrations of the methyl group, 366 mV for *trans*-butene and 268 mV for the deuterated molecule. In the reaction product, butadiene, these frequencies are missing. Moreover, the transformation of *trans*-butene into butadiene starts at threshold voltages that exactly coincide with the frequencies of the C–H and C–D stretching vibrations.

The dependence of the reaction rate W , measured statistically for a number of molecules, on the current is a power function: $W \approx I^n$, where the power exponent n depends on the voltage and the isotope composition of the molecule and varies in the range from 1.5 to 3.0. All these features indicate unambiguously that the chemical transformation is stimulated by the vibrational excitation of the C–H (or C–D) bonds by tunnelling electrons.

A remarkable feature of the *trans*-butene molecule as an experimental object is the fact that the molecule remains motionless under the tip tunnelling current, *i.e.*, it does not move across the surface (unlike other light molecules such as O_2 or C_2H_2 , considered in Sections III.1). This means that the high-frequency vibrations of the CH_3 groups interact weakly with the low-frequency vibrations of the weighty *trans*-butene molecule as a whole; therefore, the vibrational excitation of the CH_3 groups is eliminated by dissociation of the C–H (or C–D) bonds.

At the end of the discussion of studies dealing with the single-molecule chemistry, it is necessary to consider its limitations. The major one is the lack of information on the chemical transformation itself. All information on the physics of the chemical process is included in the reaction rate *vs.* current dependence ($W \approx I^n$) and in the dependence of n on V (this bears the rate of the tunnelling electrons) and on the isotope composition of the molecule. In order to extract this information, theoretical analysis of these dependences is required in terms of the theory of inelastic interaction of electrons with adsorbed molecules and energy relaxation of the molecule. This theory is well developed for gas molecules; however its extension to adsorbed molecules is an independent task. Moreover, to compare the theory with the experiment, one should know what portion of the tunnelling electrons interacts with the molecule in the inelastic mode, *i.e.*, makes a contribution to the vibrational excitation. Some estimates of this parameter for specific cases have been given above, but generally this problem is still to be solved.

IV. A single high-spin molecule as a nanomagnet

Classical nanomagnets are particles with sizes of about hundreds of nanometres. They are usually produced by dispersion or deposition of ferromagnetic materials; therefore, they are non-uniform (have particle size and magnetic moment distributions). The new class of nanomagnets, namely, single-molecule magnets, are free from these limitations. They are obtained by classical methods of chemistry and isolated and purified as pure chemical substances.⁶³ Like chemical 'cloning' products, single-molecule magnets are absolutely identical in size, structure and magnetism. As a rule, they are represented by high-spin metal clusters, which have a magnetic core made of transition metal atoms containing tens (or sometimes hundreds) of unpaired electrons (spin carriers) and a diamagnetic shell (coat) of organic ligands. The ligands eliminate the intermolecular exchange interaction of electrons and make the nucleus magnetically isolated (Fig. 17).

Each of these molecules is a nanomagnet, which shows all properties of a real magnet, in particular, spontaneous magnetisation, magnetisation anisotropy and hysteresis, domain structure, dynamic hysteresis (the imaginary part of the magnetisation detected based on the frequency dependence of the magnetisation in alternating fields). The exchange interaction of electrons and

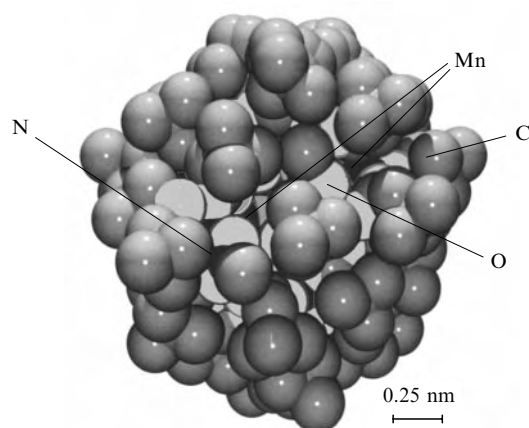


Figure 17. Three-dimensional atomic image of the molecular magnet $\text{Mn}_{30}\text{O}_{24}(\text{OH})_8(\text{O}_2\text{CCH}_2\text{Bu})_{32}(\text{H}_2\text{O})_2(\text{MeNO}_2)_4$.⁶⁴ All atoms except hydrogen are shown.

the dipole interaction of the electron spins within a molecule is a source of magnetism in these molecules. The exchange interactions (J) between the unpaired electrons in the core of the molecule usually have different magnitudes and signs: for some electrons they are positive and align the electron spins parallel (ferromagnetism), while for other electrons this interaction is negative and the spins become antiparallel (antiferromagnetism). As a result, the total spin of the molecule does not correspond to the number of unpaired electrons in it. For example, the number of unpaired electrons (N) in the $\text{Mn}_{12}\text{O}_{12}(\text{O}_2\text{CMe})_{16}(\text{H}_2\text{O})_4$ molecule is 44 while the total spin (S) is only 10 (see Ref. 63). The $\text{Mn}_9\text{W}_6(\text{CN})_6$ and $\text{Mn}_9\text{Mo}_6(\text{CN})_6$ molecules have the same numbers of unpaired electrons ($N = 51$) but different total spins: $S = 39/2$ and $51/2$. The total spin $S = 51/2$ implies that in the molybdenum cluster $\text{Mn}_9\text{Mo}_6(\text{CN})_6$ all electrons are coupled ferromagnetically. In the $\text{Fe}_{11}\text{O}_6(\text{OH})_6(\text{O}_2\text{CPh})_{15}$ molecule, $N = 55$ and $S = 1/2$. Even for the record large molecule, $\text{Mn}_{30}\text{O}_{24}(\text{OH})_8(\text{O}_2\text{CCH}_2\text{Bu})_{32}(\text{H}_2\text{O})_2(\text{MeNO}_2)_4$ (see Fig. 17), in which the number of unpaired electrons is 143, $S = 5$.⁶⁴

The dipole interaction (D) of the electron spins in the $\{\text{Mn}_{30}\}$ molecule also has different signs and forms groups of spins that compose nanodomains inside the molecule. The energy of dipole interactions (normally about 1 cm^{-1}) creates a barrier to re-orientation of nanodomains and is a source of dynamic and static hysteresis.

Unlike macroscopic ferromagnets, in the molecular magnets, nanodomains change the magnetisation direction by the tunnelling mechanism; therefore, a quantum hysteresis loop appears in these molecules, the discrete magnetisation steps being its typical feature (Figs 18 and 19).^{63, 65}

The interest in the nanomagnet molecules is determined by the following facts:

- they are individual, identical and have a clear and exact atomic and molecular architecture;
- they are soluble and, therefore, can be easily and controllably assembled into molecular ensembles (including two-dimensional lattices on the surface);
- they have a large magnetic moment and can be reliably detected and controlled by ‘point’ methods, namely, atomic force and tunnelling scanning spectroscopy.

The molecular magnets attract enormous attention as elements of high-density magnetic memories and quantum computers and as materials for spintronics. About 20–30 such molecules with Mn, Fe, V, Cr, W, Tb and Dy cores have been synthesised to date.

The theory of these molecules is now under vigorous development; the conditions to be satisfied by multispin molecules for their functioning as nanomagnets have been summarised; they

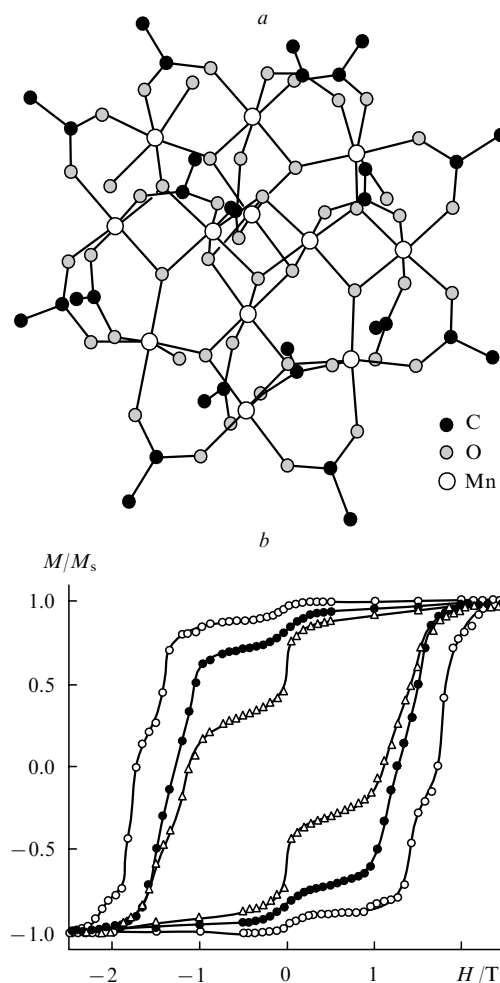


Figure 18. Atomic structure of the $\text{Mn}_{12}\text{O}_{12}(\text{O}_2\text{CC}_6\text{H}_4\text{Cl}-2)(\text{H}_2\text{O})_4$ molecule (a) (the 2-chlorobenzene rings are not shown for simplicity) and quantum hysteresis loops (b) for the molecular nanomagnets $\text{Mn}_{12}\text{O}_{12}(\text{O}_2\text{CMe})_{16}(\text{H}_2\text{O})_4$ (1) and $\text{Mn}_{12}\text{O}_{12}(\text{O}_2\text{CC}_6\text{H}_4\text{X}-2)(\text{H}_2\text{O})_4$ (2, 3) [X = Br (2) and Cl (3)] at 20 K.⁶³

include spin non-equivalence in the J and D values, the anisotropy of spin–orbit (λLS) and exchange (J) interactions. These conditions are practically implemented by combination of atoms of different metals within one molecule (in some cases, with the addition of paramagnetic organic ligands)⁶⁶ and chemical design.

In the tunnelling spectroscopy, the molecular magnets exhibit a remarkable feature, namely, spin selectivity of the inelastic interaction of the molecule with the tunnelling electrons coming out of the tip. This feature was first discovered by Dalidchik and co-workers⁵⁵ in relation to the low-spin O_2^- molecule. The spin of the unpaired electron in the O_2^- radical anion and the spin of the tunnelling electron create either a singlet (the total spin is equal to zero) or triplet (the total spin is equal to unity) state through the exchange interaction. These states differ energetically by the value of exchange energy; the difference results in the line splitting in the vibrational spectrum of the O_2^- radical anions into pairs corresponding to the singlet and triplet channels of the tunnelling current (Fig. 20).

This feature opens up new opportunities for the use of molecular magnets as spin filters (for filtering the tunnelling electrons according to the spin). This is a remarkable result of the single-molecule spin chemistry, which will be undoubtedly included into the spintronics. Kozhushner and co-workers⁶⁷ proposed using a ferromagnetic tip (a source of polarised electrons) for the same purpose and developed a theory of this spin filter. An increase in the sensitivity of optical detection by micro-

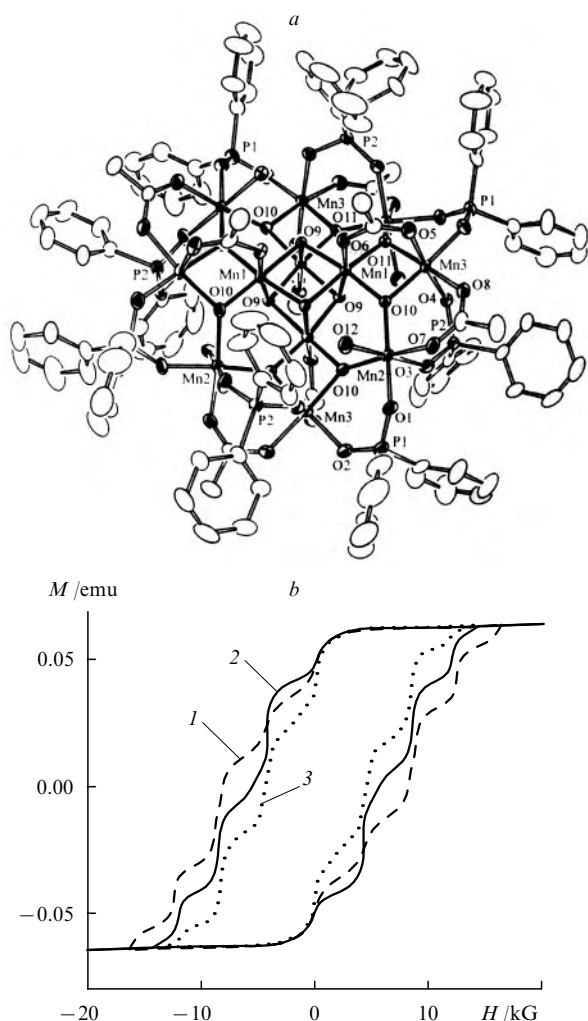


Figure 19. Atomic structure (a) and quantum hysteresis loops (b) of the molecule $\text{Mn}_{12}\text{O}_{12}(\text{O}_2\text{CMe})_8(\text{O}_2\text{PPh}_2)_8(\text{H}_2\text{O})_4(\text{CH}_2\text{Cl}_2)_2$ at 1.8 (1), 1.9 (2) and 2.0 K (3).⁶⁵

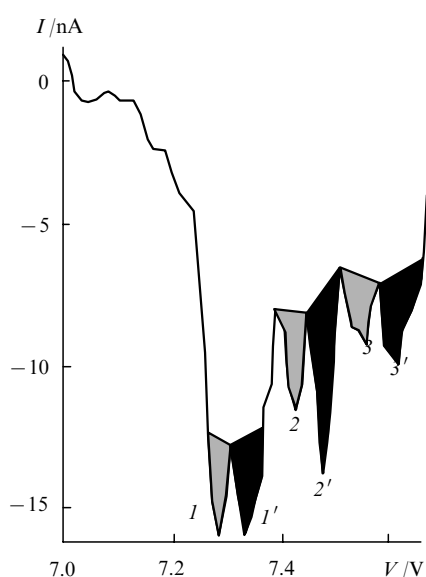


Figure 20. Tunnelling current I vs. potential V for the single O_2^- radical anion located on the oxidised titanium surface. Line splitting within the $1-1'$, $2-2'$ and $3-3'$ pairs corresponds to the exchange energy of electrons.⁵⁶

wave treatment of the spin molecule and the use of electron paramagnetic resonance in the tunnelling spectroscopy have been discussed.^{68, 69}

V. Raman spectroscopy of single molecules

Raman spectroscopy is based on inelastic light scattering on molecular vibrations. The photons that fall on the molecule lose an energy quantum, which is spent for the excitation of molecular vibrations; this loss is detected as a shift of the exciting light frequency (Stokes shift). If the molecular vibrations have been excited, the photons falling on the molecule acquire an additional energy of molecular vibrations; as a consequence, the scattered light frequency increases (the anti-Stokes shift).

Raman spectroscopy has found wide application in the chemistry and physics of gases, liquids and solids and has become a serious supplement to the usual vibrational spectroscopy. Currently, this method is a powerful tool in the study of the molecular structure. However, the probability of inelastic photon–vibration (Raman) interaction (with generation of a Stokes or anti-Stokes line) is very low (the cross-section of this interaction does not exceed 10^{-30} cm² per molecule); therefore, the sensitivity of the method is low, which makes it applicable only to large ensembles of molecules.

In 1977, it was found that the probability of the inelastic light scattering by molecules sharply increases if these molecules are adsorbed on metallic surfaces,^{70, 71} in particular, on metallic electrodes with an extensive surface or nanoparticles. This immobilisation results in an essential increase (10^{14} – 10^{15} , sometimes 10^{20} -fold) in the intensities of the Stokes and anti-Stokes lines, which allows one to reach the threshold of the photon–vibrational interaction cross-section, needed to detect a single molecule (about 4×10^{-18} cm² per molecule) and often even to exceed the threshold.⁷² The best results as regards the sensitivity were obtained on adsorption of the detected molecules on Ag or Au nanoparticles with 10–100 nm size.

Two causes (two mechanisms) for the sharp increase in the probability of Raman scattering are discussed. The first one ('physical' mechanism) involves the enhancement of the local, light wave-induced electric field on the metallic surface due to the collective excitation of the conduction electrons (surface plasmon excitation). This field stimulates a strong non-linear polarisability of the molecule occurring in the vicinity of the plasmon excitation and increases sharply the probability of the photon–vibrational transition.

The second reason ('chemical' mechanism) is the specific interaction of the molecule with the metallic surface. Unlike the plasmon interaction, which is purely physical, this interaction is often called 'chemical'. The 'chemical' interaction is considered to include electron exchange between the adsorbed molecule and the surface metal atoms to yield states of the charge-transfer complex type. The electron exchange mechanism is supported by direct observations: for example, the Raman lines of the pyridine and bipyridine molecules adsorbed on silver clusters are shifted to higher frequencies, which approach those of the pyridinium cations.⁷¹ Thus, charge transfer in the surface–adsorbed molecule system is the key element of the 'chemical' mechanism of the stimulation of Raman scattering. The reversibly generated and destroyed short-lived states are characterised by high polarisability, which is accompanied by a sharp increase in the probability of the Raman vibration transitions in the adsorbed molecule.

Both mechanisms co-exist but the contribution of each of them depends on the particular chemical systems. It is noteworthy that the predominant contribution belongs to the 'physical' mechanism. The plasmons and plasmon resonances are excited on the scale of the exciting light wavelength; this can be called a large-scale process. Conversely, the 'chemical' mechanism acts locally on a molecular scale; it refers to the local electronic interaction of the molecule with the surface.

A contribution of the ‘chemical’ mechanism to the enhancement of surface-induced Raman scattering has been detected.⁷³ Using rhodamine 6G immobilised on colloid silver clusters as an example, the researchers not only detected the contribution of the ‘chemical’ mechanism to the Raman scattering but also separated the contributions of the ‘physical’ and ‘chemical’ mechanisms. The solution containing colloid silver particles was placed into a chamber and a solution containing rhodamine 6G (in order to stabilise the adsorption–desorption equilibrium on the clusters) and various anions, F^- , Cl^- , Br^- , I^- , $S_2O_3^{2-}$, SO_4^{2-} , etc., was passed through the chamber. Measurement of the Raman scattering intensity showed that the citrate, F^- or SO_4^{2-} anions do not influence the intensity of the Raman scattering lines, Cl^- , Br^- and I^- ions enhance the Raman scattering, and the thiosulfate anions decrease scattering by 2–3 orders of magnitude. It was also found that the plasmon spectrum of Ag clusters does not depend on their treatment with anions. These results indicate unambiguously that both mechanisms, ‘physical’ and ‘chemical’, exist almost independently from each other, the former being universal and the other depending on the chemical pre-history of the clusters and their surface chemistry.

Rhodamine 6G is the first molecule for which the vibrational spectrum was recorded under conditions where each individual molecule was arranged above a separate silver nanocluster.⁷⁴

The spectra of adenine and adenosine monophosphate single molecules have also been recorded on silver clusters.⁷⁵ From comparison of the Stokes and anti-Stokes line intensities for these molecules, the cross-section of the photon–vibrational interaction was calculated to be $\sim 10^{-16}$ cm² per molecule (this is an enormous value compared with the value of 10^{-30} cm², typical of the usual Raman process); it was also shown that the cross-section does not depend on the cluster size. Moreover, the spectra of both molecules were identical, *i.e.*, chemical binding of adenine with the carbohydrate does not affect the Raman excitation of adenine.

For the dye Crystal Violet adsorbed on Ag and Au colloid clusters, the enhancement coefficients of the photon–vibrational interaction reach record values of 10^{20} (see Ref. 76).

The Stokes lines arise upon direct interaction of the light field with molecular vibrations; therefore, they are one-quantum. Their intensity is proportional to the intensity of the exciting light. The anti-Stokes lines result from a two-quantum process: one quantum excites a molecular vibration, while the other one induces its stimulated emission, *i.e.*, takes this vibrational quantum away from the molecule. The intensity of the anti-Stokes lines is proportional to the squared intensity of the exciting light. This dependence allows one to characterise quantitatively the Raman inelastic interaction of light with molecular vibrations.

The most interesting and fruitful studies of the single-molecule Raman scattering were carried out by Sweden scientists using biologically important molecules, namely, haemoglobin⁷⁷ and horseradish peroxidase.⁷⁸ Thus comparison of the structure of Ag colloid particles bearing haemoglobin molecules, determined by scanning tunnelling spectroscopy and atomic-force microscopy, with the intensity of Raman lines of the haemoglobin molecules showed that the haemoglobin molecules confined between pairs or groups of three Ag clusters scatter the light most actively. These molecules make the major contribution to the intensities of both Stokes and anti-Stokes lines; the haemoglobin molecules fixed on dimeric clusters whose axis is parallel to the electric field vector of the exciting light being the most active. This allowed the researchers⁷⁷ to conclude (which was also confirmed by theoretical estimates) that the major contribution to the enhancement of Raman scattering on haemoglobin is made by the electric-field plasmon (‘physical’) mechanism but a contribution from the ‘chemical’ mechanism cannot be ruled out either.

Yet another biomolecule studied by this method is horseradish peroxidase immobilised on colloid silver (90 nm size).⁷⁸ In this case, the protein macromolecule becomes ‘captured’ by the clusters, which enhances the plasmon mechanism and increases

the Raman scattering intensity. The intensity growth is so pronounced that the researchers cited⁷⁸ were able to record the Raman spectrum from a sole peroxidase molecule. Measurement of the enzymatic activity of the peroxidase demonstrated that immobilised peroxidase molecules are less active. However, if the silver clusters are pre-treated with hydrogen peroxide, the activity of the immobilised enzyme is retained at the level of the initial (non-immobilised) compound but the intensity of Raman scattering decreases.

This type of behaviour of biomolecules, in particular, enzymes, can be used as an indicator of their functioning at the single-molecule level. In some cases, it is necessary to retain also the ‘native’ activity of the enzyme and its high detectability by Raman spectroscopy; to this end, special techniques are used (see, for example, solution of this problem in Ref. 78).

One important fact deserves attention. To date, there is only one example where the Raman spectrum actually detects a single molecule, *viz.*, peroxidase.⁷⁸ In most cases, the spectra from ensembles of single molecules are recorded, *i.e.*, ensembles of isolated molecules distributed among different clusters. However, this circumstance does not depreciate in any way the chemical information and the advantages of surface-activated Raman spectroscopy.

Like the fluorescence of single molecules (see Section II), the Raman scattering (‘flickering’) of single molecules on the surface of metal clusters depends on time in a random manner: the spectra vary with time as regards both intensities and frequencies. This phenomenon is typical of all molecules studied including biomolecules. The random fluctuation dynamics indicates unambiguously that ‘flickering’ is due to the local surface–molecule interactions. The formation and decomposition of charge transfer states is accompanied by the migration of molecule across the surface. This migration changes both the intensities and frequencies of lines in the Raman spectrum of the analysed molecule.

The fluctuations are of a non-thermal nature; they are initiated by the exciting light, which generates Raman scattering. Direct experimental evidence for this statement was obtained.⁷⁹ For an ensemble of molecules (30 to 50), the frequencies (ν) and intensities (I_ν) of the Raman lines were measured and the fluctuation correlation functions were calculated

$$c(\tau) = \sum_{\nu} [\langle I_{\nu}(t)I_{\nu}(t+\tau) \rangle - \langle I_{\nu}(t) \rangle^2]$$

(the angular brackets mean averaging over τ).

The dependence $c(\tau)$ was used to obtain the fluctuation rate k . These measurements were carried out for various intensities of the light exciting the Raman spectrum. The fluctuation rate was found to increase linearly with an increase in the exciting light power. The thermal heating was minor and did not exceed 0.1 K,⁷⁹ *i.e.*, the spectral fluctuations are non-thermal. This remarkable feature allows single molecules as a local dynamic surface probe.

VI. Electrical conductivity of single molecules

The particular interest in the electrical conductivity of single molecules is due to two factors. First, in chemistry (and especially in biochemistry), determination of charge conductivity of a molecule is subject to many uncertainties. For example, depending on the procedure used to determine the charge conductivity, the DNA molecule was assigned either to dielectrics, or to semiconductors, or to metallic conductors, or even to superconductors.⁸⁰ Second, a molecule as an object of molecular electronics and as an element of nanoelectronic devices (molecular resistors, diodes, single-electron transistors) requires accurate electro-physical characteristics.

The electrical conductivity of single molecules is measured using two procedures. The first one is based on a combination of atomic-force and tunnelling spectroscopy: using one of them, a single molecule is ‘found’, while using the other, the electrical current is applied to the molecule and measured. The second

procedure is based on direct electrochemical synthesis of the molecule (between two electrodes) and measurement of the resistance.

The first electrical conductivity measurement of a single C_{60} molecule placed between two electrodes, one being the surface of the Ag(110) crystal and the other being the tip of a tunnelling microscope, was carried out in 1995.⁸¹ At large distances (S) from the surface of the molecule to the tunnelling tip mounted above C_{60} , the current increased exponentially with a decrease in S . When the van der Waals mechanical contact of the tip with the C_{60} molecule has been established, the current reaches a maximum value, the total resistance (R_{ef}) being 54.807 M Ω .

By substituting this R_{ef} value into the expression

$$V = R_{\text{ef}}I = R_0 \left(1 + \frac{r}{t} \right) I$$

(R_0 is the electrical resistance of the C_{60} molecule, r and t are the reflection and transmission at the Fermi level[†]) representing Ohm's law for the molecular electrical contact, the researchers calculated the resistance (R_0) of the C_{60} molecule, which turned out to be 54.794 M Ω . After the distance from the surface of C_{60} molecule to the tip becomes smaller than the van der Waals mechanical contact, the exponential pattern of the $I(S)$ dependence is violated due to the deformation of the C_{60} molecule under the action of the tip.

The conductivity of molecules depends appreciably on their compression. For example, the compression of C_{60} by 1 Å changes the current strength that passes through the molecule by two orders of magnitude.⁴² For a C_{60} molecule applied onto a dielectric, Coulomb blockade is observed at 4.2 K. The ability of the C_{60} molecule to lock the current can be used in the design of one-electron devices in which the molecule is an ideal quantum dot.⁴²

The main problem in the conductivity measurement for single molecules is to create a reliable and controllable electrical contact of one molecule with two electrodes. Convenient objects are molecules containing reactive SH groups (for example, alkanedithiols); by means of these groups, molecules can be arranged as a wire between two electrodes.

An elegant and reliable experimental technique has been developed to measure the electrical conductivity of hydrocarbon $(CH_2)_n$ chains.⁸⁰ An alkanethiol monolayer with built-in alkanedithiol molecules are applied on the surface of an Au(111) single crystal from a solution. All monolayer molecules had an electrical contact with the Au surface due to S–Au covalent bonds. The upper boundary of the monolayer is formed by the terminal methyl groups of alkanethiol and (at the sites of the admixed dithiol molecules) the alkanedithiol SH groups (these groups can be single or form islets of two, three or four SH groups).

On the alkanethiol monolayer, triphenylphosphine-stabilised gold clusters were applied from a solution. The PPh_3 ligands are known to be easily exchanged with the SH groups; hence, the positions of the alkanedithiol molecules become labelled by gold clusters. Thus Au clusters are connected to the electrical contacts on the Au(111) surface through the $-S(CH_2)_nS-$ bridges. The tip of an atomic force microscope has found an Au cluster on the surface and the voltage was applied to the cluster through the $-S(CH_2)_nS-$ chain. By measuring the tunnelling current between the tip and the Au surface, the electrical conductivity of single $-S(CH_2)_nS-$ chains (Fig. 21) was found to be $0.97 \times 10^9 \Omega$ for $n = 8$, $2.89 \times 10^9 \Omega$ for $n = 9$ and $8.26 \times 10^9 \Omega$ for $n = 10$. From this it follows that the variation of R vs. n is exponential: $R \approx \exp(\beta n)$, where $\beta = 0.6$.⁸⁰

The dependences $I(V)$ at low voltages (50 mV) proved to be linear and symmetric with respect to the sign of V . The slope of the

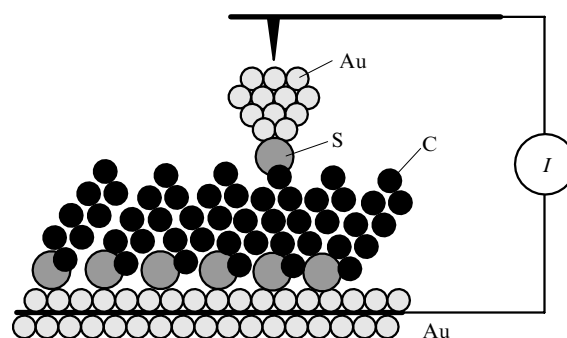


Figure 21. Scheme of the addition of electrical contacts (Au surface below and Au clusters above) to one alkanedithiol molecule incorporated in the alkanethiol monolayer.⁸⁰

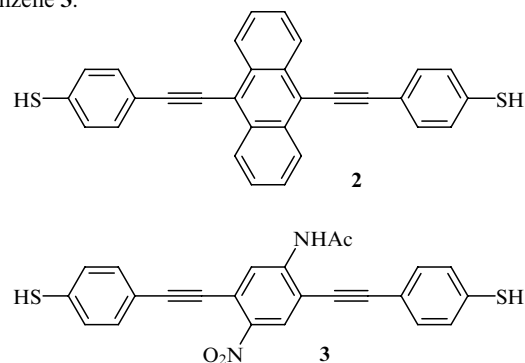
I – V straight line to the abscissa axis (axis I) corresponds to the ohmic resistance. It was found that all the R values can be divided into four groups related by the ratio 1.00 : 0.50 : 0.33 : 0.25. These values correspond to four cases of current passage, namely, through one molecule and through clusters consisting of two, three and four molecules, respectively. In the clusters, the ohmic resistance is made up from the ohmic resistances of each molecule, as in an electric circuit consisting of parallel resistors. Each molecule is an independent conductor, *i.e.*, its resistance does not depend on the neighbours in the clusters. This is a remarkable result, indicative of the reliability of the experimental technique used in the study cited.⁸⁰

Note that the electrical resistance of the $-S(CH_2)_nS-$ chain ($R \approx 10^9 \Omega$) is greater by two orders of magnitude than the resistance of the C_{60} cluster ($5 \times 10^7 \Omega$). It can be concluded that the conductivity of the molecule is mainly determined by the molecular orbitals, their energies and occupancies. Theoretical calculations⁸² of the conductance (G) of molecular wires are consistent with this conclusion. The researchers studied the dependence of the tunnelling current in a channel (wire) on the length and on the chemical structure of molecular wires using oligo(thiophene-2,5-diylalkynediyls), oligo(phenylenealkynediyls), polyenes, *etc.*, as the wires. The conductance in the metal–wire–metal channel was calculated using the formula

$$G = G_0 \exp(-\gamma L),$$

where γ is the damping factor, L is the length of the molecular wire. The G_0 and γ values depend on the chemical structure of the molecular wire.

As another example, one can consider the measurement of the conductivity of the single molecules of 9,10-bis(*p*-mercaptophenylethynyl)anthracene (**2**) and related asymmetrically substituted benzene **3**.



For 'laying' molecules **2** and **3** between electrodes made of Au atoms, an electrode pair with one movable electrode was produced by lithography. The distance between the electrodes was 'adjusted' mechanically to the length of the molecule placed between them.

[†] t is the transmission coefficient corresponding to the elastic passage of the electron Bloch wave through the C_{60} molecule from one electrode to the other, r is the coefficient of reflection of this wave from the molecule.⁸¹

The SH groups in molecules **2** and **3** were protected by acetate groups, which were substituted by Au atoms upon incorporation of the molecules between the electrodes.⁸³

The $I(V)$ plots for such molecular conductors were symmetric with respect to the sign of V . The application of a 1 V voltage to metallic surfaces gives rise to tunnelling currents of about 0.2–1.0 μA , which remain stable during long periods of time (up to 100 min). The electrical resistance of these molecular ‘wires’ was $\sim 2\text{ M}\Omega$ [almost 20 times lower than that of C_{60} and by three orders of magnitude lower than that of the aliphatic $-\text{S}(\text{CH}_2)_n\text{S}-$ chain]. It is clear that molecules **2** and **3** containing systems of highly conjugated bonds are better conductors than the C_{60} or $\text{HS}(\text{CH}_2)_n\text{SH}$ molecules; carbon nanotubes are even better conductors (their resistance is $\sim 100\text{ k}\Omega$).

Undoubtedly, the methods for the design of molecular nanowires and nanodevices based on them will be further developed; this is a route to nanoelectronics.

VII. Mechanics and mechanochemistry of single molecules

Atomic force microscopy measures the attraction force between the microscope tip and the surface of the molecule as a function of the distance between them, unlike tunnelling scanning microscopy, which measures the current between the tip and the molecule surface. In the classical version, atomic force microscopy is contactless: the tip slides along the surface without touching it. Atomic force microscopy is also capable of visualising monoatomic vacancies on the semiconductor and dielectric surface or adsorbed molecules. This allows drawing some approximate conclusions concerning the sizes and the shapes of the molecules, their densities and arrangement on the surface. However, it should be admitted that due to the low spatial resolution, this method provides more information about the surface than about the adsorbed molecules.

The situation changes fundamentally if the atomic force microscopy is made contact, *i.e.*, one end of the molecule is attached to the tip, and the other is on the surface. Then, as the tip moves away from the surface and the molecule is being stretched, one can measure the force as a function of stretching of the molecule, *i.e.*, to study the mechanics of a single molecule. In this case, the atomic force microscopy becomes force spectroscopy.

Figure 22 shows the experimental scheme used to measure the extension (x) of a molecule and the dependence of the force (F) on drawing. The function $F(x)$ is usually non-linear (non-Hookean). The curve $F(x)$ has small local peaks, rises and dips, which are indicative of the change in the conformation of the macromolecule upon drawing. The folded conformations are replaced by extended ones under the action of drawing. Finally, at some

critical elongation, the completely stretched molecule is torn; the tear strength is the strength of the chemical bond.

Force spectroscopy has reached high sensitivity for the strength and high resolution as regards deformation and operates in a broad range of deformations and strengths: 0.01–100 N m^{-1} and 10^{-13} – 10^{-8} N .

The main processes in the nanomechanical technology include ‘picking up’ of a single molecule from a solution, a gel or a solid by the microscope tip and its drawing. During drawing, the force and deformation of the molecule are measured. This technology combines science and art: usually, the tip is immersed into a solution (or film) applied on a substrate and kept there for some period using a force of several nanonewton, and then lifted, thus drawing the molecule. By changing the functional groups at the ends of the molecule, the material of the tip and the substrate from which the molecules are taken, by varying their concentration, the amplification and the type of contact between the cantilever tip and the molecule container and using the trial-and-error method, one can attain the goal, *i.e.*, pick up the required molecule and analyse its mechanics (or mechanochemistry).

Using the new technology, it is possible to measure the binding strength of molecules and complexes (for example, DNA strands or an antigen with an antibody) and the cleavage strength of chemical bonds, to observe the conformations of molecules, to measure their elasticity and to move atoms and molecules (pull or push them over the surface).

1. Nanomechanics of macromolecules

The first outstanding success in the mechanics of single molecules was achieved in a study of natural and synthetic macromolecules. In experiments with single polysaccharide molecules, the first stage was modification of the polysaccharide terminal groups in such a way that one end could be attached to a glass surface (*via* the Si–C covalent bond) or a gold surface (Au–S bond),⁸⁴ while the other end could be grafted to the cantilever. After that, the polysaccharide molecule was drawn, while measuring the force spent for deformation. The resulting $F(x)$ dependence for these molecules was similar to that shown in Fig. 22; the Si–C bond was cleaved at a force of 2 nN, while the Au–S bond, at 1.4 nN.

The nanomechanical properties of poly(*N*-isopropylacrylamide) and poly(acrylamide) in aqueous solutions have been studied.⁸⁵ For these flexible-chain macromolecules which fold into a statistical coil, back in 1942 Kuhn derived from the freely jointed chain model the $x(F)$ dependence, which is described by the Langevin function

$$x(F) = \left[\text{cth} \left(\frac{Fl}{kT} \right) - \frac{kT}{Fl} \right] L, \quad (1)$$

where l is the length of the statistically independent Kuhn segment, L is the contour length of the macromolecule (the distance between the ends of the fully drawn molecule). Within the framework of this model, the Kuhn segments are considered inelastic and non-stretchable. Direct measurements of $x(F)$ for single macromolecules have shown that the function $x(F)$ is described by this model only at very low forces F ($\sim 10\text{ pN}$), where the elasticity of the macromolecule is of purely entropic nature (the chemical bonds and angles are not strained), the elongation of the molecule being due only to the unfolding of folded conformations.

However, at $F > 10\text{ pN}$, this model does not comply with the experimental $F(x)$ dependence. If one assumes that the Kuhn segment is elastic and stretchable, the $x(F)$ dependence should be described by the generalised Langevin equation

$$x(F) = \left[\text{cth} \left(\frac{Fl}{kT} \right) - \frac{kT}{Fl} \right] \left(L + \frac{nF}{K} \right), \quad (2)$$

where n is the number of Kuhn segments ($n = L/l$), K is the elastic modulus of the Kuhn segment. The experimental data obtained

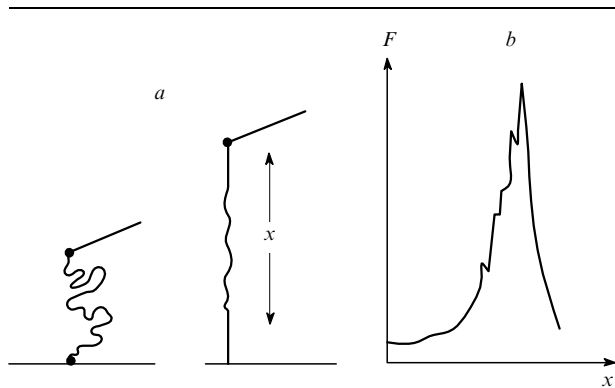


Figure 22. Scheme of the experiment with drawing of a single molecule in the atomic force microscopy (a) and schematic dependence $F(x)$ derived from this experiment (b).

for poly(acrylamide) and poly(*N*-isopropylacrylamide) are adequately described by this function up to $F = 1000$ pN.⁸⁵

Macromolecule	l /nm	L /nm	K /N m ⁻¹
Poly(<i>N</i> -isopropylacrylamide)	0.68	460	26
Poly(acrylamide)	0.625		20

If a Kuhn segment is represented as an elastic structure, the value $K = 26$ N m⁻¹ (or 26 000 dyne cm⁻¹) is indicative of a very high strength.

Note that the generalised Langevin equation (2) properly describes the elasticity of macromolecules under conditions where the intramolecular hydrogen bonds involving side groups have been destroyed (for example, in the presence of urea). However, in deionised water containing intramolecular bonds in a coil, the function $x(F)$ is no longer of the Langevin type, indicating intramolecular association.

The new atomic-force techniques have rushed like an avalanche into molecular biology.⁸⁶ Of the large number of studies,

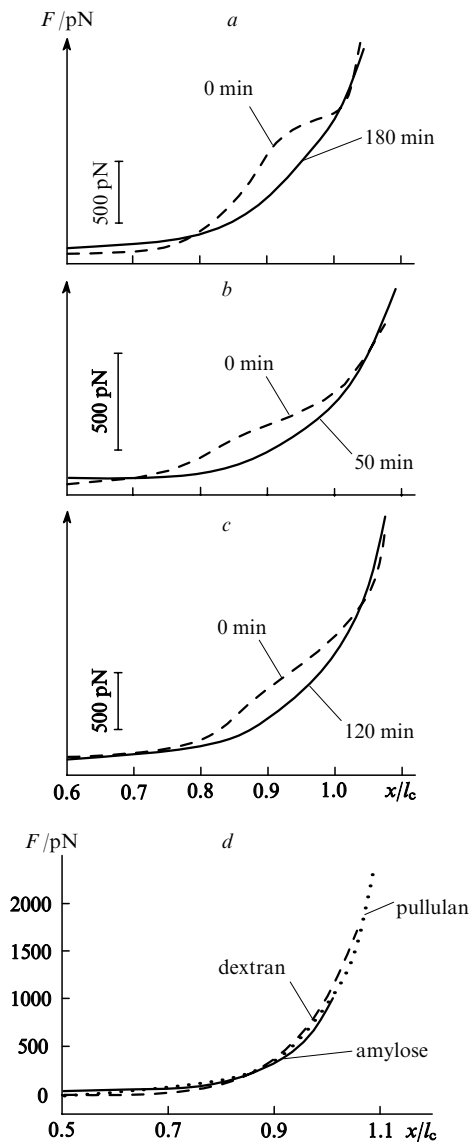


Figure 23. Force (F) vs. extension (x) related to the chemical bond length (l_c) for dextran [(1 $\rightarrow$ 6)- α -D-glycan, *a*], amylose [(1 $\rightarrow$ 4)- α -D-glucan, *b*] and pullulan [(1 $\rightarrow$ 4,1 $\rightarrow$ 6)- α -D-glucan, *c*] before (dashed lines) and after (continuous lines) periodate oxidation (5 mM solution of NaIO₄); (*d*) dependence of $F(x)$ for the same polysaccharides with the pyranose rings destroyed by periodate oxidation.⁸⁷

we consider below only those related to biochemistry and biophysics. Figure 23 shows the $F(x)$ dependences for single polysaccharide molecules, namely, dextran (*a*), amylose (*b*) and pullulan (*c*).⁸⁷ These dependences are described by Langevin equation (2) only at low forces and deformations.

For dextran, Eqn (2) holds for $l = 0.44$ nm (the size of a monomer unit) and $K = 14.6$ N m⁻¹. At greater deformations, the enthalpic component appears in the elasticity of the dextran molecule (a plateau on the dashed curves): the pyranose rings pass from the chair conformation to the boat conformation. The modified polymer chain is described again by the Langevin equation with the parameters $l = 0.2$ nm and $K = 34.2$ N m⁻¹, i.e., the Kuhn segment becomes more elastic. In this new state, the enthalpic component of the elasticity disappears, while the entropic component is retained. The same result can be attained if the pyranose rings are destroyed by periodate oxidation: for dextran, this is attained in 180 min, for amylose, in 50 min and for pullulan, in 120 min (see Fig. 23 *a–c*).

Amylose and pullulan behave in a similar way. Only the entropic elasticity remains in the polymer chains formed upon destruction of pyranose rings (see Fig. 23 *d*).

The dependence $F(x)$ obtained upon drawing of the molecule of the protein titin responsible for the passive muscle elasticity is shown in Fig. 24. It can be seen from the Figure that this dependence is periodic (the curve resembles the saw teeth). The tooth period amounts to ~ 25 nm, while the restoring force in each tooth is 0.15–0.30 nN.⁸⁸ The periodicity is in good agreement with unfolding of the immunoglobulin titin domains. In order to verify this idea, the I8 and I4 fragments containing 8 and 4 immunoglobulin domains, respectively, were tested. The $F(x)$ curves thus obtained contained eight and four teeth, respectively, which is in full agreement with the expected result.⁸⁸ Similar dependences are also typical of another protein tenascin, a component of a territorial matrix.⁸⁹

A serious drawback of the atomic-force spectroscopy of single molecules is ambiguity of the $F(x)$ function measured experimen-

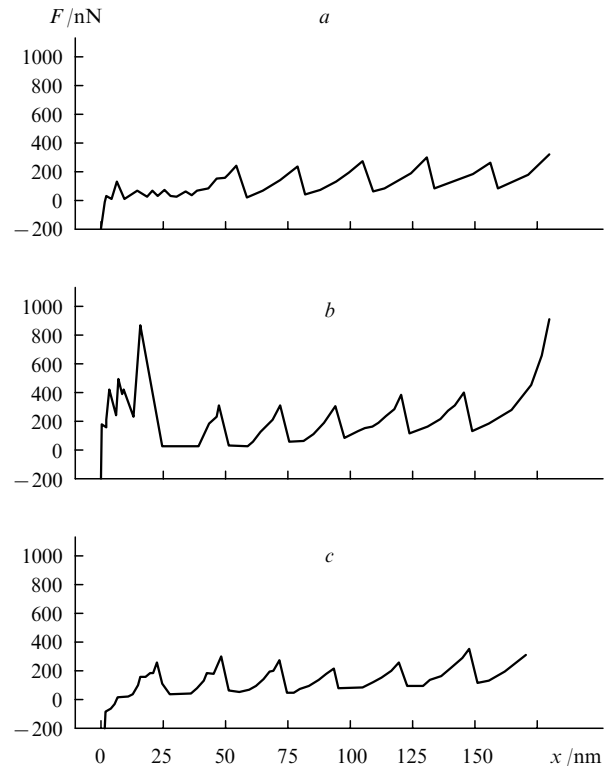


Figure 24. Force vs. extension of single titin molecules with various immunoglobulin domains. Domains I27–I34 (*a*), I28_n (*b*), I27_n (*c*).⁸⁸

tally, which is due to the difficulty or even impracticability of determining what molecular processes and atomic rearrangements are hidden therein. Therefore, the experiment is often accompanied by molecular dynamics calculations. An example of such calculation is shown in Fig. 25. The researchers obtained the dynamic drawing curves as a function of time for one titin domain, namely, for immunoglobulin I27, with a constant force applied to it [four curves are presented, for $F = 500$ (curve 1), 750 (2), 900 (3), and 1000 pN (4)]. In all cases, the initial elongation to 100–120 nm was followed by structure stabilisation (the molecule was not deformed for a certain period of time τ ; the lower the force applied, the longer the time). However, after the period τ had elapsed, further fast deformation of the domain took place due to untangling of the protein chains.⁹⁰

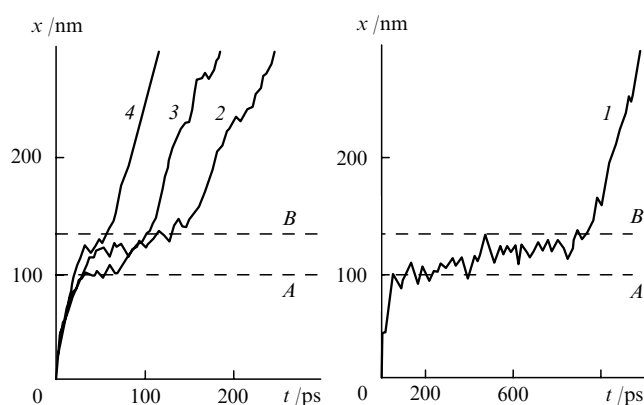


Figure 25. Dynamic (time) extensions of the domain I27 of titin at a constant force: $F = 500$ (1), 750 (2), 900 (3), 1000 pN (4). State A corresponds to the molecule with hydrogen bonds and state B corresponds to the molecule in which these bonds have been cleaved.⁹⁰

The stable state is confined between two states A and B. In the molecule occurring in state A, all hydrogen bonds function and hold the chain structure; in the molecule in state B, six hydrogen bonds have been cleaved. A sort of plastic yielding takes place between states A and B; during this period, the molecule, while resisting deformation, sacrifices six hydrogen bonds. These results are in good agreement with experimental data and provide a clearer understanding of the molecular unfolding process (including a functioning muscle) stimulated by mechanical deformation.⁹⁰

Considerable attention is attracted by the study of non-valence contacts in the host–guest, ligand–receptor, *etc.* systems. For a complex multipoint biotin–avidin contact, even the temperature dependence of $F(x)$ was measured. From analysis of the Poisson force distribution of the ruptures, the average strength of one contact was found to be 0.26 nN; the temperature dependence of the strength was found; in particular, as the temperature increases by 1 K, the strength decreases by 12.6 pN.⁹¹

Using the human serum albumin complex with a polyclonal antibody (1 : 1) as an example, the antigen–antibody interaction force was measured to be 0.244 nN.⁹² The interaction of ferritin with antiferritin is described by a low adhesion force of ~ 0.05 nN.⁹³ The adhesion of proteoglycans, which ensure cell recognition and aggregation, has also been studied.⁹⁴

2. Optical tweezers and biomechanics

Recently, a new mechano-optical technology for measurement of molecule deformation has appeared. The principal working tool is an optical trap (or optical tweezer). The optical tweezer is a set of polystyrene or quartz beads of about 1 μm size. On exposure to a focussed laser beam, the bead is drawn into the focus with a force depending on the light intensity. This trap attached to the end of a

molecule draws and deforms the molecule; actually, the optical trap acts as a cantilever in an atomic force microscope.

This technique is already widely used to study the structure and functioning of molecular motors.⁹⁵ ATPase, kinesin, myosin, immunoglobulin proteins — this is far from being the full list of biomolecules studied by this method.^{96,97} An impressive example is the study of operation of RNA polymerase (this enzyme accomplishes RNA transcription).⁹⁶ The researchers have fixed the RNA polymerase molecule on glass and connected it to one end of the DNA double strand, while the other end of DNA was equipped with an optical trap. It is known that RNA polymerase captures the DNA double strand and drags it through itself, while generating simultaneously the RNA thread. By exposing the optical trap to laser radiation, the researchers counterbalanced the force of DNA drawing-in by the enzyme at one end with the retention force of the DNA by the optical trap at the other end of DNA. After this balance of forces has been established, the enzyme stops operating. The balance is attained at 25 pN; this is the force at which RNA polymerase drags the DNA double helix through itself. It is believed that RNA polymerase is the most powerful known molecular motor: it is 5–6-fold more powerful than kinesin. Presumably, the major energy of this motor is spent for untwisting the DNA strands.

One more molecular (protein) motor, λ -exonuclease, is a component of a bacterial virus. Unlike RNA polymerase, which is energised from ATP, λ -exonuclease operates on the DNA energy: by dragging the two-stranded DNA helix through itself, it ‘swallows’ one of the strands. It is a weaker motor than RNA polymerase and develops only a 5 pN force.⁹⁸

An attempt has been undertaken to use the mechano-optical technology to study topoisomerase, a remarkable enzyme, which undoes the knots on the DNA, when DNA is unpacked in a nucleus during cell division. If one understood how this enzyme operates and its operation could be terminated, it would be possible to stop the division of the malignant cells.

3. Surface nanomechanics

The controlled migration and orientation of molecules on the surface is the major route to the combination of molecules into specified ensembles, to the creation of electrical contacts, electrical circuits and integrated nanocircuits. The procedures for manipulation of single molecules on a surface rely on atomic force microscopy and tunnelling electron spectroscopy.

The force microscopy has substantially advanced in manipulating nanotubes on the surface: the microscope tip is used not only for moving nanotubes and arranging them into diverse figures and ensembles, but also for measurement of the adhesion forces between the nanotubes and the surface.⁹⁹ Various versions of this technique have been described in a review.¹ Even greater opportunities for manipulating nanoobjects are provided by tunnelling spectroscopy. In this case, the force of the tip acting on the molecule being moved is controlled by both mechanics and the electric potential of the tip. Below we present two vivid examples of operation of the nanomechanical technology.

On the (100) face of a silicon single crystal, Si_2 pairs of atoms are aligned in rows; between the rows, a gutter is formed, which accommodates the C_{60} molecules applied on the surface.⁴⁶ In the tunnelling current, the images of the C_{60} molecule look like bright domes about 2.5 nm in diameter and with a height of 0.65 nm. The potential on the tip of the tunnelling microscope, the tunnelling current and the tip elevation above the crystal surface are related in such a way that the potential and the current are maintained constant, while the distance S between the tip and the surface is variable.

The tip, which moves along the gutter, comes across the C_{60} molecule, rises and moves above the molecule (this process is described by curve 1 in Fig. 26a). However, as the tip moves along the slope of C_{60} , this molecule jumps after the tip and lifts it again (this instant is shown by the arrow). These events are repeated several times, *i.e.*, the C_{60} molecule jumps after the tip moving

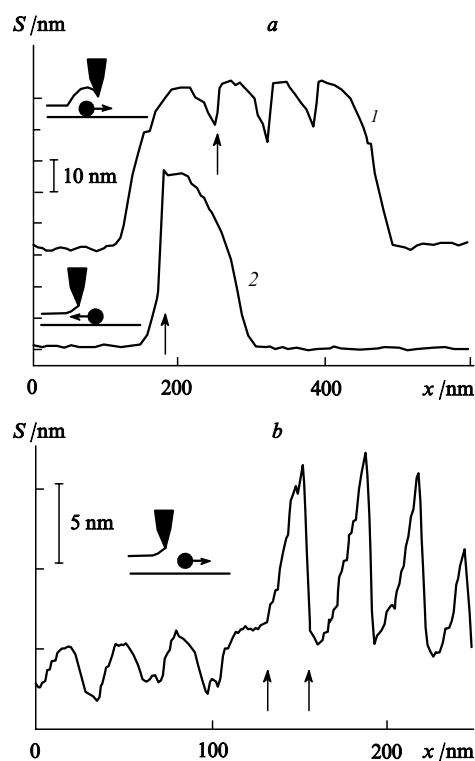


Figure 26. Vertical displacement (S) of the tip vs. horizontal displacement x (a) and horizontal displacement in the pushing mode (b).⁴⁶

away. Each jump covers a discrete distance, namely, two lattice spacings of silicon. The C_{60} molecule can behave in a different way, namely, as the tip approaches the molecule, the molecule may jump towards the tip; the tip would be sharply lifted (this type of behaviour of C_{60} is described by curve 2 in Fig. 26 a). In both cases, the molecule and the tip interact in the attraction regime: the molecule moves either to meet or to follow the tip.

By varying the tip potential, one can also implement the repulsion regime where the moving tip pushes the molecule in front of itself. This regime is clearly illustrated in Fig. 26 b. In this case, the tip meets the molecule at the instant indicated by the first arrow and repels it, and the molecule jumps away by 70–80 nm (this instant is indicated by the second arrow). Then the events are repeated. Actually, the tip ‘rolls’ the C_{60} molecule along the gutter, each migration of the molecule being accompanied by cleavage of its chemical bond with a silicon atom and the formation of a new bond in the new position. This conclusion is based on the fact that the molecule travels every time the same distance, namely, two lattice spacings. Other distances can also be detected but their probability is much lower.⁴⁶

Yet another example is the design of metallic monoatomic wires made of Au and Pd atoms on the NiAl(110) surface.¹⁰⁰ The Al atoms elevated above the (110) surface form parallel rows along the [001] direction; these rows alternate with rows of buried Ni atoms forming gutters along the same [001] direction. The Au and Pd atoms are sputtered onto the surface and then are driven together into the nickel gutters by means of a tip of a tunnelling microscope. The migration of the Au and Pd atoms starts when the distance between the atom and the tip corresponds to resistances of 150 and 50 k Ω , respectively. This means that Pd atoms are more strongly attached to the surface than the Au atoms; they migrate at tighter contacts with the tip (a smaller distance between the tip and the atom corresponds to a lower resistance).

Using this procedure, monoatomic Au and Pd nanowires and mixed wires with alternating Au and Pd atoms have been successfully obtained and their electronic properties (energy levels and

densities of the electronic states, standing waves of the electron density in the atomic chains) have been studied.¹⁰⁰ This study opens up enormous prospects for the understanding of the electronic interactions and properties of the metal alloys through the electronic properties of ‘one-dimensional’ alloys, *i.e.*, metallic nanowires.

VIII. Conclusion

By the early 21st century, chemistry has reached the limit of spatial resolution. Researchers learned to detect, locate in space and recognise a single molecule and to measure almost all of its properties, to study chemical transformations and functioning of single molecules. This gave rise to a new field of chemistry: the chemistry of single molecules.

What does this new field bring to chemistry and related sciences and what findings may be expected of the further development of this discipline?

In the general chemical sense, one should hardly expect any surprises from the study of single molecules or the appearance of new, in principle, information differing from the information obtained in the studies of large ensembles of molecules.[‡] Nevertheless, it is necessary to mention absolutely new information provided by single-molecule electrical conductivity measurements (for the theory of electron movement in a molecule) and by analysis of the energy fluxes in the molecule and on the surface (electronic-vibrational pumping and energy relaxation over vibrational oscillators).

One can hardly expect unusual results from the studies of functioning of single molecules. As shown by a known experiment, molecules are ergodic systems in which time averaging of the functioning of one molecule is equivalent to the ensemble averaging of instantaneous data; deviations from the ergodicity are due most often to artificial reasons (see Section II.5).

However, there is a field of chemistry for which studies of single molecules are of an inestimable value; this is the ‘biological wing’. Luminescence, mechanics and mechanochemistry of single biomolecules (enzymes, proteins, nucleic acids, molecular motors, antigen–antibody type complexes, *etc.*) open almost infinite prospects in the biochemistry and biophysics.

The work with single molecules stimulates the creation of the element base for molecular electronics, nanooptics and nanomechanics. Experience in the design of high-tech devices — nanoelectronic circuits, spin filters and transistors, molecular quantum dots, nanocomputer elements, optoelectronic switches, *etc.*, is being acquired. This aspect of the chemistry and physics of single molecules is infinite. The problem of creation and functioning of logical electronic circuits on a single molecule is already discussed.¹⁰¹

The author is grateful to the Ministry of Industry, Science and Technology for financial support within the framework of the Federal Program for the Support of Leading Scientific Schools of the Russian Federation (Grant NSh 1221.2003.3) and to the Russian Academy of Sciences and the Russian Foundation for Basic Research for the support within the framework of federal programs and initiative projects.

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[‡] Certainly, it is possible to improve the quality of this information, *i.e.*, resolution and accuracy.

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^b — *Russ. Chem. Bull., Int. Ed. (Engl. Transl.)*

Atomic resolution probe microscopy of the graphite surface

O V Sinitsyna, I V Yaminsky

Contents

I. Introduction	23
II. Crystal structure of graphite	23
III. Visualisation of the atomic structure of graphite surface	24
IV. Defects on the graphite surface	27
V. Conclusion	29

Abstract. The results of theoretical and experimental studies of the graphite surface by scanning tunnelling and atomic force microscopy are considered. The attention is focused on the mechanisms of formation of atomic resolution images. The reasons for the lack of coincidence between the graphite surface images obtained by these methods and its real topography are discussed. The bibliography includes 99 references.

I. Introduction

Graphite has an extremely wide range of applications. It is employed as a material for inert electrodes, neutron moderators, X-ray monochromators, strong and thermally stable coatings for spacecrafts. Technical progress has stimulated the development of new technologies of graphite production, as well as massive studies of its chemical and physical properties. In the early 1970's, it was believed that graphite is studied comprehensively. The known data were generalised in a number of reviews (see, for example, Refs 1–3).

In the 1980's, new instruments for surface studies were invented, such as scanning tunnelling microscope (STM)⁴ and atomic force microscope (AFM).⁵ Studies of graphite by these novel probe methods gave amazing results: its STM and AFM images were inconsistent with the real topography. Only one of each two carbon atoms was visible on the image. During the next decades a lot of studies were conducted in order to explain this fact. Despite the great amount of experimental data collected, there is still no consensus on the mechanism of the formation of STM images with atomic resolution.

Graphite crystals are convenient objects for the rapidly developing probe microscopy, as they have layered structure and form air-stable, atomic-smooth extended surfaces upon cleavage. Therefore they can be used as substrates in the studies of clusters, molecules and thin films. Graphite is one of a few materials for

which atomic resolution was reached under normal conditions in air.

At present, probe methods play a leading role in studies of surfaces. The portion of surface atoms in nanostructures is comparable to their volume content, therefore probe microscopy is an indispensable method in nanotechnology. Probe microscopes allow one to obtain images in liquid media, which is especially valuable in the studies of biological objects. However, STM and AFM images can differ from the topography of surfaces of the objects under study. Difficulties in the interpretation of graphite surface images suggest that one may expect serious errors in the studies of more complex systems.

In this review, the graphite atomic structure images observed with the use of STM and AFM in a contact or dynamic mode are analysed in detail. (In the contact mode, the probe is constantly in touch with the surface, while in the dynamic mode it oscillates in resonance and touches the surface periodically, thus minimising the friction force.) The mechanisms of formation of such images are discussed. A separate section is devoted to the visualisation of defects on the graphite surface and studies of their properties by probe methods.

II. Crystal structure of graphite

Among the carbon allotropic modifications, graphite is the most stable under normal conditions. Graphite consists of flat carbon layers that are shifted relative to each other to form hexagonal close packing of carbon atoms (Fig. 1 *a*). The space group is $P6_3/mmc$ and the unit cell parameters are: $a = 2.4612$, $c = 6.7078$ Å.⁶ The unit cell contains four atoms. Two adjacent carbon atoms in the layer are non-equivalent (see Fig. 1 *b*). Three of the six atoms have neighbours in the lower layer (site A), while

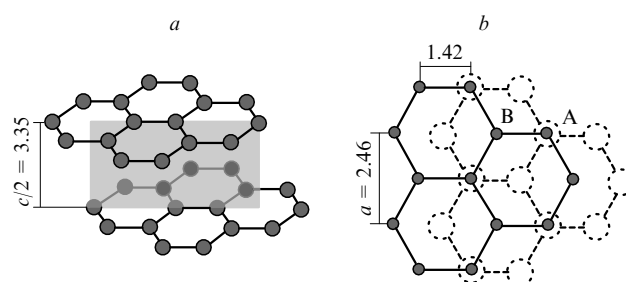


Figure 1. Graphite crystal structure. The unit cell parameters are given in Ångströms; for (*a*) and (*b*) see the text.

O V Sinitsyna Department of Materials Science, M V Lomonosov Moscow State University, Leninskie Gory, 119992 Moscow, Russian Federation. Fax (7-495) 939 09 98, e-mail: sinitsyna@gmail.com

I V Yaminsky Department of Physics, M V Lomonosov Moscow State University, Leninskie Gory, 119992 Moscow, Russian Federation. Fax (7-495) 939 10 09, tel. (7-495) 939 29 82, e-mail: yaminsky@nanoscopy.org

Received 25 August 2005

Uspekhi Khimii 75 (1) 27–35 (2006); translated by I S Neretin

other three are located above the holes, *i.e.* in the centres of hexagons (site B). Weak van der Waals forces act between layers, causing substantial anisotropy of the graphite properties. Thermal and electrical conductivities in the direction parallel to the layers are much higher than in the perpendicular direction (Table 1). Due to the weakness of the interlayer bonds, graphite is easy to cleave.

Table 1. Electric resistance and thermal conductivity of highly oriented pyrolytic graphite (HOPG) and single-crystal graphite.²

Parameter	HOPG	Single crystal
Resistance / Ω m		
along the layers	$3.5 \times 10^{-7} - 4.5 \times 10^{-7}$	4×10^{-7}
perpendicular to the layers	$1.5 \times 10^{-3} - 2.5 \times 10^{-3}$	$1 \times 10^{-4} - 1.0 \times 10^{-2}$
Thermal conductivity / $\text{W m}^{-1} \text{K}^{-1}$		
along the layers	1600–2000	200–500
perpendicular to the layers	7–9	40–80

Graphite crystals of high quality are rarely found in nature. At present, most of the studies are carried out on highly oriented pyrolytic graphite, which is obtained by pyrolysis of gaseous hydrocarbons at temperatures above 2000 °C.^{2,7,8} Graphite obtained by this method is polycrystalline; however the directions of *c* axes for all crystallites virtually coincide (mosaic spread of high quality pyrolytic graphite is 0.4°, the dimensions of crystallites reach several tens of micrometers).

III. Visualisation of the atomic structure of graphite surface

1. Scanning tunnelling microscopy

Atomic resolution STM images of the graphite surface were obtained under different conditions: in high vacuum^{9–11} (Fig. 2, the real image size is not given in the original paper), in air^{12–15} and in water.^{13,16} The resolution is atomic that indeed is supported by the possibility to visualise defects in the atomic structure of the graphite surface by STM (Fig. 3).

Two main peculiarities of the graphite surface STM images are as follows:^{18–21} considerable corrugation of the surface (from 0.8^{22,23} to 24 Å²⁴) and asymmetry of the maxima corresponding to the carbon atoms in sites A and B.

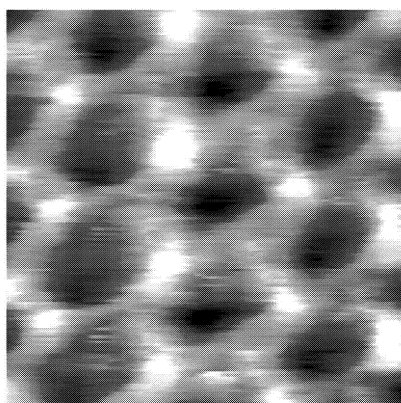


Figure 2. Topographic graphite image obtained by STM in ultrahigh vacuum at 4.2 K.¹¹

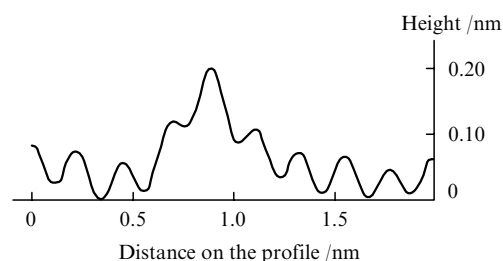
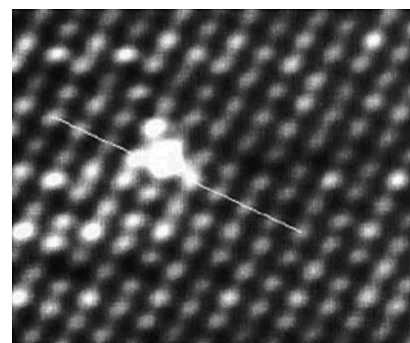


Figure 3. A defect on the graphite surface induced by its bombardment with Ar⁺ at 60 eV.¹⁷

The image was obtained in the constant-current mode, $U = -36$ mV, $I = 0.5$ nA, scanning frequency, 10 Hz.

According to the helium scattering experiments, no surface reconstruction occurs and its corrugation is 0.2 Å. The over-estimated corrugation obtained by the scanning tunnelling microscopy is due to the features of graphite electronic structure,^{13,25} as well as to the effect of the microscope tip on the surface during scanning.^{24,26,27} An increase in the tip voltage leads to decrease in the corrugation.^{9,28}

A very interesting feature of the graphite surface STM images is the non-equivalence of the maxima corresponding to the adjacent carbon atoms.^{14,29} In some experiments, the asymmetry is so great that only three of the six atoms can be seen (a triangular array in Fig. 4a), in other cases all six atoms are observed with equal intensities (carbon hexagons in Fig. 4b).

There are several concepts of this asymmetry.

1. According to the theory of Tomanek *et al.*,^{15,30} asymmetry of the tunnelling current at low voltages is related to the difference in the local density of states, which, in the case of graphite, is determined by the interlayer interaction and the structural non-equivalence of the atomic positions. The calculations have shown³¹ that the maxima in the STM images correspond to the atoms in the sites B. According to this theory, the tunnelling current asymmetry should decrease with the increase in voltage, but should not be sensitive to its polarity. This was proven experimentally.^{15,30} For alkali metal intercalates, where carbon layers are arranged exactly one over the other and therefore all carbon atoms are equivalent, this theory predicts the absence of asymmetry.

In the STM image of alkali metal intercalates (Li, K, Rb, Cs), different lattices were revealed. Their periods are determined by the arrangement of the intercalated atoms (Fig. 5).^{23,31} This feature complicates the analysis of the carbon atom asymmetry.

The graphite lattice was successfully visualised for acceptor intercalation compounds.³² For example, different lattices were observed for MoCl₅-intercalated graphite within one image, namely, a trigonal lattice of maxima in non-intercalated areas and a honeycomb network of hexagons in the areas containing molybden pentachloride molecules in the first interlayer space (Fig. 6).³³

Within the framework of Tomanek's theory, the absence of the asymmetry can be explained by the shift of the top layer with

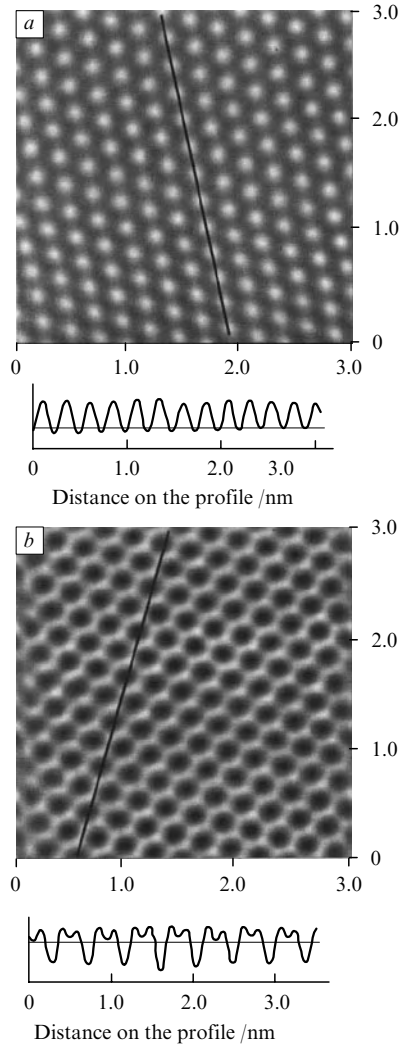


Figure 4. HOPG images with atomic resolution obtained by STM ($U = 20$ mV, $I = 1$ nA).¹⁴ Scanning frequency /Hz: 61 (a) and 122 (b).

respect to the lower layers during scanning. Indeed, the change in the character of image in the majority of cases was caused by passage to more ‘drastic’¹⁴ scanning conditions, viz. an increase in the tunnelling current or a decrease in the voltage between the tip and the sample. Moreover, in one experiment¹⁴ a change in the image type was observed with the change in the scanning speed in the constant height mode (see Fig. 4).

Evolution of the graphite surface image during scanning was described.³⁴ First scans have shown the asymmetry of maxima (A : B = 4 : 7). During the next scans, the image gradually changed until complete disappearance of asymmetry. However, on further measurements, the maxima became asymmetric again with a minimum A : B ratio. Probably, changes in the image during scanning are caused by sliding of the top layer relative to the lower layers. This sliding should occur easier in the area near to a defect, such as dislocation or vacancy. Since scanning covers a very small area, the probability of its position in the vicinity of the defect is rather low. This explains the rare appearance of the honeycomb structure.¹⁴

2. The main point of an alternative theory is that the A and B sites differ in their rigidities.³⁵ In other words, the perpendicular shift of a carbon atom in the site B requires more energy than similar shift of an atom in the site A; thus the site B is more ‘rigid’. Mechanical pressure of the STM tip on the graphite surface can result in the deformation of the layer and local changes in the

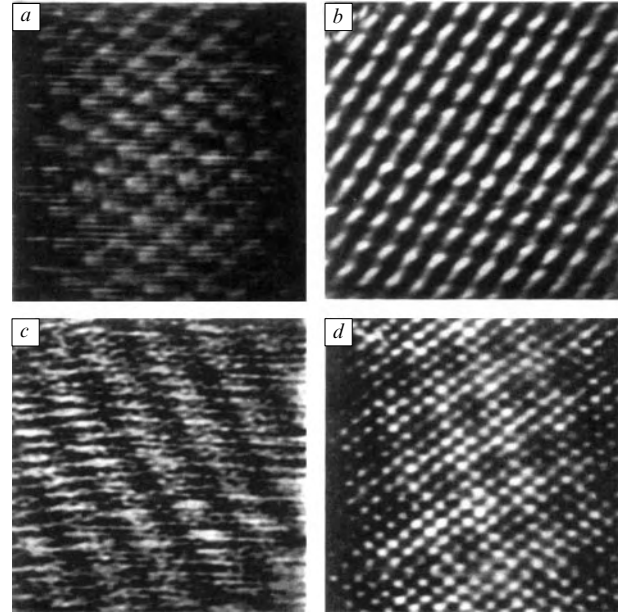


Figure 5. Images of the intercalate C_8K surface obtained by STM.³⁰ (a) constant-height mode (5×5 nm², $I = 3.5$ nA, $U = -20$ mV), a hexagonal 2×2 superlattice is visible; (b) constant-current mode (5×5 nm², $I = 5$ nA, $U = -50$ mV), a hexagonal $\sqrt{3} \times \sqrt{3}$ superlattice is visible; (c) constant-current mode (20×20 nm², $I = 10$ nA, $U = -19$ mV), a superlattice with the period of 3.3 nm is visible; (d) constant-height mode (5×5 nm², $I = 3.5$ nA, $U = -20$ mV), an orthorhombic superlattice with the period of 0.95 nm is visible.

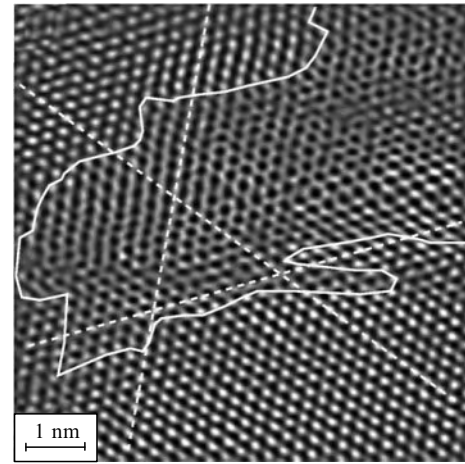


Figure 6. Surface image of the HOPG intercalated with $MoCl_5$ obtained by STM in the constant-height mode.³³

tunnelling threshold. Therefore, in the case of repulsion forces the maxima on the image should correspond to the positions of the greatest rigidity. Because of the relatively large radii of the tip material atoms (W, Pt, Ir), which are comparable to the side of the carbon hexagon, it is necessary to take into account the interaction of probe not only with the carbon atom located directly below it, but also with the neighbouring atoms. In this case, the position of the maximum rigidity can be located in the hexagon centre and the maxima of the detected value in the image correspond to the holes.²²

Whereas the difference in the tunnelling current is determined in general by the ‘rigidity’ of positions, the appearance of all six atoms in the STM image with equal intensities can be explained by the selection of ‘soft’ scanning conditions where the surface

deformation is minimal. For example, a tiny particle of graphite can become attached to the tip, or the tip-to-sample distance is fairly large.²²

3. The asymmetry of carbon atoms is caused by the formation of charge density waves.³⁶ However, according to this theory, the asymmetry value should depend on the polarity of the tunnelling voltage, which contradicts the experimental data.

4. Tunnelling can occur through the local surface states. In this case, the change in the image depending on the variation of the tunnelling current by several tenth of nanoamperes can be explained by the presence of an adsorbate on the graphite surface.³⁷

Based on the theories 1 and 2, the difference in the intensities of maxima corresponding to the carbon atoms in A and B sites is determined by the influence of lower layers. According to theory 2, this influence is manifested in the deformation of the surface by the probe. Taking this into account, it can be predicted that in the case of scanning of a graphene (single graphite layer) the asymmetry should be absent. However, such a conclusion contradicts the available data³⁸ on the observation of only three of the six atoms in an STM image of a single graphene layer on the Pt(111) surface with atomic resolution. The isolated single graphene layer is extremely difficult to obtain,³⁹ therefore the graphene properties remain almost unknown so far. It is still possible that the STM image of the graphite surface is determined solely by the properties of one layer.

2. Atomic force microscopy

Graphite atomic structure images obtained in contact and dynamic modes of AFM differ substantially. In the contact mode, it is possible to detect only the graphite unit cell as a whole (Fig. 7), but at the same time, measurements can be carried out at ambient conditions.^{41–43} In the contact mode, the friction forces dominate, therefore this variant of AFM is an indispensable tool for nanotribology.

A different situation takes place in the case of dynamic AFM. This allows visualisation of separate atoms on the graphite surface. However, the atomic resolutions can be reached only under ultrahigh vacuum at helium temperatures and using perfect vibroisolation.^{44,45} This is due to the fact that the graphite surface is relatively inert in comparison with the ionic surfaces or to the surfaces with ‘dangling’ bonds. The forces applied to the tip near the graphite surface are of about ~ 100 pN.

Let us discuss the main mechanisms of formation of AFM images of the graphite surface obtained in the contact mode, *viz.* in the stick-slip motion of the tip^{43,46,47} and in scanning with a modified tip (when a graphite flake is attached to the tip).^{48–50} In a

number of theoretical works, the influence of probe geometry on the scanning process is considered.^{46,51–53}

Now let us analyse the reasons why the tip moves with sticking while it is in the contact with the graphite surface. According to published data,⁴⁶ we will consider the dependence of the potential energy of a single-atom tip – a single graphite layer system versus the tip position relative to the sample. The virtual scanning takes place in the constant height mode at -6 Å, therefore the normal component of the force acting between the surface and the tip is repulsive. In the scanning with the sufficiently rigid cantilever (the rigidity constant for this model was 1.3 N m^{-1}), the potential energy of the system has one minimum. In the case of a soft cantilever, an additional local minimum appears. Transition from the local to the global minimum is accompanied by a drastic change in the friction force. The tip sticks in hexagon centres and its move from one hexagon centre to another occurs in jumps.^{43,46} Continuous motion is possible in the case of more rigid cantilever or more ‘flat’ potential of the tip-to-surface interaction, but these conditions are not met in the experiment.^{40,46}

Calculations have shown⁵⁴ that a single-atom tip pressed against the graphite surface with a force of *ca.* ~ 1 nN bends it by 1 Å. The deformation extends only to the first three layers. Surface curvature disappears at a characteristic length of ~ 10 Å. The influence of a many-atomic tip should span the larger area of the graphite surface.⁵⁵ In some situations, the tip as a whole is attracted to the surface, but its topmost atom is in the area of repulsive force, thus causing plastic deformation of the graphite surface.⁵²

Measurements carried out in liquid media allow a decrease in the contribution of long-distance macroscopic forces acting between the peripheric atoms of the tip and the graphite surface. Presumably,⁵⁶ under such conditions one can obtain more stable images, although the contrast for the images obtained in the liquid is lower than for those obtained in vacuum (the difference in maximum heights is 0.39 and 0.6 Å, respectively).

Periodic changes in the friction forces during scanning can also be explained by modification of the tip as a result of sticking of a graphite flake to the tip. The friction force of ~ 1 nN, which appears at the shift of a modified probe to the new equilibrium position, is due to the interaction of the sample surface with the cluster (flake) consisting of *ca.* ~ 100 carbon atoms. The radius of the contact area does not exceed 1 nm.⁵⁰ When moved along the direction $\langle 12\bar{3}0 \rangle$, the graphite flake moves rectilinearly together with the probe, while in the scanning in other directions, the tip with the particle moves in a zigzag manner⁵⁰ or the flake is reoriented according to the direction of the tip rectilinear motion.⁴⁹ In these cases, from the AFM images it is possible to determine whether the tip has been modified.⁵⁰ For example, an AFM image of the graphite surface in the widely cited work by Mate *et al.*⁴¹ should be classified as the one obtained with modified cantilever.

In the dynamic mode, features of the AFM image are determined by the character of forces acting between the probe and the sample.⁵¹ An AFM image of the graphite surface obtained in the dynamic mode while detecting the repulsion forces is presented in Fig. 8. Two forces applied to the probe from the two adjacent carbon atoms are measured to be 248 and 250 pN. Obviously, the structural non-equivalence of the carbon atoms in graphite is manifested in the atomic force microscopy as well.

A substantial asymmetry between the atoms can be seen in the graphite surface image obtained by detection of the attractive forces.⁵⁸ According to the theory by Chen,⁵⁹ the attractive force acting on the tip should unequivocally determine the tunnelling current. In this case, the attraction force is a minimum for the tip position above the hexagon centre, and hence such a position corresponds to the maximum in the AFM image.⁶⁰ Atoms in the site A give weak local maxima, while atoms in the site B correspond to minima. Thus, the contrast in AFM images of graphite surface is inverted with respect to the STM images.

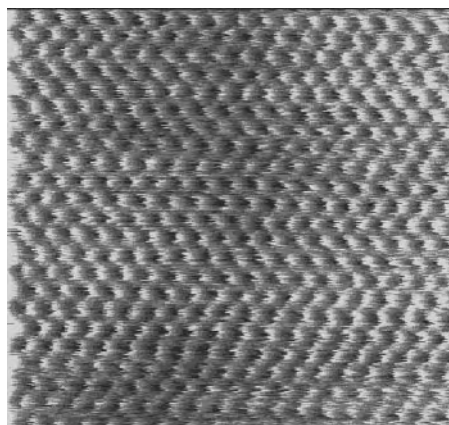


Figure 7. Image of the HOPG surface obtained by AFM in the contact mode with the friction force detection.⁴⁰ The normal force component is 40 nN, scanning frequency is 30 Hz.

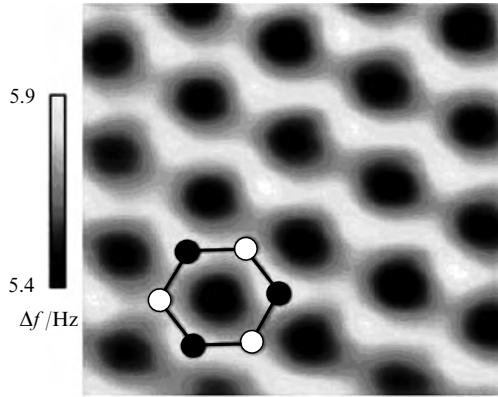


Figure 8. Graphite surface image obtained by AFM in the dynamic mode.⁵⁷ Probe oscillation amplitude is 300 pm, scanning speed is 0.2 nm s⁻¹; white and black circles denote carbon atoms in A and B sites, respectively.

For the verification of Chen's theory, scanning was performed in the constant-height mode. The tunnelling current, the force acting on the tip and the dissipated energy were detected simultaneously (Fig. 9).¹⁰ It was expected that the maxima of the tunnelling current should correspond to the carbon atoms in the B sites, while the dissipated energy should be maximum upon the holes. It was established that in the case of repulsive forces (see Fig. 9c,†f) the asymmetry is a minimum, the maximum of the force corresponds to the atoms in sites A and the minimum corresponds to the holes. In the case of scanning in the attractive forces zone (see Fig. 9a,d), the force depended on the voltage applied to the tip. At negative bias voltage of -60 mV, images based on the measurement of tunnelling current and the attractive force were inverted, in qualitative accordance with the Chen theory. However, no inversion occurred in the case of scanning at positive potential of +160 mV (see Fig. 9a).

IV. Defects on the graphite surface

Probe methods allow studying of not only the composition of defects and their electronic structures, but also their reactivities. By means of scanning tunnelling microscopy, it is possible to determine the electron energy spectra or to establish the nature of an admixture atom.⁵⁹

First let us consider point defects, *i.e.*, vacancies and admixture atoms. The concentration of point defects on the HOPG surface of different quality under normal conditions is 0.1–20 μm⁻² (Refs 61 and 62). Defects appear in the STM images as bright spots (see Fig. 3).^{19,20} When the tip approaches the surface, the defects become invisible, as the volume states of graphite make the main contribution to the tunnelling process under these conditions. Judging by the dependence of the defect height from the tip-to-sample distance, one can determine the type of the incorporated atom.^{19,20}

In the majority of works, the point defects for their subsequent study are created artificially, usually by means of graphite surface bombardment with different ions.^{17,63–66} Such a process can lead to the vacancy formation on the surface layer, as well as to the implantation of ions. Local density of states at the vicinity of the vacancy increases, making them visible in STM images, but not in AFM images.¹⁷ Structure relaxation around the point defect can lead to the formation of new bonds, including those between atoms from adjacent layers.⁶⁷ But changes in the surface topography are too subtle to be detected by AFM working in the

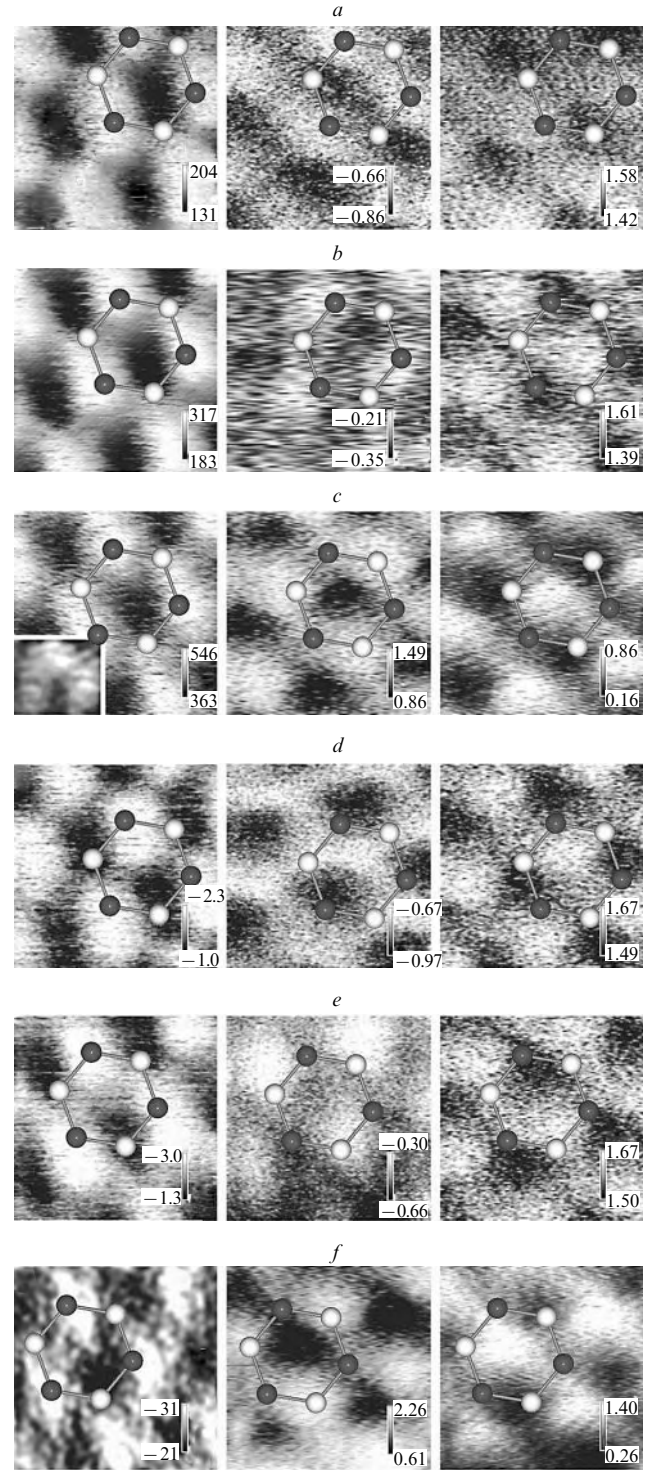


Figure 9. HOPG surface images obtained in the constant-height mode.¹⁰ The tunnelling current (pA) was measured for the images to the left; a normalised shift of the resonance frequency (fN m^{1/2}) in the middle, and the dissipated energy (eV) to the right.

U /mV: 160 (a–c), -60 (d–f); z /pm: -100 (a, d), -350 (b, e), -750 (c, f).

contact mode. The increase in the charge density occurring around the vacancy¹⁷ explains the increased reactivity of the defect area.^{68–70}

Ion implantation leads to the formation of dome-shaped structures⁶⁵ and craters on the surface.⁶³ After heating of the ion-implanted samples at 500 °C, the height of the defect area

† The insert in Fig. 9c on the left shows a higher harmonic image.

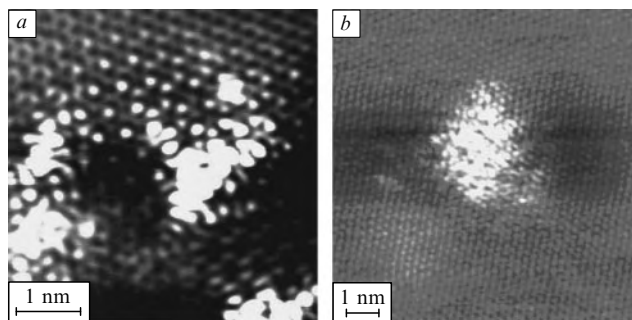


Figure 10. Atomic resolution images of the HOPG surface with implanted tungsten ions obtained by STM.⁶³ Switch of the polarity of the tunnelling voltage did not reveal any new features in the image.

increases, which can be explained by the migration of the implanted ions closer to the surface.⁶³

In STM images of graphite around point defects, as well as at step edges, the formation of $\sqrt{3} \times \sqrt{3} R 30^\circ$ structure was observed (Fig. 10). This is not due to surface reconstruction,^{71,72} but can be explained by the Friedel oscillations.⁷³ Analysis of their symmetry allows one to establish the nature of point defects and the adsorbate state.^{19,20} For example, with account of the enhancement of the Friedel oscillation amplitude, the formation of covalent C–F bond on the graphite surface was concluded.⁷⁴

Possible line defects in cleaved HOPG include steps,⁷⁵ domain borders⁷⁶ and dislocations. The steps could be of two forms, *viz.* zigzag-like and chair-like. For zigzag-like steps, the formation of edge states was predicted.⁷⁵ According to the data from scanning tunnelling microscopy studies, the energy of such states exceeds the Fermi energy by 0.02–0.15 eV.⁷⁷ STM images of zigzag-like steps show bright dots at the points of broken bonds.^{78,79}

The activation energy of graphite oxidation at single-layer steps is somewhat higher than that at multilayer ones.⁸⁰ This fact can be explained by the bend of single-layer steps upon cleavage or under the pressure of the tip.⁸¹ The stability of such structures has been analysed.⁸²

The domain borders in STM images of HOPG are visible as wide helical structures.^{76,83} The domain border for two crystallites with disorientation angle of 39° is shown in Fig. 11 *a*. A model proposed for this structure includes five- and seven-membered carbon rings. (Fig. 11 *b*).

The 2D defects observed in STM images of a HOPG surface include different superlattices. Hexagonal superlattices arising from the disorientation of the topmost graphite layers are described in the review⁸⁴ in great detail (Fig. 12), so we will just briefly concern this problem. Such superlattices are observed around dislocations^{85,86} or can occur in the rotation of the

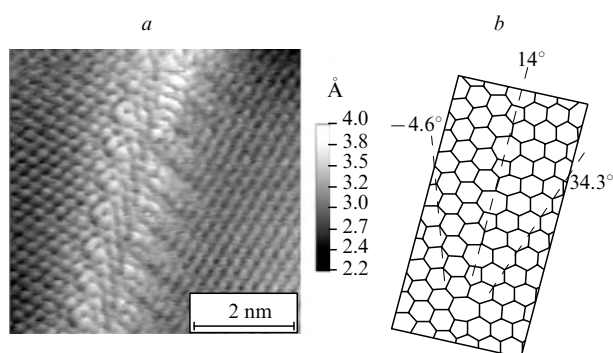


Figure 11. Image of the domain border obtained by STM (*a*), and its model (*b*).⁸³

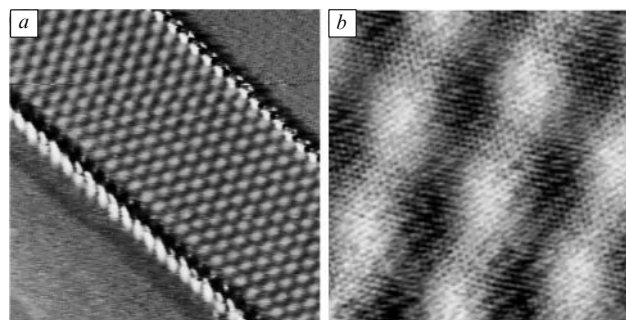


Figure 12. Images of superlattices on the HOPG surface (*a*) and superstructure area (*b*) obtained by STM.⁸⁵

(*a*): $787 \times 787 \text{ \AA}^2$, $U = 480 \text{ mV}$, $I = 0.6 \text{ nA}$, the superstructure area is embraced by clear borders. The distance between the borders is $440 \text{ \AA}$, the dimension of the area $> 1 \text{ nm}$;
(*b*): $104 \times 104 \text{ \AA}^2$, $U = 210 \text{ mV}$, $I = 0.6 \text{ nA}$, superlattice period is $40 \pm 1 \text{ \AA}$ and the angle of its rotation with respect to the graphite lattice is $28 \pm 1^\circ$.

topmost graphite layer.^{85,87} Superlattices with periods from 1.7 up to 44 nm and height from 0.5 to 20 Å have been visualised. The reason for appearance of such defects is analogous to the Moire patterns in optics, which appear upon rotation of one periodic structure relative to another.^{88,89} Due to the disturbance of layer packing, the asymmetry of maxima corresponding to the atoms in the A and B sites can differ within one superlattice unit cell.⁹⁰ Defects in the graphite lattice can lead to the vacancy formation in the superlattice.⁹¹

Lattices with different periods can be created on the surface of HOPG.⁸⁴ Such lattices can be applied in nanotechnology for the production of templates. For example, cobalt particles (1–5 nm) are adsorbed mainly on the nodes of the superlattice with the period of 3.8 nm.⁹²

The appearance of periodic structures in STM images is not necessarily caused by the layer displacement. A superlattice with changing period was observed on the nanometer-size graphite sheet consisting of two layers.⁹³ The placement of a small graphite particle on the surface of the sheet resulted in the change in the lattice (Fig. 13). The appearance of this superstructure can be explained by the dimensional quantisation in a two-dimensional system. The change in the lattice parameter is due to the presence of a potential gradient in the system, which in turn is caused by the inclination of the sheet with respect to the bulk graphite. Dimensional quantisation was revealed in studies of etching pits with

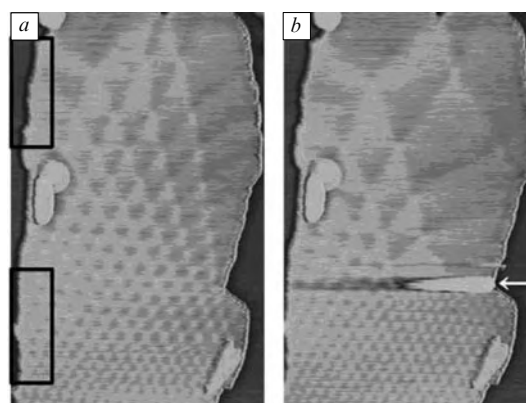


Figure 13. Images of superstructures on the nanometre-size graphite sheet obtained by STM before (*a*) and after (*b*) a graphite particle was placed on the sheet.⁹³

(*a*): $U = 0.2 \text{ B}$, $I = 0.7 \text{ nA}$ ($400 \times 250 \text{ nm}^2$); layer height measured by STM image is $\sim 0.8 \text{ nm}$ in the top corner and $\sim 0.9 \text{ nm}$ for the bottom.

small diameter (< 10 nm) by scanning tunnelling microscopy.⁹⁴ The spectra of the pits located at a distance of 1–2 nm from each other have shown the splitting of the respective energy levels.

Finally, let us discuss superlattices arising due to the dislocation networks near the graphite surface. Most often, the dislocation networks observed in the STM images consist of triangular areas with sides of 100–300 nm.^{95–98} Examination of triangle borders in the images with atomic resolution revealed a distortion of the hexagonal graphite lattice.⁹⁶ The surface corrugation increases on the borders.

On variation of the STM scanning parameters, images of the dislocation networks undergo certain changes. An increase in the tunnelling voltage leads to weakening of the contrast between the adjacent triangles.^{96,98} As the interlayer distances in hexagonal and rhombohedral graphite are similar and the Burgers vector of the network-forming dislocation lies in the [0001] plane, the contrast revealed in the STM images between the domains is not due to the surface topography. The presence of the step within the dislocation network area does not lead to its disruption or distortion. However the contrast between the perfect areas and the stacking fault areas changes (and can even be inverted) upon motion over the step.⁹⁸ For the explanation of this effect, a model has been proposed considering propagation of the electron wave along the graphite *c* axis together with the presence of defect areas below the surface. According to the proposed model, the STM scanning should reveal not only dislocations with the Burgers vector perpendicular to the base plane (screw dislocations^{85,86} and dislocation loops⁹⁹), but also other types of dislocations.

Intensive mechanical pressure by the tip on the surface causes motion of the dislocations. Data are available indicating that the superlattices generated by the rotation of the topmost layer by less than 0.5° with respect to the substrate can transform to dislocation networks under the influence of the tip.⁹⁵ A triangular net presented in the STM image (Fig. 14*a*) has transformed to the star-like structure (Fig. 14*b*) after the change in the tunnelling voltage by 0.14 V.

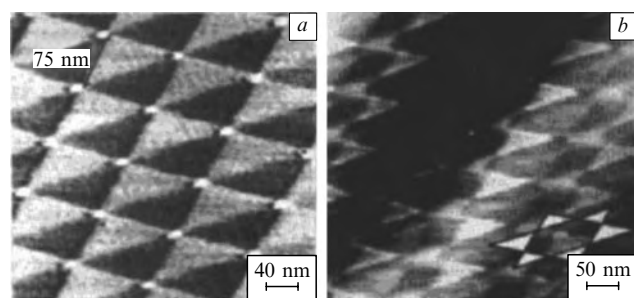


Figure 14. Dislocation network on the graphite surface (*a*) and a star-like structure (*b*).⁹⁶

(*a*): $U = 0.24$ V, $I = 0.37$ nA, scanning frequency is 26 Hz;

(*b*): $U = 0.1$ V, $I = 2.4$ nA, scanning frequency is 26 Hz.

V. Conclusion

Though the first STM image of atoms of the graphite surface was observed some 20 years ago, a consistent theory explaining why in some experiments only three atoms of the hexagonal cell are observed, and sometimes all six of them, has yet to be built. The existing theories on the nature of this effect still do not have the necessary experimental support.

Despite the obvious progress in the development of atomic force microscopy in the last 10 years, there are still only few AFM images of the defect areas of graphite. This is due to substantial difficulties of registration of extremely weak forces acting on the tip.

Methods of probe microscopy allow visualisation of the defects. However, the mechanisms of images formation sometimes remain obscure, for example, in the case of dislocations in the graphite. By the probe methods, the reactivities of different defect areas on the graphite surface were determined. With the use of STM and AFM microscopy, one can find preferable sorption sites for nanoparticles, as well as the state of adsorbates on the graphite surface.

This review was written with the financial support from the Russian Foundation for Basic Research (Project No. 04-03-32472-a).

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Modelling of the dynamic state of disperse systems

N B Uriev, I V Kuchin

Contents

I. Introduction	31
II. Fundamentals of the flow theory of disperse systems	32
III. Computer simulation of disperse systems	44
IV. Conclusion	53

Abstract. The review covers main theories and models of shear flow of suspensions and results of computer simulation of the properties of disperse systems under dynamic conditions. Emphasis is given to the state of aggregated and non-aggregated suspensions. The microstructure of disperse systems is demonstrated to play a crucial role in their bulk rheological properties. The causes and conditions of the appearance of macroscopic inhomogeneity, *i.e.*, discontinuity in highly concentrated systems are analysed and the specific features of microrheology of low-concentrated fractal colloidal gels are reviewed. The review describes the possibilities of the use of surfactants and vibration treatment for controlling the rheological properties of dispersions. The advantages and disadvantages of computer simulation of disperse systems are discussed and examples of application of these methods to the description of the dynamic state of suspensions are given. The bibliography includes 147 references.

I. Introduction

Many natural phenomena and various chemical engineering processes involve disperse systems under non-equilibrium conditions. Hence, both theoretical and applied studies of these systems are of considerable interest. In the present review, different aspects of the behaviour of dispersions under dynamic conditions are considered in terms of physicochemical dynamics of disperse systems.^{1–3} This new field supplements and extends the traditional approach to investigation of the properties of such systems predominantly under static conditions.

The physicochemical dynamics of disperse systems deals with dynamic processes taking place in ensembles of dispersed-phase particles held together by dispersion forces to form three-dimensional structural networks. Besides, it is concerned with the mechanisms of destruction of such systems under dynamic force conditions giving rise to particle aggregates (their evolution and interactions with each other and with a dispersion medium) and the reverse processes (structure formation under these conditions).¹ These problems are directly related to physicochemical hydrodynamics, including hydrodynamics of capillary systems.⁴

The ultimate aim of research in the area of physicochemical dynamics of disperse systems is to substantiate ways and procedures for achieving the maximum fluidity, which is necessary for intensification of various chemical engineering processes.¹ The control of the properties of suspensions, *viz.*, disperse systems, which are widely used in all fields of human activity, is of particular importance.

Theoretical analysis in physicochemical dynamics is based primarily on the construction of microrheological models that describe processes of interactions between particles, microstructure formation, microstructure transformations and degradation under external forces. These microprocesses determine the structural-rheological properties of suspensions characterising their response to mechanical forces.

Theoretical views of the features of microprocesses provide the basis for developing new procedures for controlling the properties of disperse systems under dynamic conditions and improving the available methods. Some rheological theories of suspensions and powders were analysed in the monograph.⁵

The continuing progress in computer technology offers opportunities to solve problems (in particular, to describe a microstructure of a medium), which are impossible to solve by analytical methods. Computer simulation occupies an intermediate place between theoretical and experimental studies. Computer experiments are based on theoretical models and are performed by numerical calculations. The models can become more complicated (to achieve better correspondence with experimental conditions) with progress in computer technology. Therefore, on the one hand, areas of theoretical research are expanded, and, on the other hand, it becomes possible to perform numerous repeated expensive experiments. Consequently, computer simulation is an important bridge between the theory and experiment.⁶

The efficiency of application of computer simulation to the dynamics of disperse systems is determined by several factors. First, theoretical models are often based on phenomenological equations, which describe phenomena at the macrolevel and ignore many microscopic features of the system. As a rule, this problem can be solved by numerical methods (in particular, a detailed view of the dynamics of structuring and microstructure transformations can be obtained). Second, computer simulation can be used as a rather efficient procedure for validating analytical theories of structures and properties of disperse systems. Third, computer simulation allows one to examine the behaviour of systems under conditions that are difficult to observe in practice (high flow rates, vibration treatment, *etc.*). In addition, this method provides information on parameters that are impossible to measure (the number of coagulation contacts between particles and the rate at which they are broken, shear stresses separately in

N B Uriev, I V Kuchin A N Frumkin Institute of Physical Chemistry and Electrochemistry, Russian Academy of Sciences, Leninsky prosp. 31, 119991 Moscow, Russian Federation. Fax (7-495) 955 46 79, tel. (7-495) 955 46 42, e-mail: uriev@phyche.ac.ru (N B Uriev), u912@yandex.ru (I V Kuchin)

Received 29 June 2005

Uspekhi Khimii 75 (1) 36–63 (2006); translated by T N Safonova

the liquid and solid phases, *etc.*). In some cases, the difficulties can be associated with hazardous experimental conditions and high cost of experiments. Because of this, computer simulation is a convenient and efficient tool for investigating the structures and properties of disperse systems. However, data obtained by this method should be compared with theoretical and experimental estimates because the results of numerical calculations may contain uncertainty due to specific features of the system under study and limitations of a particular simulation method.

The present review covers analytical and computer models used for describing the behaviour of an important class of disperse systems, *viz.*, suspensions, under dynamic conditions and predicting their structural-rheological properties.

II. Fundamentals of the flow theory of disperse systems

1. Non-structured disperse systems

The dependence of the effective suspension viscosity on the concentration of the solid phase is most simply described by the Einstein equation

$$\eta = \eta_0 \left(1 + \frac{5}{2} \varphi \right), \quad (1)$$

where η_0 is the viscosity of a pure liquid (dispersion medium) and φ is the concentration of the solid phase.

This equation is valid for highly dilute non-structured suspensions where interactions between particles can be ignored. The equation reflects an increase in the suspension viscosity due to hydrodynamic effects caused by solid particles introduced into the flow and takes into account the energy dissipation for rotation of particles in a shear flow.

If the concentration of solid particles increases so that interactions between the particles become significant, Eqn (1) provides poor agreement with experimental data. Hydrodynamic interactions can be taken into account, to some extent, by introducing higher-order terms with respect to φ (φ^2 , φ^3 , *etc.*). If only pair interactions are considered,⁷ the dependence of the suspension viscosity on the concentration of the solid phase can be described by the equation:

$$\eta = \eta_0 \left(1 + \frac{5}{2} \varphi + a\varphi^2 \right). \quad (2)$$

The coefficient a is a function of the concentration φ and the particle sizes and coordinates. This coefficient is calculated by complex statistical methods. The following dependence $a(\varphi)$ was obtained⁹ with the use of the Percus–Yevick equation:⁸

φ	0.0	0.1	0.2	0.3	0.4	0.5	0.6
a	5.00	5.38	5.81	6.31	6.91	7.65	8.66

The results of calculations according to Eqn (2) taking into consideration the dependence $a(\varphi)$ are in satisfactory agreement with experimental data at $\varphi \leq 0.25$. At higher concentrations, calculations by Eqn (2) underestimate the viscosity η , which indicates that it is necessary to take into account perturbations of the velocity fields about the particle caused by the influence of adjacent particles. Evidently, these calculations present considerable mathematical difficulties. However, there is a number of models and approximate methods that enable one to find the dependence $\eta(\varphi)$ up to the highest concentrations.

Of semiphenomenological equations describing the dependence of the suspension viscosity of spherical particles on their concentration throughout the range of φ , the Mooney equation¹⁰

$$\frac{\eta}{\eta_0} = \exp \left(\frac{\alpha \varphi}{1 - \varphi/\varphi_m} \right) \quad (3)$$

and the Krieger–Dougherty equation^{11,12}

$$\frac{\eta}{\eta_0} = \left(1 - \frac{\varphi}{\varphi_m} \right)^{-\alpha \varphi_m} \quad (4)$$

have gained wide acceptance. Here φ_m can be identified with the volume fraction of closely-packed particles (random packings of particles with φ_m varying from 0.59 to 0.65 are most typical of suspensions). The coefficient α is chosen such as to provide the agreement of Eqns (3) and (4) with the Einstein equation ($\alpha = 2.5$).

The results of calculations according to Eqn (4) are in somewhat better agreement with experimental data as compared to the Mooney equation. As mentioned above, the common drawback of these equations is their semiphenomenological character. The derivation of these equations was not based on theoretically supported microrheological views of the character of flow of concentrated disperse systems. In this respect, a more correct approach is based on the use of various cellular models that have been proposed for the first time in the publications.^{13–15} Within these models, it is generally assumed that the cell consists of a rigid spherical shell whose centre is occupied by the spherical particle under consideration. The velocity of the liquid within a circular layer between the particle and the sphere is estimated by the Stokes equation¹⁶ taking into account certain boundary conditions. With a knowledge of the velocities and mechanical stresses at the cell boundary, it is possible to calculate the energy dissipated in the cell containing a particle (E_1) and without this particle (E_0). The suspension viscosity is determined from the equation¹⁴

$$\frac{\eta}{\eta_0} = \frac{E_1}{E_0}. \quad (5)$$

One of the most perfect cellular models, which is sometimes called the free surface model, was proposed by Happel.^{14,15} Within this model, the viscosity is calculated according to the equation

$$\frac{\eta}{\eta_0} = 1 + 5.5\varphi \frac{4\varphi^{7/3} + 10 - (84/11)\varphi^{2/3}}{10(1 - \varphi^{10/3}) - 25\varphi(1 - \varphi^{4/3})}. \quad (6)$$

A substantial drawback of cellular models is that the cell shape is chosen arbitrarily. A spherical cell is simple for analysis. However, the results obtained with the use of this model at high concentrations of the solid phase are in poor agreement with experimental data. This is associated with the fact that with $\varphi \rightarrow \varphi_m$ the distance between the particles decreases to an extent that it becomes necessary to consider the liquid flow in microchannels between the particle surfaces.

This model has been considered for the first time by Frankel and Acrivos.¹⁷ This model is sometimes called the lubrication model because it is based on the lubrication theory. The model treats a test particle surrounded by z adjacent particles equidistant from the test particle. The cell consists of a sphere with a radius $r + h/2$ (r is the radius of the test particle and h is the distance between the particle surfaces). The test particle lies in the centre of the cell coinciding with the origin of coordinates. At $z = 6$ (which corresponds to a random close packing¹⁸), the centres of the adjacent particles lie on the Cartesian axes (x, y, z) (Fig. 1). It is hypothesised that an elongational flow occurs in suspensions. The hydrodynamic resistance to motion of each adjacent particle relative to the central particle is calculated according to the equations of the lubrication theory.⁷ It is assumed that the energy dissipation velocity is determined by both the perturbation of the velocity field with a single sphere and the sum of flows in microchannels between particle pairs. This model gives quantitative results for $\varphi \rightarrow \varphi_m$ when $h/2r \rightarrow 0$. The following equation for the suspension viscosity was derived from Eqn (5):¹⁷

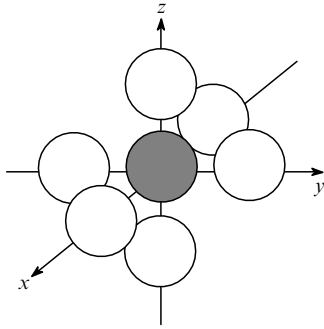


Figure 1. Arrangement of particles in the lubrication model. The shaded particle is surrounded by 6 particles.

$$\frac{\eta}{\eta_0} = \frac{3z}{16} \frac{1}{(\varphi_m/\varphi)^{1/3} - 1}. \quad (7)$$

Frankel–Acrivos’s model was criticised many times. In particular, it was noted¹⁹ that it is incorrect to extend the results, which were obtained for an elongational flow under the assumption of a special arrangement of particles, to a shear flow. It was demonstrated²⁰ that the application of the lubrication theory to the particle motion performed by parallel layers in a shear flow gives only the logarithmic dependence of the suspension viscosity on $2r/h$ when $h \rightarrow 0$, whereas experiments showed that η more sharply increases with $\varphi \rightarrow \varphi_m$. The inclusion of other factors influencing the viscosity (for example, rotation of adjacent particles) does not change the logarithmic character of the dependence $\eta(\varphi)$. This led to the conclusion⁵ that particles of a suspension in a shear flow move chaotically rather than are arranged in layers. In this case, the lubrication model becomes more correct, because particles inevitably approach each other during chaotic motion, the liquid serving as a lubricant between the particle surfaces. Assuming that particles move chaotically, the equation analogous to Eqn (7) was derived²¹ with the use of the dense gas kinetic theory.

Another way of describing the configuration of particles surrounding the test particle is based on an effective medium model.²² Within this model, the configuration of particles is considered as a particular effective homogeneous medium containing the test particle. The viscosity of the medium η^* is equal to the viscosity of a pure liquid η_0 on the surface of the test particle, increases with increasing distance from this surface and is identified with the viscosity of the suspension as a whole at infinity

$$\eta^* = \eta_0 + (\eta - \eta_0)\psi(x, \varphi), \quad (8)$$

where $\psi(x, \varphi)$ is a function of the particle coordinates and concentration.

The field of velocity perturbations (u) induced by the test particle in the medium is determined by the Stokes equations,¹⁶ which are written for this model taking into account the dependence $\eta^*(x)$

$$\nabla p = \nabla(\eta^* \nabla u), \quad \nabla u = 0$$

The simplest assumption about the change in η^* can be made by identifying the effective medium with a suspension as a whole, *i.e.*, taking $\psi = 1$. This assumption,²³ which corresponds to the mean-field model widely accepted in physics, gives the following equation for the average stress tensor:

$$\langle \hat{\sigma} \rangle = 2\hat{E}\eta_0 + 5\varphi\eta\hat{E}, \quad (9)$$

where $\hat{E}$ is the strain rate tensor.

From Eqn (9), the following equation for the relative suspension viscosity was derived:^{23–25}

$$\frac{\eta}{\eta_0} = \frac{1}{1 - (5/2)\varphi}. \quad (10)$$

At small φ , this equation turns into Eqn (2). At high concentrations, the viscosities calculated according to Eqn (10) are overestimated. Evidently, this is associated with an arbitrary choice of the function $\psi(x, \varphi)$. To obtain more accurate results, a more realistic function ψ should be used in the effective medium model. However, in this case, it is impossible to derive analytical equations for the suspension viscosity due to mathematical difficulties.

The results of calculations according to Eqns (4), (6), (7) and (10) and experimental dependences of the viscosity of poly(methyl methacrylate) (PMMA) in decalin are presented in Fig. 2. A comparison of the curves shows that the results obtained with the use of the effective medium model and the free surface model agree with experimental data at low concentrations ($\varphi < 0.4$), whereas the results obtained with the use of the lubrication model are in agreement with experimental data at high concentrations ($\varphi > 0.4$). In the calculations, φ_m was taken to be 0.61, which corresponds to conditions of many experiments. Detailed analysis of the possibilities of using the above-considered models for the description of the viscosity of non-aggregated and aggregated suspensions was performed in the study.²⁶

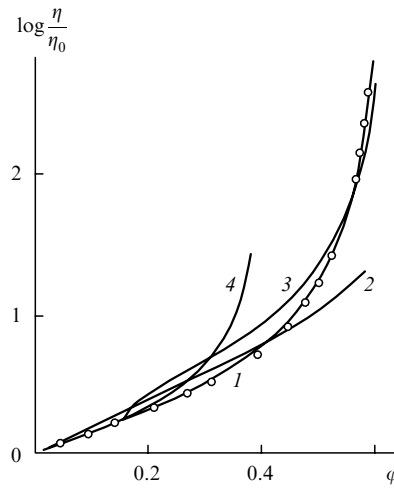


Figure 2. The relative suspension viscosity vs. the volume fraction of particles.²⁶

Curves (1–4) were calculated according to Eqns (4), (6), (7 at $z = 6$) and (10), respectively; the points correspond to the experimental data²⁷ for PMMA particles ($d = 0.5 \mu\text{m}$) in decalin (the viscosity for $\dot{\epsilon} \rightarrow \infty$).

The influence of Brownian motion of particles on the viscosity of suspensions formed by these particles can be taken into consideration with the use of the Peclet number

$$\text{Pe} = \frac{d^2 \dot{\epsilon}}{D},$$

where d is the particle size, $\dot{\epsilon}$ is the shear rate and D is the particle diffusion coefficient.

The suspension viscosity can be represented as a function of the only parameter, *viz.*, the Peclet number²⁸

$$\frac{\eta - \eta_\infty}{\eta_1 - \eta_\infty} = \frac{1}{1 + \text{Pe}/\text{Pe}_c}, \quad (11)$$

where η_1 and η_∞ are the suspension viscosities at $\text{Pe} \ll \text{Pe}_c$ and $\text{Pe} \gg \text{Pe}_c$, respectively, and $\text{Pe}_c \approx 1$ is the critical value of the Peclet number.

Brownian suspensions of spherical particles were studied experimentally in broad ranges of particle concentrations and sizes.^{29–31} The results of these studies agree well with the results of calculations according to Eqn (11), Pe_c being dependent on φ . It

was found that $Pe_c = 1.5$ at $\varphi = 0.2$ and $Pe_c \rightarrow 0$ at $\varphi \rightarrow \varphi_m = 0.6$, *i.e.*, the influence of the Brownian motion on the suspension viscosity decreases as the packing of particles approaches the close-packing density. At the same time, as was demonstrated in the studies,^{9,32} the Brownian motion in dilute suspensions, for which the function $\eta(\varphi)$ can be expanded in a power series of φ , has an effect only on the quadratic term accounting for particle-pair interactions. The linear term in Eqn (2) is independent of the Peclet number.

Therefore, the Brownian motion influences most substantially the rheological properties of suspensions at a concentration $\varphi \approx 0.1-0.2$. However, this conclusion is true only for suspensions composed of strictly spherical particles. If the Brownian motion is taken into account in the case of anisometric particles, it is the linear term in Eqn (2) that becomes dependent on the Peclet number due to reorientation of the particles in a flow.

The development of a unified two-phase model for suspensions and powders^{5,21} has assisted in developing the rheological theory of disperse systems. The use of this model made it possible to derive the general equation, which is valid at low and high viscosities of a medium for powders and suspensions, respectively. This model was based on the lubrication model,¹⁷ which treats the test particle moving among z surrounding stationary particles. The following equation for the viscosity of a system of rigid spheres in a viscous medium was derived with the use of the Eyring equation of state:³³

$$\eta \approx 0.16\varphi_m\alpha \frac{\rho dv}{[(\varphi_m/\varphi)^{1/3} - 1][1 - \exp(-v/v_c)]}, \quad (12)$$

where α is the coefficient that depends on the parameters of particle collisions, ρ is the particle density, v is the velocity at which particles approach each other and $v_c = (9/4)z\eta_0/\rho d$ is the value identified with the minimum velocity v , which must be imparted to particles in order that they overcome the hydrodynamic resistance on collisions.

For two limiting flow types, the following equations were derived for the viscosity of a system when $\varphi \rightarrow \varphi_m$:⁵

$$\eta \approx \frac{c_1\eta_0}{(\varphi_m/\varphi)^{1/3} - 1} \text{ at } v \ll v_c, \quad (13)$$

$$\eta \approx \frac{c_2\rho dv}{(\varphi_m/\varphi)^{1/3} - 1} \text{ at } v \gg v_c. \quad (14)$$

Here $c_1 \approx 0.1$ and $c_2 \approx 0.05$.

For particle collisions, the hydrodynamic factor plays the determining role in the former case [Eqn (13)], *i.e.*, the viscosity of the system is determined by the energy dissipation in a flow in the space between the particles. This is typical of suspensions. Equation (14) is valid for low-viscosity media, where the viscosity is determined by the energy dissipation due to inelasticity of particle collisions, which is characteristic of powders. The advantage of Eqn (12) is that it is universal and describes both limiting flow types. Equation (13) corresponding to suspensions is equivalent to Eqn (7), which was derived in another way, by comparing the energy dissipated in a unit volume of a suspension with the energy supplied to the system upon its shear deformation. The drawbacks of Eqns (12)–(14) are that they are based on two-particle collisions, which, in the case of concentrated systems, is unlikely to be justified.

2. Structured disperse systems

The above-considered rheological models describe the viscosity of non-structured systems. However, it is known that the structure formation in disperse systems leads to a drastic change in their rheological properties.³⁴ The rheological properties of structured disperse systems under conditions of their continuous shear deformation are most often described with the use of the overall rheological flow curve, *e.g.*, the plot of the effective shear viscosity

vs. the shear rate $\dot{\epsilon}$ (or the shear stress σ) on condition that destruction is isotropic. The overall flow curve with a viscosity drop of up to 8–10 orders of magnitude was described for the first time in the study.³⁵ In this study, the authors introduced the concepts of ‘the highest viscosity of a virtually non-destroyed structure’ corresponding to the upper plateau in the flow curve and ‘the lowest Newtonian’ viscosity of a maximum destroyed structure. More recently, it has been demonstrated^{1–3} that the true maximum destruction can be achieved only under shear deformation used along with other external mechanical forces (for example, vibration), as well as by lyophilisation of the particle surface with surfactants.

To estimate the fluidity of structured systems, certain assumptions about the character of structuring should be made. There are two types of such assumptions and the corresponding structural models of disperse systems. Models of one type treat particles that are held together to form a continuous structure. Its homogeneity is retained, under deformation, at distances much larger than the particle diameter. Parameters having the dimensionality of length are not used for the description of the structure. In another type of models, the structures are composed of particle aggregates. The parameter characterising inhomogeneity of the structure is generally identified with the aggregate size.⁵

Thus, simulation is the main method of theoretical studies of structured systems. This is associated with the lack of experimental methods that would allow one to study in-depth the structures of disperse systems and their changes in flow. The available methods have been insufficiently developed. Only rheological experiments provide reliable data on the structures, the construction of alternative microrheological models being a necessary step in these investigations.

In the study,²¹ the rheological properties of a system were related to its structural characteristics, such as the diameter of spherical aggregates and the distance between their centres. It was assumed that deaggregation in flow occurs due to detachment of particles from the aggregate surface until an equilibrium state is established at a given shear rate $\dot{\epsilon}$, at which further detachment of particles becomes impossible. The space between the aggregates is filled with a suspension of particles detached from the aggregate surface. The viscosity of this suspension is equal to that of completely deaggregated system of spheres at the same concentration, *i.e.*, to the viscosity of this system after its complete destruction.

Under the assumptions used for deriving Eqns (13) and (14), the following equation was obtained²¹ for the dependence of the viscosity of a weakly aggregated suspension on the shear rate:

$$\frac{\eta}{\eta_\infty} = \left(\frac{\dot{\epsilon}_c}{\dot{\epsilon}} \right)^{1/2}, \quad (15)$$

where η_∞ is the viscosity when $\dot{\epsilon} \rightarrow \infty$, $\dot{\epsilon}_c = 6.4F/(\eta_\infty d^2) = 6.4k'/(\eta_\infty d)$ is the critical shear rate $\dot{\epsilon}$ corresponding to the complete deaggregation, F is the strength of bonding between the particles and k' is the coefficient that depends on the nature of the surface forces.

Equation (15) can be used at shear rates $\dot{\epsilon}_c(L_1/L_2)^2 \ll \dot{\epsilon} \ll \dot{\epsilon}_c$, where L_1 is the average distance between the particles and L_2 is the average distance between the centres of aggregates. At $\dot{\epsilon} < \dot{\epsilon}_c(L_1/L_2)^2$, the distance between the aggregate surfaces is comparable to the particle diameter and this equation is inapplicable. Equation (15) does not include the aggregate diameter and contains only parameters having a precise physical meaning, such as the viscosity of the completely destructured system η_∞ , which can be interpreted as the minimum viscosity at high $\dot{\epsilon}$ until dilatancy appears, and the coefficient k' . The latter is expressed in terms of the Hamaker constant A (see Refs 36 and 37) and the distance between the particle surfaces. Hence, with a knowledge of A , it is possible to determine the shape of the rheological curve. If the constant A is unknown, the order of A in this system can be estimated by measuring η_∞ and $\dot{\epsilon}_c$.

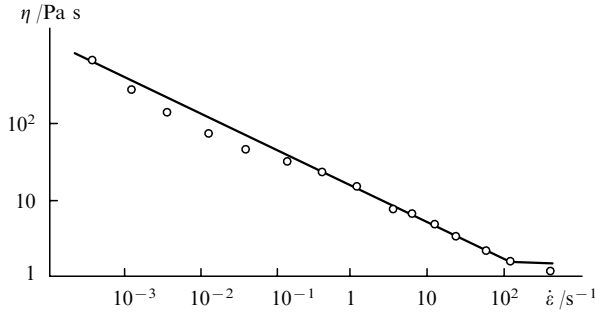


Figure 3. Calculated curve and experimental data (points) for a PMMA suspension in decalin ($\varphi = 60.1\%$, $d = 0.47 \mu\text{m}$, $\eta_0 = 2.8 \text{ mPa s}$ at $T = 293 \text{ K}$).²¹

In spite of a good agreement between the experimental data and the results of calculations according to Eqn (15) for a monodisperse suspension of PMMA particles in decalin (Fig. 3), this equation is of limited application. Actually, the dependence of the suspension viscosity on the shear rate

$$\eta \sim \dot{\epsilon}^{-1/2}$$

describes well the region of intermediate gradients for a model system considered in the study.²¹ However, for many other systems, even if this dependence at intermediate gradients is searched in the form

$$\eta \sim \dot{\epsilon}^{-n},$$

n can vary from $1/2$ to 1 .³⁸ In addition, at small $\dot{\epsilon}$ the dependence $\eta(\dot{\epsilon})$ generally becomes sharper, including that for the model system described in the study.²¹ The way of generalising Eqn (15), according to which n can assume the values $> 1/2$, and the relationship between n and the structural characteristics were discussed.³⁸ The authors believed that aggregates can form higher-order structures, *viz.*, superaggregates. The motion of superaggregates is treated in a non-aggregated suspension serving as a non-Newtonian medium, and the viscosity is determined according to Eqn (15). Under these assumptions, the following equation was obtained for the viscosity of strongly aggregated suspensions:

$$\frac{\eta}{\eta_\infty} = B\left(\frac{3k+1}{2k}, \frac{3-k}{2k}\right) \frac{3 \times 2^{1/k} (2+k)^{1/k}}{4} \times \left[\frac{p \dot{\epsilon}_c^{2(k+1)/(3-k)}}{(2+k)^{1/k} 2^{1/k} \eta_\infty \dot{\epsilon}^{(k+1)/(3-k)}} \times \frac{1}{B((k+1)/2k, (3+k)/2k)} \right]^{(3-k)/(3+k)}. \quad (16)$$

Here $B(\dots, \dots)$ is the β function, $k = 1/(1-n)$ and p is the strength of the superaggregates.

In particular, at $n = 0$ and $k = 1$, Eqn (16) can be represented as Eqn (15).

At concentrations $\varphi < 60\%$, the rheological curves, which were constructed with the use of the notions of the aggregation mechanism, agree well with experimental data throughout the range in which the shear stress σ was varied (Fig. 4). However, at $\varphi > 60\%$ and low σ , a substantial deviation from this dependence was observed, and the curve has a plateau, which can be attributed to discontinuity of structure. This phenomenon, its possible manifestations and factors responsible for its occurrence both in well-characterised disperse systems and systems formed by poly-dispersed (in some cases, anisometric) particles of dispersed phases in liquid media were analysed in-depth.^{39,40} The conditions

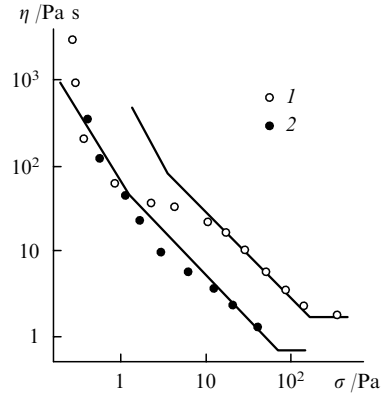


Figure 4. Effective viscosity η vs. the shear stress for a PMMA suspension in decalin at $\varphi = 60.1$ (1) and 59.5% (2).³⁸

determining the possibility of discontinuities under deformation of concentrated disperse systems were formulated in the study.⁴¹

In real systems with a non-uniform packing of particles in a quasi-crystal lattice, accumulations of vacancies, *i.e.*, cavities free from dispersed particles, are present. As in the crystalline substances, these cavities can be transformed into discontinuities (cracks) under shear stresses. The possibility of an increase in the cavity size is determined by the ratio of the relaxation times of the following processes that occur in the vicinity of this cavity under deformation of the system:⁴¹

elastic energy release due to the development of discontinuity

$$\tau_1 \sim l \frac{(\rho G)^{1/2}}{\sigma};$$

the formation of a new surface due to the development of a macroscopic crack

$$\tau_2 \sim l \left(\rho \frac{l}{\gamma} \right)^{1/2};$$

the mass transfer to the discontinuity zone as a result of vacancy drift

$$\tau_3 \sim \frac{l}{a} \sqrt{\frac{m \Delta^2}{U_0}} \exp\left(\frac{U_0}{k_B T}\right) \times \left[\sqrt{1 + \frac{m \Delta^2}{U_0} \left(\frac{\eta_0}{\rho a h} \right)^2} - \sqrt{\frac{m \Delta^2}{U_0} \frac{\eta_0}{\rho a h}} \right]^{-1} \times \left[\exp\left(\frac{\sigma a^2 \Delta}{k_B T}\right) - \exp\left(-\frac{\sigma a^3}{k_B T}\right) \right]^{-1}.$$

Here l is the linear size of the cavity in the quasi-crystal lattice, $G \sim F/\Delta a$ is the shear modulus, ρ is the density of the solid phase, $\gamma \sim U_0/a^2 \sim F\Delta/a^2$ is the specific surface energy, a is the quasi-crystal lattice spacing, Δ and U_0 are the half-height and half-width of the potential well, respectively, h is the distance between the particle surfaces and m is the particle mass.

The equations for the relaxation times of the first two processes were derived based on the dimensionalities of the physical parameters. The latter equation was obtained based on the Frenkel and Eyring hole theories assuming that the motion of dispersed particles is analogous to that of molecules of the liquid.

The development of discontinuity occurs if the relaxation time of elastic energy release (τ_1) is shorter than the relaxation times of processes, which can hinder the appearance of discontinuities (τ_2 and τ_3), *i.e.*, on the condition⁴¹

$$\frac{1}{\tau_1} \gg \frac{1}{\tau_2} + \frac{1}{\tau_3} \quad (17)$$

or

$$\sigma \gg \frac{F_c}{a^2} \sqrt{\frac{a}{l}} + G \left[\exp\left(\frac{\sigma a^2 \Delta}{k_B T}\right) - \exp\left(-\frac{\sigma a^3}{k_B T}\right) \right] \times \\ \times \exp\left(-\frac{U_0}{k_B T}\right) \times \left[\sqrt{1 + \frac{m \Delta^2}{U_0} \left(\frac{\eta_0}{\rho a h}\right)^2} - \sqrt{\frac{m \Delta^2}{U_0} \frac{\eta_0}{\rho a h}} \right].$$

This condition is fulfilled at

$$\sigma_1 \ll \sigma \ll \sigma_2, \quad (18)$$

where σ_1 and σ_2 are determined from the equations

$$\sigma_1 \sim p_h \left(\frac{a}{l}\right)^{1/2}, \quad (19)$$

$$\sigma_2 \sim p_h - \frac{k_B T}{a^2 \Delta} \times \\ \times \ln \left\{ \frac{G}{\sigma_2} \left[\sqrt{1 + \frac{m \Delta^2}{U_0} \left(\frac{\eta_0}{\rho a h}\right)^2} - \sqrt{\frac{m \Delta^2}{U_0} \frac{\eta_0}{\rho a h}} \right] \right\}, \quad (20)$$

where $p_h \sim F/a^2$ is the shear strength of an ideal (homogeneous) structure.

The development of discontinuity as a result of deformation occurs only at σ corresponding to the range (18), if the packing of particles was inhomogeneous before deformation. Under lower or higher shear stresses, a homogeneous viscous flow occurs. The structure inhomogeneity (regions with a closer packing) serve as nucleation sites for discontinuities. The parameters σ_1 and σ_2 calculated according to Eqns (19) and (20), respectively,⁴¹ are in satisfactory agreement with experimental data.

Some models of structured systems are based on the Eyring viscosity theory. This theory was used for deriving the equation for the viscosity of flocculated colloidal dispersions⁴²

$$\eta = (\eta_1 - \eta_\infty) \frac{[\text{sh}(\beta \dot{\epsilon})]^{-1}}{\beta \dot{\epsilon}} + \eta_\infty, \quad (21)$$

where η_1 and η_∞ are the limiting viscosities of the suspension when $\dot{\epsilon} \rightarrow 0$ and $\dot{\epsilon} \rightarrow \infty$, respectively;

$$\beta = k \frac{d^2}{D} \left(\frac{U}{k_B T}\right)^{-1} \exp\left(\frac{U}{k_B T}\right),$$

k is the proportionality coefficient that depends on the properties of the structure and U is the activation energy (potential barrier to particle shear migration).

The activation energies U were calculated by Churaev on the assumption that particles are fixed in the sites of a body-centred cubic lattice.⁴³ The migration of the particle A to the vacant site B through the potential barrier due to its interaction with the adjacent particles was considered. The potential barrier was calculated by summarising the energies of pair interactions between the particle A and the nearest neighbours. As a result, the forces acting on the transferred particle were determined taking into consideration the viscous resistance of interlayers of the liquid between particles. The time dependence of the deformation rate determined from the migration rates of the particle A is similar to that found within the limits of the well-known Calvin rheological model with a variable viscosity. Using these calculation methods, an attempt was made to establish the functional relationship between the potential curves of particle pair interactions in a disperse system, on the one hand, and its structural-mechanical properties, on the other hand. It became possible to reveal changes in the structural-rheological parameters of a

dispersion caused by changes in the electrolyte concentration, the surface charge, hydrophilicity of the particle surfaces and adsorption of surfactants and polymers on the particle surface. The drawback of the approach proposed⁴³ is that the properties of dispersions can be predicted only qualitatively.

In a model developed by Ogawa *et al.*,⁴⁴ the shear stress σ in colloidal suspensions can be divided into two components: the viscous stress and strain associated with interactions between particles. The first term can be determined from the Krieger–Dougherty equation (4). The second term depends on the inter-particle potential and was determined based on a knowledge about activation processes. Hence, the equation for the relative viscosity can be written as follows

$$\frac{\eta}{\eta_0} = \left(1 - \frac{\varphi}{\varphi_m}\right)^{-2.5\varphi_m} + c_1 \varphi \exp\left(\frac{U}{k_B T} - \frac{c_2 d^3 \sigma}{\varphi k_B T}\right), \quad (22)$$

where c_1 and c_2 are numerical constants (theoretically equal to $\pi/6$). The height of the energy barrier U is taken to be proportional to the particle pair potential at the midpoint between the particles. The parameter φ_m is chosen so as to achieve an agreement with experimental data at $\eta_\infty = \eta(\sigma \rightarrow \infty)$ for a suspension of solid spheres.^{29,45} With $\sigma \rightarrow 0$, Eqn (22) is identical to the equation corresponding to the model proposed earlier.⁴⁶ However, the author⁴⁶ considered U as the difference between the total potentials for the particles in the initial and final positions. The potentials were calculated taking into consideration the nearest neighbours under the assumption of a face-centred cubic lattice.

In the case of strong repulsions between the particles, the yield stress is described by the equation⁴⁴

$$\sigma_y = \frac{\varphi U}{c_1 d^3}. \quad (23)$$

This equation is equivalent to the equation for σ_y reported in the study.⁴⁷ Equation (23) can be easily obtained with the use of an effective medium model and assuming that $c_1 = 1/3$ rather than $\pi/6$. For systems characterised by a considerable attraction between the particles, several equations relating the yield stress to the energy required for deaggregation were proposed. These models were reviewed in detail in the publication.⁴⁸

In the study,⁴⁹ another class of models describing the viscosity of structured suspensions was considered. These models are based on approach including the following sequence of operations:

- a variable S that characterises the structure is introduced;
- the equation for the change in S under forces, which cause microstructure degradation (viscous friction forces in a shear flow) and assist in restoring the initial state (Brownian and dispersion forces) is written;
- the relationship between the viscosity and S is derived.

Let us consider one of the possible definition of the structural variable and its relationship with the suspension viscosity.^{50,51} Dispersions are represented as mixtures of individual particles and groups of particles (structural units, aggregates) suspended in a liquid. Particles comprising a structural unit move together as a rigid cluster thus transferring the liquid immobilised in this cluster. Therefore, a decrease in the viscosity with increasing shear rate is considered as a result of rapid degradation of structural units, which is accompanied by an increase in both the concentration of individual particles and the free liquid volume. An increase in the viscosity is, on the contrary, related to the formation of new structural units in a shear flow. The characteristics of the structural units (the size, shape and the possibility of the appearance or destruction in a shear flow) depend substantially on the type of interactions between the particles. If attractive forces between the particles prevail, the structural units can exist as flakes, aggregates or clusters of aggregates. In some systems, small aggregates are held together so tightly that deaggregation does not occur under shear forces. Hence, such aggregates can be considered as individual particles.⁵² If interactions are weak, the

structural units are merely groups of particles in a suspension of more or less free individual particles.

Let us denote the volume fractions of the structural units and individual particles by φ_s and $\varphi_p = \varphi - \varphi_s$, respectively. The structural variable can be given⁵⁰ as $S = \varphi_s/\varphi$. The effective volume fraction of the dispersed phase is

$$\varphi_{\text{ef}} = \frac{\varphi_s}{\varphi} + \varphi_p = \varphi(1 + CS),$$

where $C = 1/\varphi - 1$ is the compactness factor.

The equation specifying the change in S with time can be written as follows:

$$\frac{dS}{dt} = \frac{1}{\tau_1}(S_1 - S) - \frac{1}{\tau_2}(S - S_\infty), \quad (24)$$

where τ_1 and τ_2 are the characteristic relaxation times of the Brownian and hydrodynamic forces, respectively, and S_1 and S_∞ are the limiting values of the variable S when $\sigma \rightarrow 0$ and $\sigma \rightarrow \infty$, respectively. Under conditions of dynamic equilibrium, the variable S reaches a particular stationary value. In this case,

$$\frac{S_1 - S}{S - S_\infty} = \frac{\tau_1}{\tau_2} = \theta,$$

where θ is the kinetic ratio. For dilute suspensions of solid spheres, the time $\tau_1 \sim d^2/D$, which corresponds to the diffusion time of a particle to a distance comparable to its size. The characteristic time of hydrodynamic interactions in a shear flow τ_2 is similar in order of magnitude to $\dot{\epsilon}^{-1}$. Consequently, θ in dilute systems is equal to the Peclet number $\text{Pe} = d^2\dot{\epsilon}/D$, which can be considered as the ratio of the viscous friction work to the energy of thermal motion of the particles. In concentrated suspensions, the diffusion motion of the particles is strongly hindered and the suspension viscosity is substituted into the equations for the characteristic times instead of the viscosity of a medium. Then

$$\theta \sim \frac{\sigma d^3}{k_B T}.$$

Assuming that $\theta = \sigma/\sigma_c$, the critical shear stress can be determined as

$$\sigma_c = \frac{k_B T}{d^3}.$$

This relationship is the known Krieger correction (for Brownian motion) for colloidal suspensions.¹²

In the last step, the relationship between the viscosity and the shear stress is determined. In the study,⁵⁰ the following equation, which describes the non-Newtonian behaviour of suspensions under conditions of shear stress, is derived:

$$\eta(\sigma) = \eta_\infty \left(\frac{1 + \sigma/\sigma_c}{R_r + \sigma/\sigma_c} \right)^2. \quad (25)$$

Here, the rheological index R_r is expressed by the equation

$$R_r = \frac{1 - \varphi/\varphi_1}{1 - \varphi/\varphi_\infty} = \begin{cases} (\eta_\infty/\eta_1)^{1/2} & \text{if } \varphi < \varphi_1, \\ -\sigma_y/\sigma_c & \text{if } \varphi \geq \varphi_1, \end{cases} \quad (26)$$

where

$$\varphi_1 = \frac{\varphi_m}{1 + CS_1},$$

$$\varphi_\infty = \frac{\varphi_m}{1 + CS_\infty}.$$

At $\varphi < \varphi_1$, the calculated function $\eta(\sigma)$ represents a curve consisting of two regions, which correspond to the Newtonian

viscosity at low and high shear stresses, and an intermediate region in which the viscosity decreases. The plateau corresponding to low shear stresses disappears as the concentration φ increases and approaches φ_1 , i.e., the yield point σ_y is achieved. At $\varphi > \varphi_1$, the system exhibits the plastic properties.⁵³ In addition, at $R_r > 1$ the model can reflect the dilatant properties of suspensions.^{54,55}

Let us consider the differential method used for calculating the effective properties of disperse systems. The method consists of the following. A dispersed phase is added portionwise to the system under study. In each step, the effective properties of the disperse system are calculated with the use of the effective properties of the system determined in the previous step. In the zeroth step, the disperse system does not contain a dispersed phase and consists completely of a dispersion medium. The effective coefficients are determined in each step using a linear approximation, which was obtained from solving the problem at a low concentration of the dispersed phase. This approach allows one to derive differential equations or related differential equation systems, which describe the dependence of the desired characteristics on the concentration of the dispersed phase. The effective constants of the disperse system can be determined by solving the differential equation system. In the studies,^{56,57} this method was used to calculate the effective characteristics of porous media, in particular, to evaluate the viscosity of a dilute suspension containing porous particles.

A porous particle is modelled by a system consisting of N spherical liquid-impermeable particles with a given packing density. It is assumed that the liquid flow inside the porous particle obeys the Brinkman equations

$$\nabla p = \eta \Delta \mathbf{u} - K \mathbf{u},$$

where p is the pressure, $\mathbf{u}$ is the fluid velocity vector, η and K are the viscosity and the resistance coefficient of a porous medium, respectively.

The solution of this equation gives the following differential equations for the effective suspension viscosity and the resistance coefficient:⁵⁷

$$\frac{d\eta}{d\varphi} = \frac{5}{2} \frac{\eta}{1 - \varphi}, \quad \frac{dK}{d\varphi} = \frac{9\pi}{2R^2} \frac{\eta}{1 - \varphi}.$$

The boundary conditions: $\varphi = 0$, $\eta = \eta_0$ and $K = K_0$, where R is the radius of the porous particles, η_0 and K_0 are the viscosity and the resistance coefficient of the Brinkman fluid free of additional inclusions.

This differential equation system has the following solution:

$$\eta = \eta_0(1 - \varphi)^{-5/2}, \quad K = K_0 + \frac{9}{7} \frac{\pi \eta_0}{R^2} [(1 - \varphi)^{-5/2} - 1].$$

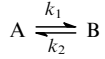
These equations determine the dependence of the effective suspension viscosity and the flow resistance coefficient taking into account the particle permeability to a dispersion medium.

An important class of rheological models includes models that are based on analysis of the processes of formation and cleavage of bonds between the particles. These models are called kinetic models because they are described by kinetic equations that characterise the changes in the bond numbers. The best known model of this type was developed in the study.⁵⁸ The kinetic equation for this model is as follows

$$\frac{dN_1}{dt} = -k_1 N_1^n + k_2 N_2^m, \quad (27)$$

where N_1 and N_2 are the concentrations of non-broken and broken bonds, and k_1 , k_2 , n and m are the constants characterising the rates of destruction and regeneration of the system.

An analogous model was proposed by Stolin *et al.*⁵⁹ The authors used a rheological system consisting of the structures A and B and identified the destruction and regeneration of the system with the forward and reverse chemical reactions



The constants k_1 and k_2 are similar in meaning to the analogous parameters in Eqn (27). Their dependence on the shear rate was taken into consideration under the following assumptions:

- (i) an increase in the deformation intensity leads to stronger structural changes (up to destruction);
- (ii) noticeable structural changes occur after elastic deformation (development of high-elastic deformations).

It is taken that

$$k_1 = k_{10} \exp\left(\frac{\omega}{2k_B T}\right),$$

$$k_2 = k_{20} \exp\left(-\frac{\omega}{2k_B T}\right),$$

where $\omega = (G/\tau)\dot{\epsilon}^2$ is the energy accumulated during elastic deformation τ .

The equation relating the dimensionless stress $\bar{\sigma}$ and the shear rate $\bar{\epsilon}$ was written in the following form⁵⁹

$$\bar{\sigma} = \frac{\bar{\epsilon}(1 + \kappa \exp \bar{\epsilon}^2)}{\lambda + \kappa \exp \bar{\epsilon}^2} \quad (28)$$

Here $\bar{\sigma} = F_A \alpha^{1/2} \sigma$, $\alpha = G/\tau$, $\bar{\epsilon} = \alpha^{1/2} \dot{\epsilon}$, $\kappa = k_{10}/k_{20}$, $\lambda = F_A/F_B$, F_A and F_B are the fluidities of the structures A and B, respectively.

Therefore, the viscosity of a system in the kinetic models is related to the concentrations of broken and non-broken structures (bonds) and it can be estimated from the corresponding kinetic equations.

Equation (28) describes the viscosity superanomaly, *viz.*, a decrease in the deformation resistance with increasing shear rate in stationary flows, characteristic of tixotropic structured systems. In this case, the flow curve (the shear rate vs. the shear stress) is a multivalued function. Its plot has a lower and upper branches, jumps from one branch to another being possible. This dependence was observed experimentally for various disperse systems and it is associated with the above-discussed discontinuity effect.⁴¹ It should also be noted that an agreement between the experiment and Stolin's model is evidently due to a free choice of a large number of independent parameters.

The kinetic model of aggregation–fragmentation of particles in a hydrodynamic shear flow of a coagulated suspension was developed by Dolgonosov.^{60, 61} In the equilibrium state, where the rates of attachment of the particles to aggregates is equal to the detachment rate, a dispersed phase was demonstrated to be separated into two fractions. One fraction consists of large aggregates, whereas another fraction is composed of small particles (initial particles and small aggregates). The formation of a two-fraction pattern was attributed to the fact that the growth of small and larger aggregates occurs by different mechanisms (Brownian and gradient). Within this model, the particles of the small and larger fractions are characterised by continuous spectra of masses $f(\mu)$ and $F(m)$ (μ and m are the particle masses of the corresponding fractions). The functions f and F were each normalised to the number of particles in the corresponding fraction. Under the assumptions used for the description of coagulation of small particles and their uptake by aggregates, as well as of the growth and degradation of aggregates, the following kinetic equations were derived:

$$\frac{\partial f(\mu)}{\partial t} = \int_0^{\mu/2} \beta(\mu - \mu', \mu') f(\mu - \mu') f(\mu') d\mu' - \int_0^\infty \beta(\mu, \mu') f(\mu) f(\mu') d\mu' - \int_0^\infty \beta(m, \mu) F(m) f(\mu) dm +$$

$$+ \int_\mu^\infty \gamma(m - \mu, \mu) F(m) dm,$$

$$\frac{\partial F(m)}{\partial t} = \int_0^{m/2} \beta(m - \mu, \mu) F(m - \mu) f(\mu) d\mu - \int_0^\infty \beta(m, \mu) F(m) f(\mu) d\mu + \int_0^\infty \gamma(m, \mu) F(m + \mu) d\mu - \int_\mu^{m/2} \gamma(m - \mu, \mu) F(m) d\mu. \quad (30)$$

Here $\beta(x, y)$ is the kernel of coagulation (the specific rate of coagulation of the particles x and y into the aggregate $x + y$) and $\gamma(x, y)$ is the kernel of degradation (the specific rate of degradation of the aggregate $x + y$ into the fractions x and y). The functional type of the sites of coagulation and degradation is written with consideration for the mechanism of aggregate growth with the use of approaches developed in the studies.^{62–65}

Calculations within this model allow one to reveal the changes in the spectrum of particles of a dispersed phase with time (Fig. 5). Analysis of the results of calculations showed that the evolution of the dispersed phase involves three steps: 1) the initial step: as a result of coagulation of aggregates, a coarse fraction manifests itself as several modes in the spectrum, which are transformed into one resulting asymmetric mode upon coalescence; 2) the intermediate step: aggregate coagulation continues, resulting in a decrease in asymmetry of the mode; 3) the final step: aggregation ceases, and ageing of the dispersed phase occurs due to capture of particles of the fine fraction by aggregates and detachment of fragments from aggregates under hydrodynamic stresses.

Calculations demonstrated that the peak in the spectrum of the fine fraction decreases in height and is broadened with time. In the studies,^{60, 61} it was demonstrated that the fine and coarse fractions do not overlap throughout the process, which is a condition for the applicability of the two-fraction model of a dispersed phase. The cited studies dealt with low-concentration disperse systems, in which the possibility of structuring is excluded, and only the kinetics of the formation of a dispersed phase was calculated taking into account coagulation and fragmentation of the particles. Apparently, the proposed model can be used also in calculations of the rheological characteristics of such systems.

Of the processes that substantially influence the rheological properties of dispersions, immobilisation of a liquid with aggregates and particles deserves notice. A liquid can be immobilised both on the particle surface and within aggregates. The immobilised liquid is not a true component of the liquid phase because it is bound to particles, and this liquid would be more properly considered as a supplement to solid particles, which increase the effective volume concentration of the dispersed phase

$$\varphi_{ef} = \varphi + \varphi_s + \varphi_v,$$

where φ_s and φ_v are the fractions of the liquid immobilised on the particle surface and in the bulk of aggregates, respectively.

The influence of immobilisation of the liquid on the rheological characteristics of suspensions was discussed by Windhab.⁶⁶ The volume of the immobilised liquid depends substantially on the degree of aggregation of the system, the particle surface roughness, the viscosity of the liquid, the porosity of aggregates, their density (Fig. 6) and other factors. Deaggregation of the system leads to release of the liquid located between the particles in the aggregate, resulting in a decrease in the volume of the immobilised liquid (φ_{ef}). However, further deaggregation leads to immobilisation of the liquid on the newly formed particle surface resulting in an increase in φ_{ef} . The effective concentration φ_{ef} directly affects the suspension viscosity. Therefore, the viscosity of the system

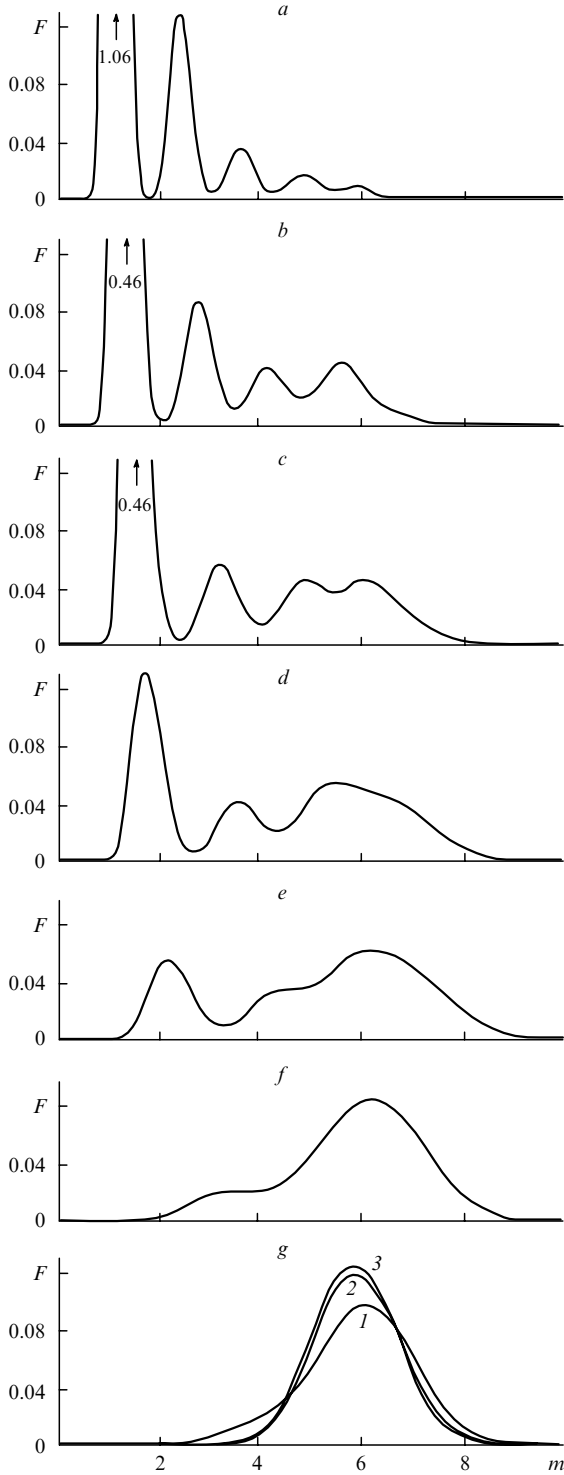


Figure 5. Mass distribution density of large aggregates vs. the time (t).⁶¹ $t = 0.1$ (a), 0.2 (b), 0.3 (c), 0.4 (d), 0.6 (e), 1.1 (f), 1.5 (g, curve 1); 7.0 (g, curve 2); 3, the Gaussian approximation of the equilibrium distribution; t is a dimensionless value.

changes with a change in the shear rate resulting in the aggregation or deaggregation and immobilisation or release of the liquid.

The following equation for the effective volume concentration was obtained:⁶⁶

$$\varphi_{\text{ef}} = \varphi \left\{ 1 + \frac{1 - \varphi_m}{\varphi_m} \left[1 + (\psi - 1) \frac{3}{4} n^{-1/3} \varphi_m^{1/3} \right] \right\}. \quad (31)$$

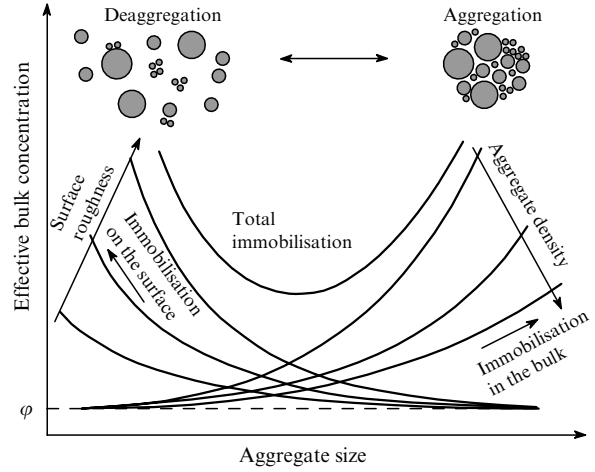


Figure 6. Degree of immobilisation of the liquid on the surface and in the bulk of particles or aggregates as a function of aggregability of the system.⁶⁶

Here $\psi = \Delta V_s / \Delta V_v$ is the ratio of the volume increments of the liquid immobilised on the surface (ΔV_s) and in the bulk (ΔV_v) of aggregates due to aggregation (deaggregation) of the system and n is the number of particles in the aggregate. Aggregation can lead to either a decrease or increase in the viscosity depending on ψ (at $\psi > 1$ and $\psi < 1$, respectively).

The number of the particles in the aggregate is calculated according to the equation

$$n = n(0) \left\{ \frac{k_a + k_d \exp[-(k_a + k_d)t]}{k_a + k_d} \right\}, \quad (32)$$

where $n(0)$ is the number of particles at the initial point of time and k_a and k_d are the rate constants of aggregation and deaggregation, respectively.

In the study,⁶⁶ it was suggested that Eqns (31) and (32) combined with the Krieger–Dougherty equation (4) be used for the estimation of the suspension viscosity:

$$\eta(\varphi, \dot{\epsilon}, t, \delta) = \eta_0 \left[1 - \frac{\varphi_{\text{ef}}(\varphi, \dot{\epsilon}, t, \delta)}{\varphi_m} \right]^{-\alpha(\delta)\varphi_m}. \quad (33)$$

The additional parameter δ takes into account the influence of the orientation of aspherical particles in a flow.

A comparison of the results of calculations according to Eqn (33) with experimental data showed that the model gives underestimated viscosities (Fig. 7). Apparently, this can be attributed to the fact that this model does not take into consideration the microstructure formation, which affects the viscosity of disperse systems.

The microrheology of low-concentration fractal colloidal gels was documented in several publications.^{67–74} If the shear stress applied to such gels is small, the gels exhibit ‘solid-like’ properties, viz., a high viscosity and the modulus of elasticity at low frequencies. If the stress is higher than the threshold value, the viscosity and, in some cases, the modulus of elasticity fall by several orders of magnitude and the system exhibits ‘liquid-like’ properties. An explanation of the nature of solid- and liquid-like states was given in the studies.^{67, 68} It was assumed that, at stresses higher than the threshold value ($\sigma > \sigma_c$), the structure consists of fractal aggregates, which are in contact with each other but are not linked in a network, and the system exhibits liquid-like properties. At $\sigma < \sigma_c$, the system occurs in the gel state, i.e., it consists of aggregates linked in a network and exhibits solid-like properties.

For the solid-like state, the viscosity can be estimated according to the equation^{67, 73}

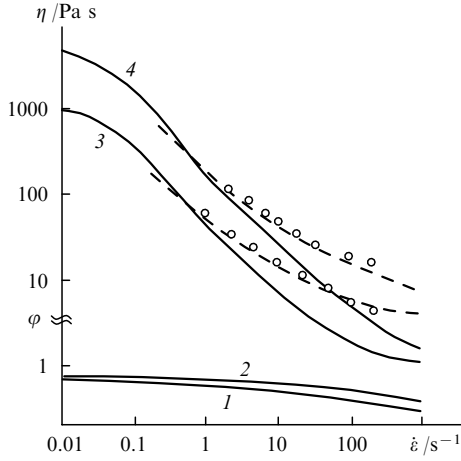


Figure 7. Calculated (solid curves) and experimental (points) dependences of the shear viscosity of a sugar dispersion in silicon oil.⁶⁶ The results of approximation of experimental points by polynomials are indicated by dashed curves.

(1) φ_{ef} at $n_0 = 1000$; (2) φ_{ef} at $n_0 = 5000$; (3) η at $n_0 = 1000$; (4) η at $n_0 = 5000$; (n_0 is the number of particles in the aggregate in the absence of shear).

$$\eta_s \cong \alpha G_0 \tau_0 \exp\left(\frac{E}{k_B T}\right) c^{(3+2f_r)/(3-f_a)}. \quad (34)$$

Here $\alpha < 1$ is the coefficient that takes into consideration a decrease in the shear modulus in the space between the particles, G_0 is the shear modulus of the material of colloidal particles, τ_0 is the period of thermal oscillations of a pair of bound particles, E is the bond energy of the particles, c is the volume concentration of the particles in the system $c = c_N d^3$ (c_N is the numerical concentration of colloidal particles), f_r is the fractal dimensionality of unreplicated bonds in the backbone of the aggregate and f_a is the fractal dimensionality of the aggregates.

The viscosity of a gel in the liquid-like state is

$$\eta_l \cong B \pi \eta_0, \quad (35)$$

where $B > 1$ is the coefficient that takes into account the asphericity of the aggregate.

The critical (threshold) stress is

$$\sigma_c = K \frac{p_c E}{\xi^3}, \quad (36)$$

where $K \approx 1$ is the coefficient, p_c is the critical fraction of broken bonds, which is determined based on the percolation concepts, for a three-dimensional problems $p_c \approx 0.6-0.8$, and ξ is the linear size of the aggregate.

In the study,⁶⁷ it was concluded that at $\sigma = \sigma_c$, the system is inhomogeneous and stratifies into two phases, which are characterised by the viscosities η_s and η_l and the shear rates σ_c/η_s and σ_c/η_l . The shear rate changes stepwise with height. In regions corresponding to solid-like layers, the shear rate is lower than the average rate, whereas it is higher than the average rate between the layers.⁷⁴

The possibility of the co-existence of solid-like and liquid-like layers in a shear flow of low-concentration colloidal gels was considered in detail.^{72,74} In those studies, the co-existence of the layers in a shear flow in the shear rate range $\sigma_c/\eta_s \leq \dot{\epsilon} \leq \sigma_c/\eta_l$ was demonstrated to be responsible for the minimum energy dissipation rate, *i.e.*, the presence of these layers is energetically favorable. The fraction of the cross-section, which is perpendicular to the sample flow and is occupied by liquid-like layers, is determined by the equation

$$\varphi_l = \frac{\dot{\epsilon}/\sigma_c - 1/\eta_s}{1/\eta_l - 1/\eta_s}. \quad (37)$$

An idea of the co-existence of solid- and liquid-like phases was extended to gels under periodic shear deformation.⁶⁸ In the publication,⁷¹ the theoretical views about the structures of low-concentration gels were used for the description of the state of such gels under shear compression. In particular, it was noted that compression can lead to contacts between the branches (formed by particles) attached to the backbones of fractal cells and their gluing, on the one hand, and the cleavage of the most burdened branches, on the other hand.

The criterion formulated in the study⁶⁹ allows one to predict whether aggregates can fill the volume of the system and form a gel. This criterion is based on parameters of dilute colloidal systems in which fast coagulation of particles occurs and non-equilibrium fractal aggregates are formed. If the gel formation does not occur, aggregates fill a small volume fraction of the system, and their average sizes remain virtually unchanged with time because aggregation is compensated by fragmentation of aggregates (a stationary state). The volume concentration of the particles in the system was taken to be small, the aggregates were considered as consisting of a large number of particles, and the scaling solution of the Smoluchowski equations for large stationary aggregates, which was obtained earlier,⁷⁵ was used. The Smoluchowski equations include only pair collisions of aggregates and these equations are approximate, when the volume fraction occupied by aggregates φ_a is large.

In the case of formation of stationary fractal aggregates, their characteristics are described by the following expressions: the weighted-average mass of aggregates

$$M \cong \left(c_N \frac{k}{f}\right)^{1/(2+\beta-\alpha)}; \quad (38)$$

the average aggregate size

$$R \cong d M^{1/f_a} \cong d (c A n)^{(1/f_a)/(2+\beta-\alpha)}; \quad (39)$$

the number of aggregates per volume unit

$$n \cong \frac{c_N}{M} \cong d^{-3} c (c A n)^{-1/(2+\beta-\alpha)}; \quad (40)$$

the volume fraction occupied by aggregates

$$\varphi_a \cong n R^3 \cong c (c A n)^{(1/f_a)/(2+\beta-\alpha)}; \quad (41)$$

the time of establishment of a stationary state

$$\tau \cong \frac{d^3}{c k} (c A n)^{(1-\alpha)/(2+\beta-\alpha)} \cong \frac{1}{f} (c A n)^{-(1+\beta)/(2+\beta-\alpha)}. \quad (42)$$

Here k and f are the coagulation and fragmentation constants, respectively, α and β are the parameters that characterise the homogeneity upon coagulation and fragmentation, respectively, d is the particle size, f_a is the fractal dimensionality of the aggregates and $A n = d^{-3} k/f$ is the dimensionless parameter that characterises the ability of the system to undergo aggregation.

In the case of fast Brownian aggregation in the absence of cyclic (closed) fragments in the structure of fractal aggregates, the parameters α and β are equal to zero. Taking $f_a = 2$, the criterion of the existence of a gel can be obtained from Eqn (41) as the condition $\varphi_a \cong 1$ (aggregates fill the total volume).

$$c^{5/4} (A n)^{1/4} \cong 1. \quad (43)$$

The region of the parameters c and $A n$, at which the aggregates are not linked to each other and exist in a stationary state, is shown in Fig. 8. This region is limited by the weighted-average mass of the aggregates $10^2 < M < 10^6$. The requirement of large aggregate masses is associated with the fact that fractal models are

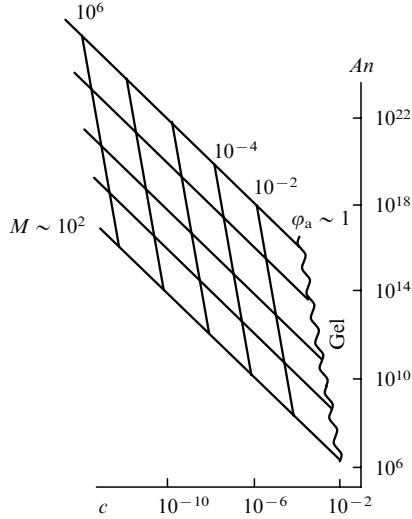


Figure 8. Region of the existence of stationary aggregates (without cyclic fragments) on the coordinates particle volume concentration – aggregability of the system.⁶⁹

The region is bounded by the straight lines $M = 10^2$ and 10^6 . The region of the existence of a gel is on the right from the wavy line.

adequate only in this case. However, the mass of real fractal aggregates cannot be much larger than 10^6 , because their structure will be substantially deformed under gravitation and thermal fluctuations. The wavy line in the Figure corresponds to the boundary of the gel formation $\phi_a \sim 1$.

It should be noted that aggregates occupy virtually the whole volume of the system at $\phi_a \sim 1$. In this case, the gel formation is beyond doubt. At the same time, the gel formation can occur at lower concentrations as well. The approximate character of the above criterion is associated also with the fact that the Smoluchowski equation that lies at the basis of this criterion is valid (as mentioned above) only at low ϕ_a .

3. Suspension dynamics under vibration in the presence of surfactants

A decrease in the viscosity of disperse systems (an increase in their fluidity) is one of the main conditions of optimisation of many heterogeneous chemical engineering processes. This problem is of particular importance for highly disperse systems with a high concentration of a solid phase, which are used in virtually all important industrial processes. The viscosity can be decreased by increasing the shear rate, which leads to decoagulation. However, high fluidity of disperse systems can be achieved also at low shear rates, if the dynamic state is created under other external forces, for example, under vibration, particularly, in the presence of surfactants.

The results of vibration treatment are in many aspects similar to the effect of Brownian motion, which hinders the formation of a coagulation structure from particles, thus providing aggregation stability of disperse systems. Vibration induces dispersion of structures. Hence, the vibration effect is analogous to lyophilisation of the system. However, it differs from the Brownian motion in that its parameters can be changed by many orders of magnitude, whereas the only controlled parameter of the Brownian motion, *viz.*, the temperature, can be varied only within an order of magnitude.

Experimental vibrorheological curves represent plots of the effective suspension viscosity *vs.* the vibration intensity³⁹ analogous to usual rheological curves $\eta_{ef}(\dot{\epsilon})$. Approaches to the theoretical analysis of vibrorheological curves were covered in the monograph.⁵

Within the model of a homogeneous structure, the effective viscosity of a disperse system is calculated according to the equation⁵

$$\frac{\eta_{ef}}{\eta_0} \sim \frac{(\xi \tau_i / \tau_f)^{1/2} \exp(U_a / \theta)}{(1 + \tau_f / \tau_i)^{1/2} - (\tau_f / \xi \tau_i)^{1/2}}, \quad (44)$$

where $\xi = h_1/d$, h_1 is the effective range of surface forces, τ_i and τ_f are the characteristic relaxation times of inertial motion of particles and their interaction due to the surface forces, U_a is the potential energy of particle interactions and θ is the parameter that characterises the kinetic energy of chaotic motion of particles.

For the suspensions considered in the monograph,⁵ $\tau_f \gg \tau_i$. In this case, Eqn (44) takes a simple form

$$\frac{\eta_{ef}}{\eta_0} \sim \exp\left(\frac{U_a}{\theta}\right). \quad (45)$$

When Eqns (44) and (45) are applied to suspensions under vibration conditions, the parameter θ includes, along with the energy of thermal motion of particles, the energy imparted to the particles under vibration,

$$\theta = k_B T + m(A\omega)^2,$$

where A and ω are the vibration amplitude and frequency, respectively.

At rather high θ (high vibration intensity), destruction occurs to give aggregates. In this case, models of aggregated suspensions can be used in the vibrorheological analysis of disperse systems.

The equations for the viscosity of low-concentrated aggregated suspensions with a fractal structure can be derived based on the concepts of sedimentation stability of suspensions by replacing the acceleration of gravity g by the acceleration produced by vibration $A\omega^2$. The following equations for the viscosity under vibration were thus obtained:⁵

within the mean-field model

$$\frac{\eta_{ef}}{\eta_0} = \left[1 - \frac{\phi}{\phi_m^2} \left(\frac{1.1}{\xi_v} \right)^{\sigma(3-f)/(f-1)} \right]^{-1.5}; \quad (46)$$

within the lubrication model

$$\frac{\eta_{ef}}{\eta_0} = \frac{6.2}{\xi_v} \left(\frac{\phi}{\phi_m^2} \right)^{\gamma_1[(3-f)+(f-2)]/(3-f)}. \quad (47)$$

Here

$$\xi_v = \frac{2}{9} \frac{|\rho - \rho_0| d A \omega^2}{\sigma_{0v}},$$

σ_{0v} is the resistance to vibration $\sigma_{0v} = \kappa \sigma_0$, $\kappa \ll 1$, f is the fractal dimensionality, σ_0 is the stability of the structure in the absence of vibration

$$\sigma = \frac{f-1}{(3-f)\gamma_1 + (f-2)} = \frac{f-1}{1+f(1+1/f_r)},$$

$f_r = f/f_c$, f_c is the chemical dimensionality;^{76,77}

$$\gamma_1 = \frac{2\alpha}{(3-f)(f-1)},$$

α is the parameter that depends on the degree of anisometry of the cluster, $0 \leq \alpha \leq f-1$.

The viscosity of highly concentrated suspensions can be estimated from the equation

$$\eta_{ef} \approx 17\eta_{ext} \left[\frac{\phi_m - \phi}{1 - \phi_m} \frac{|\rho - \rho_0| R A \omega^2}{\kappa \sigma_0} + \left(\frac{\eta_{ext} \dot{\epsilon}}{\sigma_0} \right)^{1/2} \right]^{-1}, \quad (48)$$

where

$$\eta_{\text{ext}} \equiv \frac{9}{8} \frac{\eta_0}{(\varphi_m/\varphi_{\text{ext}})^{1/3} - 1},$$

η_{ext} and φ_{ext} are, respectively, the viscosity and concentration of the suspension that fills the space between aggregates.

At low shear rates $\dot{\epsilon}$, Eqn (48) takes the form

$$\frac{\eta_{\text{ef}}}{\eta_{\text{ext}}} \approx 17 \frac{1 - \varphi_m}{\varphi_m - \varphi} \frac{\kappa \sigma_0}{|\rho - \rho_0| R A \omega^2}. \quad (49)$$

The influence of the particle surface modification with surfactants can be taken into account by varying the parameters U_a , h_1 and κ in Eqns (44)–(49).

Analysis of the resulting equations and their comparison with experimental data showed that the plot of the viscosity η_{ef} vs. the vibration intensity $I = A^2 \omega^3$ is characterised by the presence of the following two regions. At small values, the viscosity is calculated according to Eqns (44) and (45). At large values, the viscosity is calculated from to Eqns (48) and (49). These regions are associated with different flow mechanisms: a flow with a continuous structure (a model of a homogeneous structure) and degradation of the structure into aggregates and individual particles (a model of finite aggregates). In the former case, the viscosity decreases exponentially with increasing vibration intensity due to destruction of a homogeneous system. In the latter case, a weaker (power) dependence is observed, which corresponds to the aggregation mechanism of destruction. Since the viscosity depends on $A\omega$ and $A\omega^2$ in the first and second segments of the curve, respectively, it is reasonable to use relatively low-frequency vibrations to perform destruction in the initial step, whereas higher-frequency vibration must be used to achieve deeper destruction giving rise to aggregates. Vibration makes it possible to eliminate the segment of abnormally high viscosities at low shear rates in the rheological curve, in particular, to provide fluidity at shear stresses much lower than the effective yield point.

The influence of orthogonal oscillations on a disperse system (chocolate, $T = 32^\circ\text{C}$) under shear is shown in Fig. 9.⁷⁸ Measure-

ments were performed on a MCR-500 rotational rheometer. The experimental data showed that the viscosity substantially decreases in a wide range of shear rates.

The addition of surfactants to disperse systems reduces the lyophilic–lyophobic surface mosaicity of particles and favours a decrease in the viscosity in all regions, the general view of the rheological curve remaining unchanged (Fig. 10). Analysis of the dependences presented in Figs 9 and 10 revealed the effect of vibro-dilatancy consisting of the increase in the viscosity with increasing shear rate under vibration. The mechanism of this effect associated with the change in the structure of the flow remains unclear.

A high degree of deformation homogeneity can be achieved using vibration along with a decrease in the viscosity of a structured suspension due to ‘healing’ of discontinuities.⁴¹ Hence, vibration (particularly, combined with the addition of surfactants) can be considered as a universal tool for controlling the rheological properties of disperse systems.

An interesting synergism was observed under the combined action of different types of vibrations and surfactants on disperse systems. It was demonstrated⁷⁹ that low-frequency mechanical vibrations combined with high-frequency ultrasonic vibrations (60 Hz and 22 kHz, respectively) provide a higher degree of microstructure homogeneity of experimental samples (epoxy-based composite materials were examined as the samples). The possibilities of controlling the properties of disperse systems with the use of surfactant mixtures are much wider than those with individual surfactants. The colloid-chemical properties of aqueous solutions of high- and low-molecular-weight surfactants, viz., propanol 228 and sodium alkylbenzenesulfonate, respectively, and their 1 : 1 mixture were investigated.⁸⁰ The surfactant properties of the mixture were demonstrated to be more pronounced than the properties of the individual surfactants. Besides, the use of the mixture ensures higher aggregation stability of the system. Therefore, a combination of high- and low-molecular-weight surfactants results in the effect that is not observed in the case of individual surfactants.

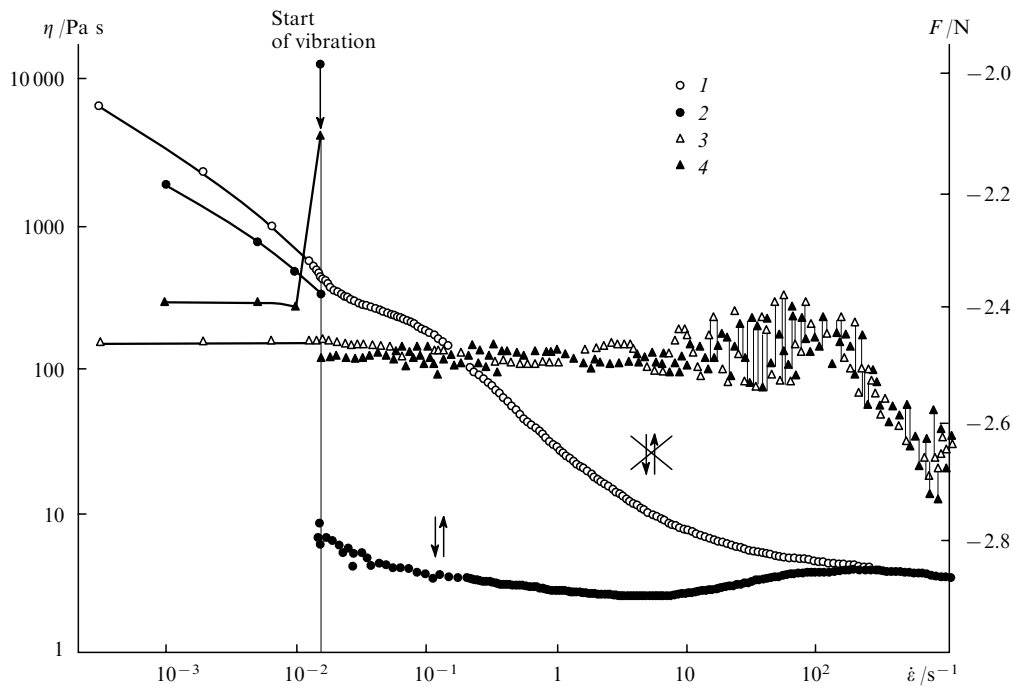


Figure 9. Changes in the shear viscosity (1, 2) and the normal force (3, 4) (chocolate, $T = 32^\circ\text{C}$, a MCR-500 rotational rheometer) under orthogonal oscillations.⁷⁸

(1, 3) Without vibration; (2, 4) under vibration ($\nu = 60\text{ Hz}$, $A = 0.5\text{ mm}$).

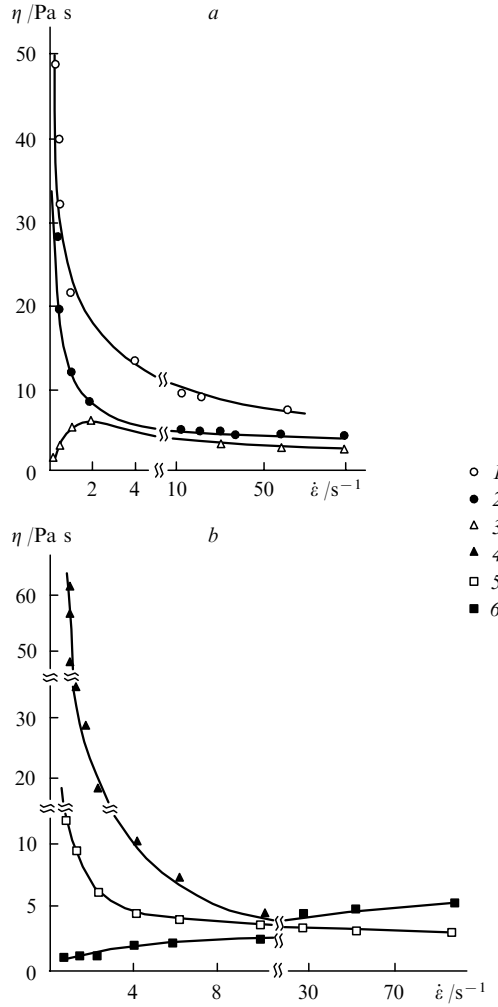


Figure 10. Changes in the rheological curves of water–coal suspensions in the presence of surfactants and under vibration based on brown coal from the Moscow Coal Basin with $\phi = 41\%$ (a) and thermal coal from the Belovskii deposit with $\phi = 72.5\%$ (b).³

(1, 4) In the absence of surfactants; (2) in the presence of potassium lignosulfonate (0.4%); (3) in the presence of potassium lignosulfonate combined with vibration, $\nu = 50$ Hz, $A\omega^2 = 10g$; (5) in the presence of the condensation product of naphthalenesulfonic acid and formaldehyde (1%); (6) with the same additive as that used in 5 combined with vibration, $\nu = 50$ Hz, $A\omega^2 = 2.5g$.

The resistance of structured disperse systems to vibration and the knowledge of conditions under which destruction becomes impossible are of considerable importance. These problems were examined⁸¹ by analysing vibrations of a particle caused by oscillations of the fluid in a potential well in the vicinity of an equilibrium state. The equation for forced vibrations of a particle oscillator near equilibrium takes the form⁸²

$$\frac{\partial^2 x_{ij}}{\partial t^2} + 2\lambda_i \frac{\partial x_{ij}}{\partial t} + \omega_i^2 x_{ij} = \frac{F_j}{m} \sin \omega t, \quad (50)$$

where x_{ij} is the displacement of the particle from the equilibrium position, $i = 1$ and 2 correspond to the long- and short-range coagulation, respectively, $j = 1$ and 2 correspond to different calculation methods of the force F_j , $\lambda_i \sim z\eta_0 r^2/(H_i m)$, z is the coordination number, r is the particle radius, H_i is the distance which corresponds to the long- and short-range coagulation, m is the particle mass and ω_i is the eigenfrequency of vibrations of the particle.

The law of forced vibrations of a particle was derived from the equation of motion (50)⁸²

$$x_{ij}(t) = b_{ij} \sin(\omega t + \psi_i),$$

where

$$b_{ij} = \frac{F_j}{m[(\omega^2 - \omega_i^2)^2 + \lambda_i^2 \omega^2]^{1/2}},$$

ψ_i is the phase difference between the vibrations of the particle and the fluid.

The particle can escape from a potential well when exposed to the force F_j , if one of the following inequalities is fulfilled:⁸¹

$$b_{ij} \gg H_i, \quad (51)$$

$$mb_{ij}^2 \omega^2 \gg U_i. \quad (52)$$

If inequality (51) is fulfilled, the particle will be displaced from the equilibrium position to a distance larger than the potential well width, *i.e.*, will go beyond the range of action of the surface forces. If inequality (52) is fulfilled, the particle will acquire an energy higher than the potential well depth U_i and move as though there were no surface forces, $\omega_i = 0$. In both cases, the particle breaks free of the bonds that hold it in the structure, *i.e.*, destruction occurs. Detailed analysis of the particular form of conditions (51) and (52) for various modes of estimation of the force F_j as applied to long- and short-range coagulation, respectively, was performed in the study.⁸¹

In the case of destruction of structured systems that hinder high fluidity of dispersions the inertial effects are of importance in achieving the isotropic dynamic state of solid/liquid (S/L) disperse systems. When moving in an oscillating fluid, the vibration amplitude of the particle does not necessarily coincide with the vibration amplitude of the fluid. This effect becomes more pronounced as the particle mass increases, the oscillation frequency of the fluid increases or the viscosity of the fluid decreases. Under steady-state vibration mode, the proportionality coefficient β between the vibration amplitudes of the fluid (A) and the particle (A_p)

$$A_p = \beta A$$

is calculated according to the equation⁸³

$$\beta = \frac{\lambda}{(1 + \lambda^2)^{1/2}},$$

where

$$\lambda = \frac{9\eta_0}{\pi d^2 \rho \nu},$$

ν is the vibrational frequency of the liquid in Hz.

The coefficient β is essentially the criterion that indicates whether destruction and deaggregation can occur in a suspension. Destruction can take place if the particles that form the system are characterised by different values of coefficient β . The wider is the range of variations in β , the faster and more efficient is destruction. This condition means that only polydisperse systems with a wide range of variations in the particle size can undergo destruction in a suspension of rigid spheres under vibration. In this case, particles with different masses oscillate with different amplitudes due to which the particles are displaced with respect to each other resulting in destruction.

It should be noted that A_p are the amplitudes of free (*i.e.*, non-interacting) particles. The real amplitudes can be lower than A_p if there are interactions between the particles. This means that the above criterion provides evidence only for the possibility of destruction of structured components. Structural stability determined by interparticle forces is responsible for whether or not destruction will occur. To overcome these forces, it is necessary that the energy supplied under vibration be sufficient for cleavage of coagulation contacts [see Eqns (51) and (52)]. In other words,

this criterion describes the conditions necessary but insufficient for destruction of S/L disperse systems.

Undoubtedly, destruction and deaggregation under vibration depend on the degree of anisometry of the particles involved in the structures and aggregates. The value and character of the hydrodynamic forces acting on the particles depend substantially on their shape. At high anisometry, not only relative displacements of particles but also their more complicated translational-rotational motions take place resulting in faster deaggregation.

It is known that the presence of a surfactant layer on the particle surface leads to an increase in aggregation stability of disperse systems due to high viscosity, mechanical strength of the absorption layer and lyophilicity of its outer surface. Based on these facts, the structural-mechanical barrier is considered as one of factors stabilising disperse systems under static conditions.^{34, 84} However, stability of systems under dynamic conditions is of particular importance and there is a need for a theoretical description of the parameters and prerequisites for the appearance of the structural-mechanical barrier in the dynamic state. The processes that occur in adsorption layers on the surface of the particles during their high-speed collisions were analysed.⁸⁵ The layers are characterised by the viscosity coefficient η_l and the modulus of elasticity E_l . It was noted that the breakdown of an adsorption layer can take place at a rather high velocity of approach of particles to each other V_s . The breakdown occurs if the mechanical stress in the layer is comparable to the strength of the layer p_l . The inertial breakdown, *i.e.*, the breakdown due to the kinetic energy of particles received from an external source, was considered. Under these conditions, the viscous properties of the layer at particle velocities close to breakdown values can be ignored because the collision time is much shorter than the relaxation time (the time of elastic after-effect) $\tau_r \sim \eta_l/E_l$. In this case, the layer behaves as a purely elastic layer.

A quantitative expression for the criterion for the layer breakdown can be derived by comparing the kinetic energy $\Delta\epsilon_k$, which is received by particles from an external source, with the sum of the elastic energy $\Delta\epsilon_{ei}$, which can be accumulated in the layer without destruction, and the energy $\Delta\epsilon_{hi}$ dissipated for viscous friction as the surfaces approach each other.

The breakdown criterion is determined by the inequality

$$\Delta\epsilon_k > \Delta\epsilon_{ei} + \Delta\epsilon_{hi}. \quad (53)$$

According to the results of the study,⁸⁵ the terms in this inequality can be estimated according to the formulas

$$\begin{aligned} \Delta\epsilon_k &\sim \frac{2\pi}{3} r^3 \rho V_s^2, \\ \Delta\epsilon_{e1} &\sim E_l L^2 r_1 \left(\frac{p_l}{E_l}\right)^3, \\ \Delta\epsilon_{e2} &\sim E_l L^2 r_2 \left(\frac{p_l}{E_l}\right)^3 \left(\frac{r}{r_2}\right)^{3/2}, \\ \Delta\epsilon_{hi} &\sim \int_L^{h_{0i}} F_i dh. \end{aligned} \quad (54)$$

Here $r = [3m/(4\pi\rho)]^{1/3}$ is the linear size of anisometric particles (m is the particle mass and ρ is the particle density), L is the thickness of the adsorption layer, r_1 is the local curvature radius of the particle surface for angular collisions ($i = 1$), r_2 is the curvature radius of the lateral surface of disk-like particles ($i = 2$), h_0 is the initial distance between the particles and F_i is the hydrodynamic drag force when the particles approach each other

$$F_i \approx 6\pi\lambda_i\eta_l \frac{V r_i^2}{h}, \quad (55)$$

where $\lambda_1 = 1$, $\lambda_2 = 2(r/r_2)^{3/4}$.

Using relations (54) and (55), let us rewrite the criterion (53) as follows

$$V_s^2 - 9 \frac{\eta_l}{\rho r} \left(\frac{r_i}{r}\right)^2 \lambda_i \ln\left(\frac{h_{0i}}{L}\right) V_s - \frac{E_l}{2\rho} \left(\frac{L}{r}\right)^2 \frac{r_i}{r} \lambda_i^2 \left(\frac{p_l}{E_l}\right)^3 > 0. \quad (56)$$

This expression corresponds to the general criterion for the loss of aggregation stability under dynamic conditions. The structural-mechanical barrier is an essential factor of stability of dynamic systems, if the thickness of the layer and its modulus of elasticity are rather large. At low values of these parameters, particles are prevented from approaching each other only by hydrodynamic forces, and the minimum breakdown velocity of the layer is independent of the thickness and the modulus of elasticity of the layer.

Inertial coagulation is most probable for anisometric particles, *i.e.*, the creation of a structural-mechanical barrier in dynamics can be used as an efficient way of stabilising real disperse systems. It should be noted that the electrostatic factor is of lesser importance in dynamic systems compared to static systems.⁸⁶

In Section II, we have reviewed the most widely used rheological models of S/L disperse systems and some conclusions and criteria that are based on theoretical analysis of these models. However, the dynamic properties of disperse systems cannot be studied only by analytical methods because of their complexity. It is necessary to use calculation methods and computer simulation to understand the true mechanisms of many phenomena under particular conditions. Below we consider such methods, discuss the possibilities of computer simulation of disperse systems and summarise most characteristic results obtained with the use of these methods.

III. Computer simulation of disperse systems

1. Computer simulation methods for disperse systems

Let us consider approaches to computer simulation of disperse systems at different length scales and the corresponding numerical methods.

Three most important length scales are used in studies of colloidal suspensions (Fig. 11): the microscopic or atomic-molecular level, the mesoscopic level characterised by lengths of the order of colloidal particle size and the macroscopic level where suspensions are considered as a homogeneous fluid. Since the length scales corresponding to these levels differ by several orders of magnitude, it is impossible to perform simultaneous simulation of a suspension at all levels. Each simulation method is, as a rule, intended for the use at a particular level.

Simulations at the atomic-molecular level are carried out with the use of the molecular dynamics method (non-equilibrium molecular dynamics), in which the trajectories of the motion of molecules are calculated taking into account intermolecular forces based on Newton's laws. This method was developed about 50 years ago and was considered in numerous publications (for example, the description of this method has been given in the publications^{88–95}). However, the molecular dynamics method is very time consuming. To perform relatively reliable calculations of the fluid bulk properties with the use of this method, it is necessary to simulate systems containing more than 10^9 particles.⁹¹

The Monte Carlo method can serve as an alternative to the molecular dynamics method in simulations of equilibrium states of systems. The characteristic feature of the Monte Carlo method is its stochastic nature (strictly deterministic equations are used in the molecular dynamics method). In simulations of multiparticle systems, various modifications of the Monte Carlo method are used.^{95–100} The essence of the simplest modification is that all particles of the system are alternately subjected to random displacements. After each displacement, the system is tested to ensure whether the whole system satisfies a particular criterion and, if not, a new random displacement is done. After a rather large number of steps, the method gives an equilibrium configuration of particles, which best satisfies the desired criterion (the total energy of the system is generally used as this criterion).

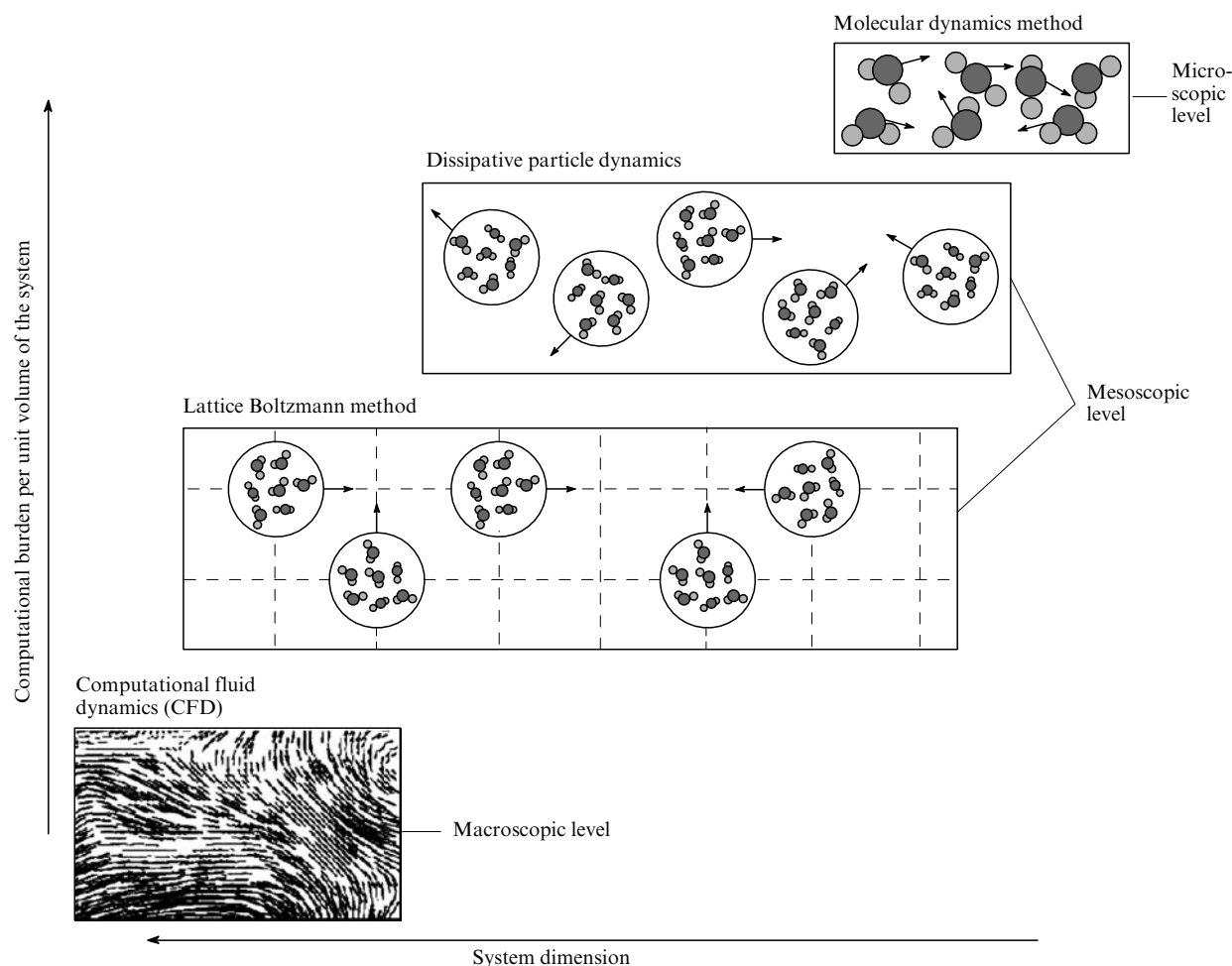


Figure 11. Scheme illustrating the applicability of different approaches to computer simulation of disperse systems at different length scales and the numerical methods used.⁸⁷

Although the Monte Carlo method works faster than the molecular dynamics method, it is unlikely that this method can be used for the description of dispersion flows because it completely ignores the dynamics of the system under consideration.

It is difficult to simulate the behaviour of dispersed particles suspended in a medium of fluid molecules by the molecular dynamics method because it requires a large volume of calculations. To calculate the motion of even one dispersed particle, it is necessary to take into consideration collisions of this particle with at least several thousand 'background' molecules. Moreover, the time of particle–molecule collisions τ_{pm} ($\sim 10^{-9}$ s) is several orders of magnitude shorter than the time of particle–particle collisions τ_{pp} ($\sim 10^{-4}$ s). This means that detailed simulation of a suspension consisting of at least 1000 particles for a time much longer than τ_{pp} requires the use of a giant number of model units and an unrealistic number of iterations.

Brady has demonstrated¹⁰¹ that the time required for calculations of particles suspended in a fluid with the use of this method increases proportionally to the sixth power of the ratio of the particle size to the molecule size. Even for nanoparticles the sizes of which are larger than those of the fluid molecules by only a factor of 10, the time consumed for calculations increases billion-fold. Nevertheless, if simulations are performed for a period of time comparable to τ_{pp} , the use of this method, though being time consuming, is practically possible. However, in most cases, information on the motion of each fluid molecule seems to be excessive in simulation of suspensions because the parameters of the behaviour of particles in suspensions are determined primarily

by the macroscopic characteristics of the medium (viscosity, density, flow rates, *etc.*). In this connection, simulations are performed with the use of a continuous homogenous medium with specified macroproperties instead of the fluid molecules. In this case, interactions between particles are determined not only by molecular attraction and electrostatic repulsion but also by hydrodynamic forces transmitted through the fluid.

For small particle sizes ($< 1 \mu\text{m}$), thermal fluctuations of fluid molecules cause Brownian motion, which, after the replacement of fluid molecules by a continuous medium, can be represented as the result of action of a random force that obeys particular statistical regularities (Brownian dynamics^{102–104}). Since the motion of particles generally occurs at low Reynolds numbers ($\text{Re} = \rho v / \eta_0 \ll 1$, where v is the velocity of particles), hydrodynamic interactions are described by the linearised Navier–Stokes equations known simply as the Stokes equations. The corresponding simulation method is called the Stokesian dynamics.^{105–107} This method is used for suspensions of particles with a wide range of sizes ($10^{-8} - 10^{-3}$ m). The only limitation is that the sizes of dispersed particles should be larger than the sizes of fluid molecules to an extent that the medium can be considered as continuous, and the Reynolds number should be low.¹⁰¹

A family of methods, which treat fluids neither at the molecular level nor as a continuous medium but as a medium consisting of particles with sizes larger than the sizes of individual molecules, occupies an intermediate place between molecular and Stokesian dynamics. In these methods, the motion of particles obeys the law of momentum conservation. This law is at the basis

of the Navier–Stokes equations. As a result, the hydrodynamically plausible motion of the fluid is provided without the direct solution of these equations. Of these methods, dissipative particle dynamics^{108–112} and the lattice Boltzmann method^{113–122} are most widely used. The advantage of these methods is that they are less time consuming than the molecular dynamics method (in some cases, than the Stokesian dynamics as well) and yet adequately reproduce hydrodynamic effects. It should be noted that these methods are based on continual equations of a continuous medium, fluid particles serving as discrete elements, due to which the equation in terms of partial derivatives can be reduced to the difference system of ordinary differential equations. These methods are essentially continual and their discreteness is purely computational. To the contrary, the molecular dynamics method is based on the equations of motion of particles/molecules (ordinary differential equations) determined by the balance between the quantity of motion and the interaction potential between particles, *i.e.*, it is the true discrete method.⁶

One of the modern approaches to simulation at the macro-level, the so-called computational fluid dynamics (CFD), reproduces the behaviour of gas flows, Newtonian fluids and non-Newtonian fluids under different conditions. This extensively developed method was considered in numerous papers and monographs (see, for example, Refs 123–128), specialised journals and conferences. The detailed description of this method is beyond the scope of the present review. Let us only note that it is based on macroscopic equations (Navier–Stokes, *etc.*), whose solutions are sensitive to the boundary conditions. The available CFD program packages that implement numerical methods provide wide possibilities for solving problems of the dynamics of single-phase fluids, which are used in various fields of science and technology.¹²⁹ However, the application of these methods to simulation of suspensions presents difficulties because the boundaries move together with particles. These methods can be applied to systems composed of a small number of particles^{130, 131} having simple and symmetrical geometry.^{132, 133}

For this reason and also because the present review is devoted primarily to microrheological simulation, emphasis is given to methods oriented to simulation of suspension dynamics at micro- and mesoscopic levels. Let us briefly consider the mathematical backgrounds of some these methods.

a. Molecular dynamics method

The molecular dynamics method treats molecules and atoms as moving Newtonian particles. The equations of motion of classical mechanics for systems of interacting particles take the form

$$m_i \frac{d^2}{dt^2} x_i^{(\alpha)} = - \frac{\partial}{\partial x_i^{(\alpha)}} U(x_1^{(1)}, \dots, x_n^{(3)}), \quad (57)$$

where $\alpha = 1-3$; $i = 1, 2, \dots, n$, $x_i^{(\alpha)}$ is the α -component of the vector x_i of the position of the i th particle from the set n , $U(x_1^{(1)}, \dots, x_n^{(3)})$ is the potential energy of the system, which is calculated by summing the energies of interparticle interactions, which depend on the distances between pairs of interacting particles

$$U(x_1^{(1)}, \dots, x_n^{(3)}) = \frac{1}{2} \sum_{i \neq j} u(|x_i - x_j|).$$

An integration of the system of $3n$ equations of motion (57) with certain initial conditions gives the trajectories of particle motion. Particular (in the general case, arbitrary) coordinates and velocities of molecules are used as the initial conditions. In many cases, the velocities are chosen so that the total kinetic energy of the system corresponds to the given temperature. The density determined by the number of particles per unit volume can be used as another macroparameter. As a result of evolution, the system reaches an equilibrium state that depends on the temperature and the density, as well as on the interparticle interaction potential. The choice of the latter is of considerable importance because the

properties of the system strongly depend on this parameter. On the one hand, the potential should correspond well to the physical meaning of the model and, on the one hand, it should be convenient for calculations. The surface effects at the boundaries of the system can, to a certain degree, be compensated with the use of the so-called periodic boundary conditions: if the particle moves outside the computational space through the right boundary, it simultaneously enters the space through its left boundary. As a result, the density and energy of the system are retained. To eliminate interactions of the particle ‘with itself’, the pair interaction potential is cut at a particular distance from the particle.

b. Stokesian dynamics method

The Stokesian dynamics method has been proposed for the first time by Brady and Bossis.¹⁰⁵ According to this method, the motion of n undeformable particles suspended in incompressible Newtonian fluid is described in a vector form by the equation

$$\mathbf{m} \frac{d\mathbf{V}}{dt} = \mathbf{F}^h + \mathbf{F}^c. \quad (58)$$

Here $\mathbf{m}$ is the generalised mass tensor (the moment of inertia tensor) of particles, $\mathbf{V}$ is the vector of dimensionality $6n$ of the translational and rotational velocities of particles, $\mathbf{F}$ are the vectors of forces acting on the particles (moments of force) of dimensionality $6n$: $\mathbf{F}^h$ are the hydrodynamic dissipative forces caused by the motion of particles relative to the fluid and $\mathbf{F}^c$ are the conservative forces, which can be dispersion interaction forces of colloidal particles or external forces (for example, the gravity force).

At low Reynolds numbers ($Re \ll 1$), it is assumed that the hydrodynamic forces linearly depend on the velocities of particles

$$\mathbf{F}^h = \mathbf{R}\mathbf{V}, \quad (59)$$

where $\mathbf{R}$ is the resistance tensor the elements of which characterise the influence of the medium on the particle.

In disperse systems consisting of particles with sizes of about 10^{-6} m (or smaller), the characteristic times of inertial displacements are very short. Hence, in some cases, the left-hand side of Eqn (58) can be ignored. Then the equation for the velocities of particles can be written as follows:

$$\mathbf{V} = -\mathbf{R}^{-1}\mathbf{F}^c. \quad (60)$$

To calculate the velocities (and positions) of particles, a matrix inverse to $\mathbf{R}$ must be calculated in each step. Since the time consumed for the inversion of the resistance tensor increases proportionally to n^3 , this operation is one of the main limitations in simulations of systems with a large number of hydrodynamically interacting particles. A simplified modification of the Stokesian dynamics can be used¹⁰⁷ to increase the efficiency of calculations. This method allows simulations of motion of highly concentrated suspensions in a shear flow. At high concentrations, the components in the resistance tensor responsible for long-range hydrodynamic interactions can be ignored due to a small gap between the particles. As a result, the matrix $\mathbf{R}$ becomes sparse and contains only components of short-range hydrodynamic interactions, which are calculated from the lubrication theory. This substantially simplifies the inversion of the matrix and results in proportionality between the calculation time and the square of the number of particles, due to which calculations of systems with much larger n become possible. To reveal the nearest neighbours of the particle, Voronoi and Delaunay tessellations were used.¹⁰⁷ In this approach, the space is partitioned into regions within which all points are closer to a particular point than to any of the other points (Fig. 12). This region is called the Voronoi region and it represents a convex polyhedron and a convex polygon in a three- and two-dimensional space, respectively. The Voronoi and Delaunay tessellations are widely used in simulations of ensembles of discrete particles arbitrarily arranged in the space. A detailed description of this geometric method was presented and the

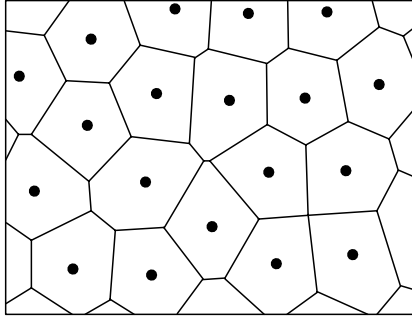


Figure 12. Voronoi tessellations of a point centre system in the plane.¹³⁴

possibility of its application to the solution of particular physicochemical problems was considered in a monograph.¹³⁴

In other modifications of the Stokesian dynamics, the Stokes law for an individual particle is used. It should be noted that this is valid only for low-concentrated suspensions.

The thermal motion of particles is described by the Brownian dynamics method. The stochastic force $\mathbf{F}^B$ responsible for the Brownian motion is added to the right-hand side of Eqn (58). In this case, the equation for the velocity of particles (60) takes the form

$$\mathbf{V} = -\mathbf{R}^{-1}(\mathbf{F}^c + \mathbf{F}^B). \quad (61)$$

The force $\mathbf{F}^B$ is chosen so as to fulfill the following conditions:

$$\langle \mathbf{F}^B \rangle = 0, \quad (62)$$

$$\langle \mathbf{F}^B(0)\mathbf{F}^B(t) \rangle = 2k_B T \delta(t) \mathbf{R},$$

where the angular brackets indicate the averaging over the total ensemble of particles and δ is the Dirac delta function.

The first condition means that the total result of the random Brownian forces is equal to zero. The second condition reflects the correlation between the random force at points of time 0 and t , which follows from the fluctuation-dissipative theorem of statistical physics. This condition is also indicative of the relationship between the Brownian and hydrodynamic forces, thus underlining their common nature.

The colloidal component of the force $\mathbf{F}^c$ in Eqn (58) is a combination of the molecular attractive and electrostatic repulsive forces. At moderate concentrations of particles and at their moderate velocities, this component can be determined by summing the pair interaction potentials of particles based on the Deryaguin–Landau–Verwey–Overbeek (DLVO) theory.^{36, 37}

c. Dissipative particle dynamics

The dissipative particle dynamics method has been proposed in the studies.^{108, 109} As mentioned above, this method is based on the representation of a fluid as a combination of hypothetical particles at a supramolecular level (dissipative particles), the motion of which occurs according to the laws of classical mechanics under the action of conservative, dissipative and random forces⁹⁵

$$\mathbf{F}_i = \sum_{j \neq i} [\mathbf{f}^c(\mathbf{r}_{ij}) + \mathbf{f}^d(\mathbf{r}_{ij}, \mathbf{V}_{ij}) + \mathbf{f}^r(\mathbf{r}_{ij})], \quad (63)$$

where $\mathbf{F}_i$ is the total force acting on the i th particle.

At first glance, this method is similar to the Brownian dynamics method. The radical difference is that Eqn (63) corresponds to forces acting on fluid particles rather than on dispersed particles.

The conservative force $\mathbf{f}_{ij}^c$ can be obtained, for example, from the interaction potential between the particles i and j . The dissipative force $\mathbf{f}_{ij}^d$ corresponds to the friction force that depends on the relative velocities of particles,

$$\mathbf{f}_{ij}^d(\mathbf{r}_{ij}, \mathbf{V}_{ij}) = -\gamma \omega^d(\mathbf{r}_{ij})(\mathbf{V}_{ij} \mathbf{e}_{ij}) \mathbf{e}_{ij},$$

where $\mathbf{r}_{ij} = \mathbf{r}_i - \mathbf{r}_j$, $\mathbf{V}_{ij} = \mathbf{V}_i - \mathbf{V}_j$, γ is the coefficient that controls the friction force, the function $\omega^d(\mathbf{r}_{ij})$ describes the change in the friction coefficient with distance and $\mathbf{e}_{ij}$ is the unit direction vector $\mathbf{r}_{ij}$. The random force $\mathbf{f}_{ij}^r$ is described by the equation

$$\mathbf{f}_{ij}^r(\mathbf{r}_{ij}) = \sigma \omega^r(\mathbf{r}_{ij}) \xi_{ij} \mathbf{e}_{ij}.$$

Here σ determines a random pair interaction force, the function $\omega^r(\mathbf{r}_{ij})$ describes the change in the random force with distance, ξ_{ij} is a random value characterised by the normal distribution law and the unit variance, $\xi_{ij} = \xi_{ji}$.

The parameters γ and σ and the functions $\omega^d(\mathbf{r}_{ij})$ and $\omega^r(\mathbf{r}_{ij})$ are specified so as to fulfill the following conditions:⁹⁵

$$\omega^d(\mathbf{r}_{ij}) = [\omega^r(\mathbf{r}_{ij})]^2,$$

$$\sigma^2 = 2k_B T \gamma.$$

Dissipative particles that move under the action of these forces interact with colloidal particles according to the mechanics laws thus providing their displacement and simulating the hydrodynamic and Brownian effects. Another essential difference between this method and the Brownian dynamics is that calculations according to the method under consideration ignore the momentum conservation in the system. In this case, the number of particles in the system is virtually the only unchangeable parameter. The equations of dissipative particle dynamics are written so as to provide the automatic fulfillment of the momentum conservation law, thus imparting the hydrodynamically realistic (satisfying the Navier–Stokes equation) behaviour to the system over rather wide time and space scales.

Consequently, the dissipative particle dynamics method makes it possible to go to the macroscopic level of pure fluids due to which certain properties of fluids (for example, the viscosity^{110, 111}) can be calculated. Usually, dissipative particles are considered as spheres with fixed diameters and masses. However, Flekkoy and Coveney¹¹² suggested that the dissipative particle dynamics method be extended to the microscopic level by identifying dissipative particles with the Voronoi polyhedra of different sizes (Fig. 13). The Voronoi tessellation of dissipative particles based on the configuration of a system makes it possible to allocate computational burden depending on the required degree of detailing (a higher degree is required in narrow channels between colloidal particles than in the fluid bulk). This increases the flexibility and efficiency of the method and makes it possible to

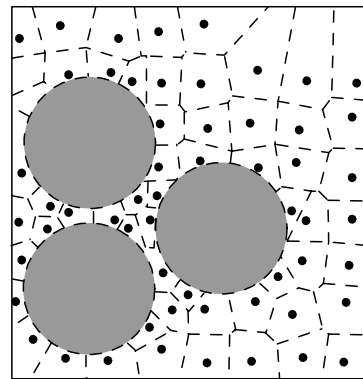


Figure 13. Scheme illustrating the applicability of the Voronoi tessellation in the dissipative particle dynamics method.¹¹²

Dissipative particles are identified with Voronoi regions. Four different length scales are presented: the scale of large colloidal particles, two scales of dissipative particles (between colloidal particles and in the fluid bulk) and the particle scale of the molecular dynamics method (solid points); the boundaries between dissipative particles are calculated depending on the arrangement of these scales.

apply this method to simulations of systems of concentrated suspensions, polymer solutions and flows in porous media with complex geometry on different length scales.

d. Lattice Boltzmann method

Among methods that are also based on the representation of fluids as discrete particles, the lattice Boltzmann method is worthy of note. In recent years, this method has been widely used for simulating hydrodynamic interactions in colloidal dispersions¹¹³ and was described, for example, in the publications.^{114–116} It belongs to the family of lattice methods and is based on the lattice gas model,¹¹⁷ in which the space filled with a gas or fluid is divided into regions using a regular lattice. The motion of a fluid is described by the dynamics of hypothetical particles of unit mass, which are transferred, with certain probability, to the adjacent sites along the links of a fixed lattice (Fig. 14). In the sites, particle collisions take place. The collisions are considered taking into account the conservation laws. The time and space averages satisfy the Navier–Stokes equation. The advantage of the lattice gas method is its stochastic nature, which, however, is responsible for its main drawback, *viz.*, a high noise level.

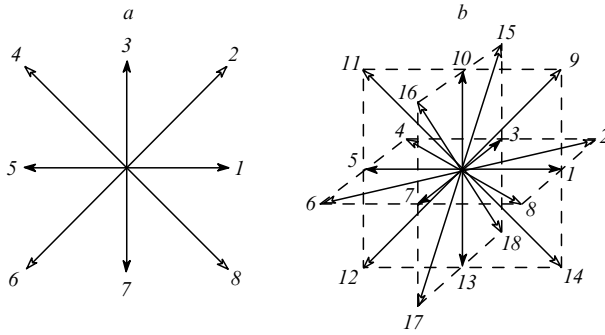


Figure 14. Possible displacements of a particle to the adjacent sites of two-dimensional (a) and three-dimensional (b) lattices. (1–18) are the numbers of the positions. The diagonal directions are indicated by empty arrows. The vertical and horizontal directions are marked by solid arrows.

This method can be improved by using the Boltzmann equation for the description of lattice gases. In the relaxation time approximation, this equation takes the form

$$\frac{\partial}{\partial t} f(\mathbf{r}, \mathbf{v}, t) + \mathbf{v} \cdot \nabla f(\mathbf{r}, \mathbf{v}, t) = -\frac{1}{\tau} [f(\mathbf{r}, \mathbf{v}, t) - f^{\text{eq}}(\mathbf{r}, \mathbf{v}, t)]. \quad (64)$$

Here $f(\mathbf{r}, \mathbf{v}, t)$ is the Maxwell–Boltzmann distribution function, $f^{\text{eq}}(\mathbf{r}, \mathbf{v}, t)$ is the equilibrium distribution function and τ is the relaxation time of the system due to particle collisions.

The Boltzmann equation can be transformed into the Navier–Stokes equations using the Chapman–Enskog expansion of Eqn (64). The Boltzmann equation for an incompressible Newtonian fluid can be solved in different ways with the use of lattice partitions. In the simplest modification of the lattice Boltzmann method, the summation in the lattice gas model is over particles, resulting in the replacement of this parameter with the density $f_i(\mathbf{r}, t)$ of particles with velocities $\mathbf{c}_i$ in this region of the lattice. The velocities $\mathbf{c}_i$ are chosen so that a particle can either move to the adjacent lattice site during the time Δt or stay in its initial position. The mass and momentum conservation laws must be fulfilled. In this case, the main hydrodynamic parameters, by analogy with the parameters of the kinetic gas theory, are the moments of different orders of a random value $\mathbf{c}_i$. For example, the local fluid density is the zero-order moment

$$\rho(\mathbf{r}, t) = \sum_i f_i(\mathbf{r}, t);$$

the local momentum density is the first-order moment

$$\rho \mathbf{v} = \sum_i f_i(\mathbf{r}, t) \mathbf{c}_i;$$

the momentum flux is the second-order moment

$$\Pi = \sum_i f_i(\mathbf{r}, t) \mathbf{c}_i \mathbf{c}_i.$$

Calculations of the displacements of particles can be substantially simplified by linearising the collision operator (the function that relates the state of the lattice node before a collision to its state after the collision) in the deviation of the particle density from its equilibrium value. The best form of the operator for this type of collision was proposed by Bhatnagar, Gross and Krook (BGK)¹¹⁸ and it provided the basis of the corresponding BGK models:¹¹⁹

$$f_i(\mathbf{r} + \mathbf{c}_i, t + 1) = f_i(\mathbf{r}, t) + \frac{1}{\tau} [f_i^{\text{eq}}(\mathbf{r}, t) - f_i(\mathbf{r}, t)] + \mathbf{F}. \quad (65)$$

Here $\mathbf{F}$ is an external force acting on a fluid (the mechanical force, the force of gravity, *etc.*). In Eqn (65), the unit time step was accepted, $\Delta t = 1$.

One of the possible ways of describing solid particles suspended in a fluid in terms of the lattice Boltzmann method is as follows.^{120, 121} In a particle placed on a lattice, internal and boundary nodes are distinguished (Fig. 15). The node is considered as a boundary node if it shares at least on edge with nodes surrounding the fluid particle. For simplicity of calculations, it is sometimes assumed that the particle is filled with a hypothetical fluid. The collision operator is used for each node, including the boundary and internal nodes of the particle. The condition of the absence of sliding at the L/S interface in this method is generally fulfilled due to ‘bounce-back’ of fluid particles from the surface of colloidal particles with momentum conservation. The concept of the bounce-back of particles can be extended to the moving colloidal particles^{120, 121}

$$f_i(\mathbf{r} + \mathbf{c}_i, t + 1) = f_{i'}(\mathbf{r} + \mathbf{c}_i, t_+) + 2\rho_f B_i (\mathbf{v}_w \mathbf{c}_i), \quad (66)$$

where t_+ is the time immediately after a collision, i' is the lattice link, which is a direction of bounce-back, B_i are the coefficients that depend on the lattice partition, ρ_f is the fluid density, $\mathbf{v}_w$ is the velocity of the wall (the surface of a colloidal particle) at a point $\mathbf{r}_w$, and the latter term characterises the momentum transfer between the fluid and the solid wall.

The velocity $\mathbf{v}_w$ is determined by the position of the centre of mass of the particle $\mathbf{r}_c$ and its linear ($\mathbf{V}$) and angular ($\boldsymbol{\omega}$) velocities.

$$\mathbf{v}_w = \mathbf{V} + (\mathbf{r}_w - \mathbf{r}_c) \times \boldsymbol{\omega}.$$

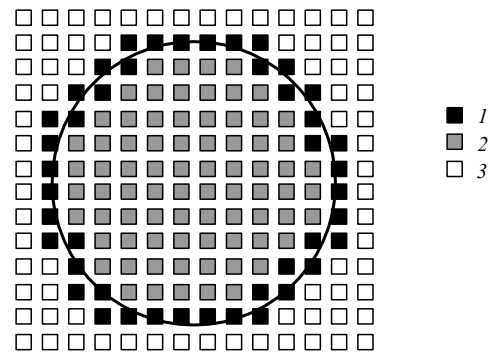


Figure 15. Schematic representation of a colloidal particle on a regular lattice.¹³⁵ (1–3) are the boundary, internal and external (with respect to the particle) lattice nodes, respectively.

The overall hydrodynamic forces and moments of forces acting on a solid particle from the fluid can be determined by summation of the effects calculated according to Eqn (66) over all boundary nodes of a solid particle in each time step. The result is the movement of this particle under the action of the above-mentioned forces according to Newton's laws.

Since the density of particles, unlike their number, is not a discrete parameter, solutions obtained by the lattice Boltzmann method are not exposed to fluctuations associated with discreteness of the number of particles. This is often an advantage of the method. However, in simulations of the Brownian motion, it is necessary to specify statistical deviations from the calculated positions. This can be done by introducing an additional random force into Eqn (65).¹²² On the whole, the lattice Boltzmann method provides a detailed description of the behaviour of a fluid and is efficient from a computational standpoint, due to which this can be successfully used in simulations of flows with complex geometry, *i.e.*, flows in porous materials, the dynamics of colloidal suspensions, *etc.*

In the next Section, we consider selected results of computer simulation of the dynamics of S/L disperse systems obtained with the use of the above-mentioned methods.

2. Results of computer simulation of dynamics of disperse systems

In Russia, computer simulation of the suspension dynamics has been performed for the first time in 1999.¹³⁶ Dispersions of spherical quartz particles in water consisting of 100, 400 and 900 particles were examined. Only pair interactions of particles were taken into account. The interaction potential curve was constructed based on the DLVO theory. The simulation was performed by a simplified method of the Stokesian dynamics based on the Stokes law for a single particle. Under shear conditions, the formation of a region with a low concentration of a dispersed phase was observed. This was attributed to the formation of layers oriented along the shear direction in a suspension flow. Earlier, this phenomenon has been observed and studied experimentally. In subsequent studies, computer simulations of disperse systems under dynamic conditions were carried out by the authors of the present paper using simplified Stokesian dynamics method.

The behaviour of dispersions in a shear flow was simulated by specifying a constant shear gradient at which the velocity of a fluid increases in the vertical direction. Particles in a fluid flow experience the Stokes force (viscous friction) exhibited by the fluid due to which they move together with the flow. The inertia component of the resistance force caused by the fluid was taken into account through the particle effective mass including, along with the particle mass, the added fluid mass, which is equal (in the case of spherical particles) to one-half of the mass of the displaced fluid,

$$m_{\text{ef}} = m + \frac{\pi d^3 \rho_0}{12}.$$

The characteristics of the systems were as follows: $\eta_0 = 10^{-3}$ Pa s, $\rho_0 = 10^3$ kg m⁻³, $\rho = 2.6 \times 10^3$ kg m⁻³, $\phi = 20\% - 40\%$, $d = 5 - 100$ μm . The particle interactions were calculated by specifying a potential curve with two energy minima corresponding to long- and short-range coagulation. Since the particle sizes of the systems under consideration differ by at most two times, the interaction energy was taken to be equal for each pair of particles regardless of their sizes.

In simulations of the influence of the physicochemical inhomogeneity of the particle surface (its lyophilic–lyophobic mosaicity) on the character of flow of a disperse system, it was assumed that the lyophilic and lyophobic regions are uniformly distributed over the particle surfaces. The probability of the formation of a contact in a lyophilic region, which is proportional to the fraction of the lyophilic particle surface γ , was determined using a random number generator. Each time, interactions between two particles were calculated assuming the parameters

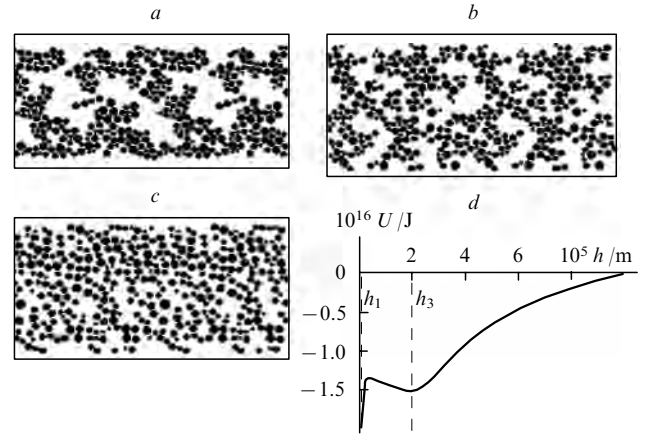


Figure 16. Flow of a disperse system with different degrees of lyophilicity (γ) of the particle surface (a–c) and the interaction curve of two lyophobic particles (d).

Parameters of the system: $n = 200$ particles; $\dot{\epsilon} = 40$ s⁻¹, $\phi = 40\%$; $d = 5 - 10$ μm ; $\gamma = 0$ (a), 50 (b), 100% (c).

of the potential curve corresponding to a lyophilic or lyophobic contact. Since the presence of lyophilic regions results in weakening of attractions between particles, an increase in the degree of lyophilicity of the surface leads to an increase in the aggregation stability of the system (Fig. 16).

Computer simulations of disperse systems under dynamic conditions revealed many features of their behaviour characteristic of this state. The formation of layers and particle aggregates in flows of disperse systems was confirmed. Destruction and deaggregation of such systems can be performed by supplying additional energy as external mechanical forces (for example, vibration). Orthogonal oscillations of particles of disperse systems occur through vibrations of a dispersion medium in the direction perpendicular to the flow direction. This type of vibration effects causes a sharp increase in the fluidity of dispersions by promoting degradation of structured components in a disperse system, thus noticeably increasing its shear viscosity.^{1–3}

All characteristic steps of formation of a layered structure in a dispersion flow are presented in Fig. 17. In the formation of layers oriented along the shear direction, long-range attractive forces that act on particles are of considerable importance. Numerical experiments showed that layered structures are not formed in systems consisting of particles with a weak force field effective at a

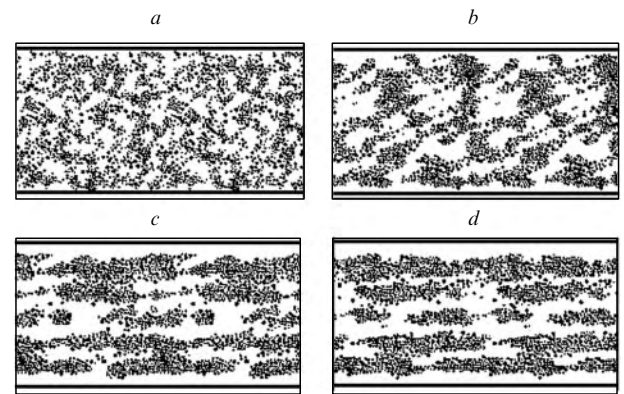


Figure 17. Sequence of the formation of a layered structure in a shear flow of a polydisperse system.

Parameters of the system: $n = 800$ particles; $\dot{\epsilon} = 85$ s⁻¹, $\phi = 35\%$; $d = 50 - 100$ μm ; the time after the start of flow /s: (a) 0, (b) 0.05, (c) 0.3, (d) 0.5.

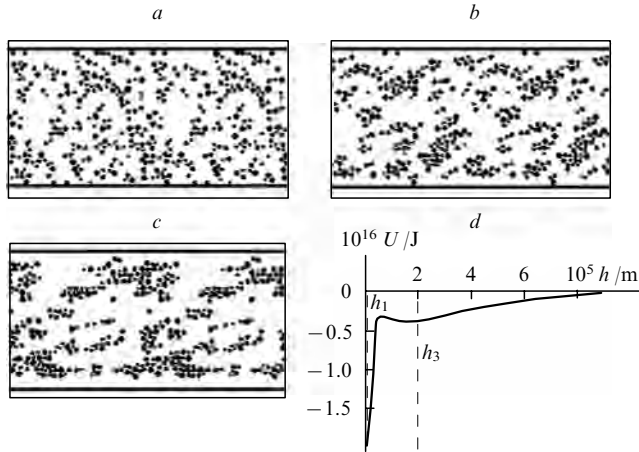


Figure 18. Illustration of the formation of aggregates in a dispersion flow due to dynamic coagulation of particles (a–c) and the interaction curve of two particles (d).

Parameters of the system: $n = 200$ particles; $\dot{\epsilon} = 50 \text{ s}^{-1}$, $\phi = 20\%$; $d = 50\text{--}100 \text{ }\mu\text{m}$; the time after the start of flow /s: (a) 0, (b) 0.1, (c) 0.2.

short distance; instead, a nearly isotropic dynamic state is reached in a flow or (in the case of a deeper short-range potential well) aggregation occurs due to dynamic coagulation of particles (Fig. 18). The formation of a layered structure is responsible for anisotropy of the viscosity along and across the shear flow (in the latter case, the viscosity can be substantially higher).

Computer simulations of destruction under vibration were performed for a disperse system with particle sizes from 50 to 100 μm . Such large particles (which are nevertheless able to form coagulation structures due to cohesion^{1,39}) were chosen because of the necessity to develop inertial effects under vibration, which cause displacements of particles relative to each other and lead to destruction. The results of calculations of inertial displacements of particles relative to the medium depending on the particle size and the vibrational frequency are given in Table 1.³⁹ It can be seen that the larger the particle size and the higher the vibrational frequency, the larger the difference in the vibrational amplitudes of the particles and the medium. This means that destruction of systems formed by particles of colloidal sizes can occur only under ultrasonic vibrations.

Table 1. Relative inertial displacements of solid-phase particles in a liquid dispersion medium depending on harmonic vibrational frequency and the particle size.³⁹

ν/Hz	Relative displacement at particle radii /m				
	10^{-5}	5×10^{-5}	10^{-4}	5×10^{-4}	10^{-3}
50	0.9999	0.9611	0.7933	0.4977	0.4869
100	0.9995	0.9002	0.6760	0.4903	0.4853
200	0.9982	0.7953	0.5849	0.4869	0.4846
300	0.9963	0.7240	0.5501	0.4859	0.4843
400	0.9938	0.6760	0.5325	0.4853	0.4842
500	0.9910	0.6423	0.5219	0.4850	0.4841
1000	0.9723	0.5642	0.5016	0.4844	0.4840

The harmonic oscillations of the fluid along the y direction were specified according to the law

$$y_f = A \sin \omega t,$$

where A is the vibrational amplitude, ω is the circular vibrational frequency and $\omega = 2\pi\nu$ (ν is the frequency in Hz).

In vibrations, the vibrational amplitude of a dispersion medium was 0.1 mm and the frequency was 100–200 Hz. The

choice of these parameters ensures a change in the ratio of the vibrational amplitudes of the particles and the medium for these vibrational frequencies in the ranges of approximately 1.0–0.7 and 0.9–0.5, respectively, thus providing conditions necessary for destruction.⁸³ However, the colloidal (surface) interaction forces of particles can be so large that the energy supplied by vibrations will be insufficient for destruction of structured ensembles in the dispersion.

As an example, the results of computer simulation of vibration effects on a disperse system under shear are presented in Fig. 19. It can be seen that the layered structure that is formed in a dispersion flow cannot be completely destroyed under vibrations of the medium. Moreover, in this case vibrations lead to coalescence of layers, *i.e.*, to the formation of larger structural inhomogeneities, which can apparently be accompanied by an increase in the shear viscosity of the disperse system. Presumably, this is one of the mechanisms of vibro-dilatancy, *viz.*, an increase in the dispersion viscosity under vibration.

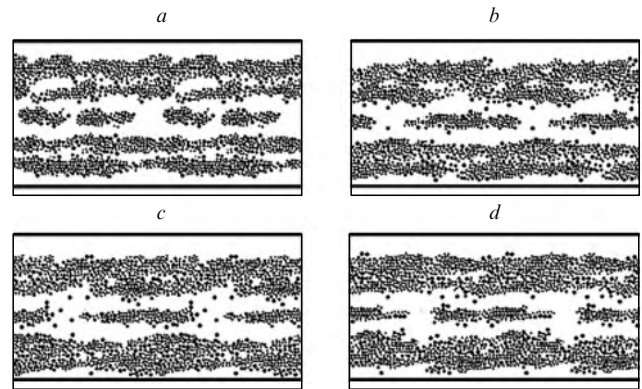


Figure 19. Changes in the layered structure under vibration.

Parameters of the system: $n = 800$ particles; $\dot{\epsilon} = 85 \text{ s}^{-1}$, $\phi = 35\%$; $d = 50\text{--}100 \text{ }\mu\text{m}$; the time after the start of vibration /s: (a) 0, (b) 0.05, (c) 0.1, (d) 0.2.

Vibrations also cause ‘grading’ of particles according to sizes (see Fig. 19). This phenomenon is easy to explain as follows. Large particles are grouped predominantly with large particles; small particles, with small. This is due to the fact that particles are characterised by different vibrational amplitudes: small particles go ahead, whereas large particles go behind, resulting in the separation of the dispersion into fractions. At the same time, the possibility of adhering the smallest particles to the surface of large particles cannot be ruled out, which follows from the DLVO theory.^{36,37}

As mentioned above, the surface modification with surfactants facilitates destruction of coagulation structures because it eliminates the lyophilic–lyophobic mosaicity of the surface. As a result, virtually complete lyophilisation is achieved and, as a consequence, interactions between particles are weakened. In addition, coating of the surface with a surfactant layer creates a structural-mechanical barrier, which hinders dynamic coagulation.^{1,34}

Simulations of surfactant-modified systems were carried out under the assumption that neither surfactant desorption from the surface nor mechanochemical destruction of surfactants under dynamic forces take place. It was assumed that uniform coating of the particle surface is provided by surfactant molecules with short hydrocarbon radicals or with the use of a mixture of low- and high-molecular-weight surfactants.

The changes in the microstructure of surfactant-modified disperse systems in a shear flow can be seen from Fig. 20. The formation of a surfactant layer on the surface and its lyophilisation are accompanied by changes in the shape of the potential

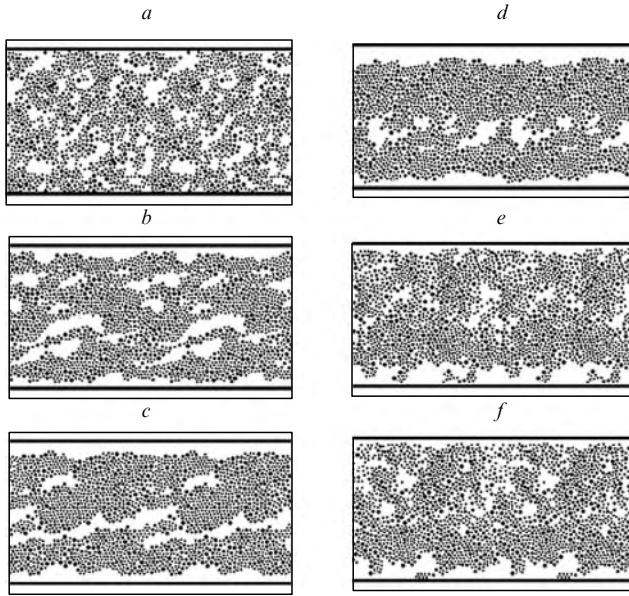


Figure 20. Formation (*a–c*) of an internal microstructure of a dispersion modified by treating the particle surface with surfactants and its destruction under vibration (*d–f*). Parameters of the system: $n = 800$ particles; $\dot{\epsilon} = 85 \text{ s}^{-1}$, $\varphi = 35\%$; $d = 50\text{--}100 \text{ }\mu\text{m}$.

curve of particle interactions, for example, by a decrease in the depth of potential wells. Besides, the presence of a structural-mechanical barrier can prevent particles from approaching each other to a distance at which a short-range potential energy minimum exist. In this case, we can say that the short-range potential well is absent. Under these conditions, coagulation structures can be formed only due to long-range coagulation contacts, resulting in a lower density and a larger looseness of layers and other structured components in the dispersion (see Fig. 20). Under external vibrations, coagulation structures in such systems are rapidly destroyed (see Fig. 20 *d–f*) and a nearly isotropic dynamic state is achieved.

The data presented in Fig. 20 (and partially in Fig. 19) suggest also that discontinuities, which accompany the formation of a layered structure, are healed due to vibrations.^{1,41}

The results of computer simulation of disperse systems under dynamic conditions confirm the above conclusion that surfactants combined with vibration create the desired synergetic effect. The use of the latter allows one to control the rheological properties of dispersions. This procedure can be used to perform isotropic destruction of coagulation systems accompanied by a decrease in the viscosity (an increase in the fluidity) of dispersions by several orders of magnitude.

Let us consider the results of computer simulation that demonstrate other possibilities of this method. Of a large number of publications on computer simulations of disperse systems, we discuss here studies most closely related to the problems under consideration.

The use of the full form of the Stokesian dynamics method in simulations of disperse systems provides a highly accurate description of the hydrodynamic effects, which however sharply increases the volume of calculations. In the studies,^{101,106} the behaviour of a system consisting of 27 solid particles in a fluid was described by the Stokesian dynamics. The authors compared the results of these calculations with the data obtained by Brownian dynamics simulations, where the hydrodynamic effects are ignored, and demonstrated that it is important to take into consideration hydrodynamic interactions. In both cases, calculations were carried out for suspensions of solid spheres at a concentration $\varphi = 45\%$ in a simple shear flow. The plots of the equilibrium shear

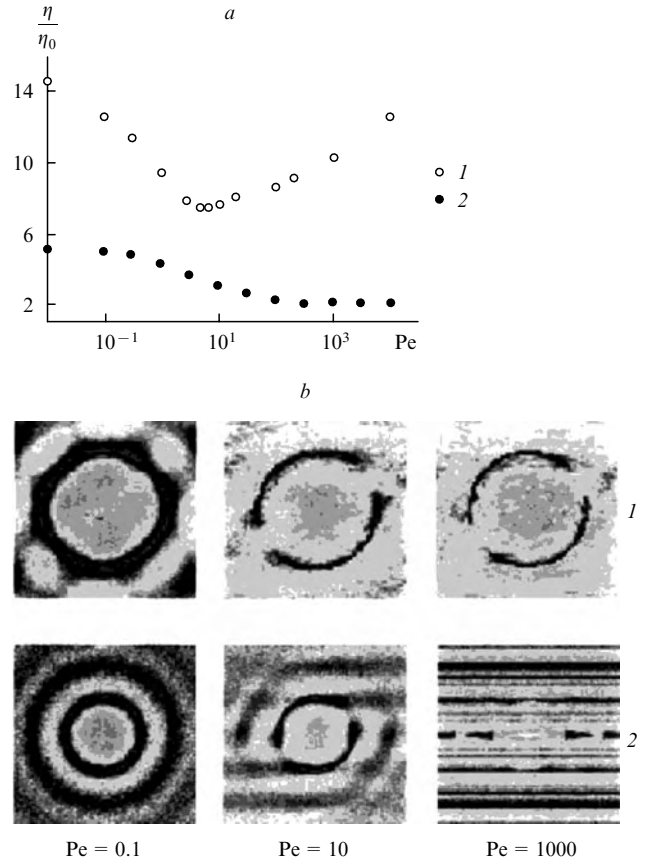


Figure 21. Computer simulation of changes in the viscosity (*a*) and the pair distribution function that characterises the microstructure of a suspension under shear (*b*).¹⁰¹ (1) Stokes dynamics, $n = 27$; (2) Brownian dynamics, $n = 1331$; $\varphi = 45\%$.

viscosity vs. the Peclet number are shown in Fig. 21 *a*. The viscosities were calculated by non-equilibrium statistical mechanics methods with the use of the Green–Kubo equation.^{92,137} It can be seen from Fig. 21 that the quantitative contribution of hydrodynamic interactions consists of an increase in the suspension viscosity. However, the qualitative difference, *viz.*, an increase in the viscosity at high shear rates (the dilatancy effect), is more important. The qualitative difference in the behaviour is associated with the shear-induced microstructure. The pair distribution functions of particles for three different shear rates (different Peclet numbers) are shown in Fig. 21 *b*. At small Peclet numbers, the microstructures formed in the presence of hydrodynamic interactions are similar to those formed in the absence of these interactions and are also similar to microstructures characteristic of fluids. Dark regions correspond to high probabilities of the presence of particles; light regions, to low probabilities. Rings corresponding to the nearest neighbours of the particle under consideration are clearly seen in the figure. The time necessary for calculations of a system consisting of 1331 Brownian particles is approximately equal to that necessary for calculations of a system consisting of 27 Stokesian particles. At $Pe = 10$, patterns that are calculated taking into account the hydrodynamics are also analogous to those, where the hydrodynamic effects are ignored, and demonstrate a shear-deformed microstructure.

The results obtained by the Stokesian and Brownian dynamics simulations, are qualitatively different at $Pe = 1000$. In the former case, a shear-deformed microstructure typical of fluids is seen but it is characterised by the more thinner nearest ring. In the studies,^{101,138} the dilatancy effect was demonstrated to be directly related to this feature of the pair distribution function. In the absence of hydrodynamic interactions, the particles are arranged

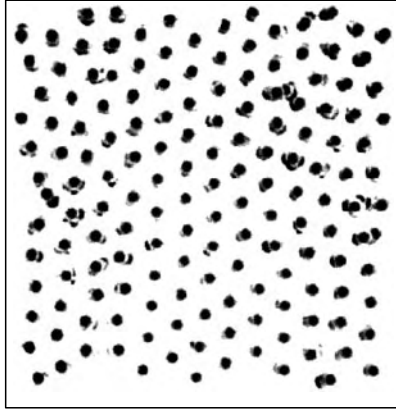


Figure 22. Brownian dynamics simulations of the arrangement of the particles in the plane perpendicular to the flow direction.¹⁰¹

in chains one after another, and the chains are located in hexagonal order in the plane perpendicular to the flow (Fig. 22). These chains are formed at high shear rates (when Brownian motion is of little importance): particles collide, rebound and adhere to other particles, again collide, rebound and so on until an ordered structure is formed. In the presence of hydrodynamic interactions, particles that are transferred by a flow do not rebound after collision and are held close to each other due to short-range hydrodynamic lubrication forces. Two particles rotating together in a flow hinder the formation of ordered chains. Therefore, the hydrodynamic effects influence both quantitatively and qualitatively the rheology and microstructure of colloidal dispersions. A detailed review of shear-induced microstructures in colloidal suspensions and analysis of the conditions of their formation and the role of hydrodynamic interactions between particles were given in the recent paper.¹³⁹

It is particularly important to take into account the dilatancy effect under shear deformation and vibration accompanied by a spontaneous increase in the viscosity and shear stress because it inevitably influences the character of dispersion flows and the possibility of achieving the maximum fluidity.

In the study,¹³⁵ simulations of the dilatant properties of suspensions were carried out by the lattice Boltzmann method. The Couette flow of a suspension between two planar plates, which are located at a distance H from each other and move at a velocity u_w in opposite directions, was considered. The lattice partitions of dimensions 128×128 and 256×256 points were used. The particle diameter was 10 lattice nodes. The concentration of the solid phase was varied from 12% to 52%.

In the absence of the Brownian forces, the Reynolds number was used instead of the Peclet number for characterisation of shear flows

$$Re = \frac{\rho_0 d^2 u_w}{\eta_0 H}.$$

The suspension viscosity was determined from the equation

$$\eta = \frac{\sigma_t}{\dot{\epsilon}},$$

where σ_t is the total shear stress on the walls and $\dot{\epsilon} = 2u_w/H$ is the shear rate.

Plots of the relative suspension viscosity vs. the Reynolds number determined by computer simulations are given in Fig. 23 *a*. It can be seen that the higher is the suspension concentration, the earlier (*i.e.*, at lower shear rates) the dilatancy is observed. In the study,¹³⁵ these effects were related to the changes in the components of the total shear stress σ_t and σ_s corresponding to the liquid and solid phases. The changes in the relative contributions of σ_t/σ_t and σ_s/σ_t to the total shear stress depending on the Reynolds number at two suspension concentrations are

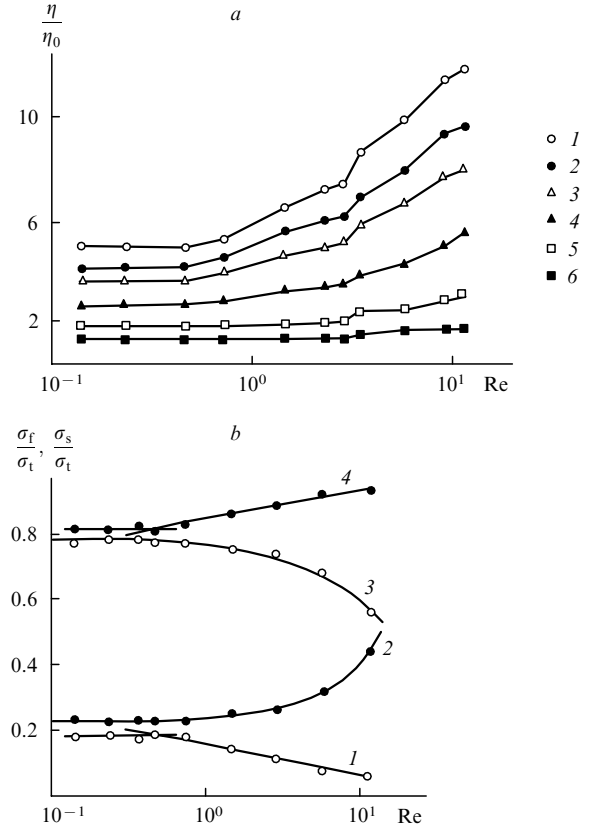


Figure 23. Suspension viscosity (*a*) and the shear stress corresponding to the fluid and solid phases (*b*) vs. the Reynolds number.¹³⁵

(*a*): $\phi = 52$ (1), 48 (2), 44 (3), 36 (4), 24 (5), 12% (6);

(*b*): σ_t/σ_t (1, 3); σ_s/σ_t (2, 4); $\phi = 12$ (2, 3) and 52% (1, 4).

shown in Fig. 23 *b*. It can be seen that the components of the total shear stress are independent of the Reynolds number in the initial region and begin to change only at a particular value that depends on the concentration of the solid phase. This change consists of the increase in the contribution of the shear stress corresponding to solid-phase particles. A comparison of the curves presented in Fig. 23 *a, b* demonstrated that an increase in the suspension viscosity and an increase in the shear stresses in the solid phase are observed at the same Reynolds number, which is indicative of the relationship between these phenomena.

The shear stress corresponding to solid particles is an important parameter. Figure 24 shows the plot of the relative suspension viscosity vs. σ_s/σ_t . The points in the figure were determined for Re varying from 0.1 to 11.7. All calculated points corresponding to different Re and the concentrations of the solid phase fall in a single curve, *i.e.*, the suspension viscosity is a mere function of σ_s/σ_t and does not directly depend on either the concentration or the shear rate.

In the study,¹³⁵ the simple equation was derived for the dependence of the viscosity on the contribution of the solid phase to the total shear stress:

$$\frac{\eta}{\eta_0} = \frac{1}{1 - \sigma_s/\sigma_t}. \quad (67)$$

However, the author of this work did not analyse the obtained results.

The results of computer simulations of the viscosity of a suspension consisting of solid spheres that were performed by different research groups using different methods^{135, 140–145} agree well with the results of calculations according to the Krieger–Dougherty equation (4) and the experimental data (Fig. 25). This demonstrates the efficiency of computer simulations in studies of

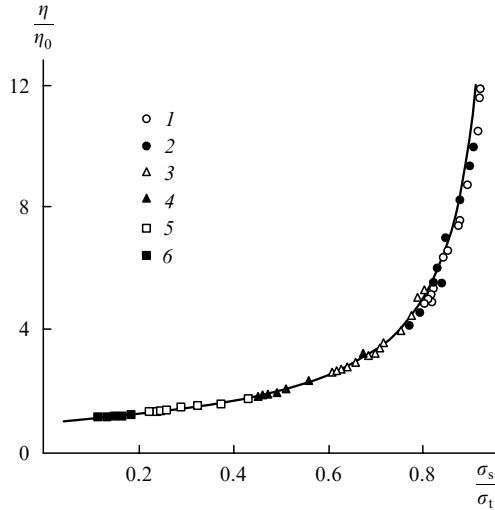


Figure 24. Relative suspension viscosity vs. the ratio σ_s/σ_t .¹³⁵ Points correspond to different concentrations and different Reynolds numbers. The solid line represents calculations according to Eqn (67). $\varphi = 52$ (1), 48 (2), 36 (3), 24 (4), 12 (5), 6% (6).

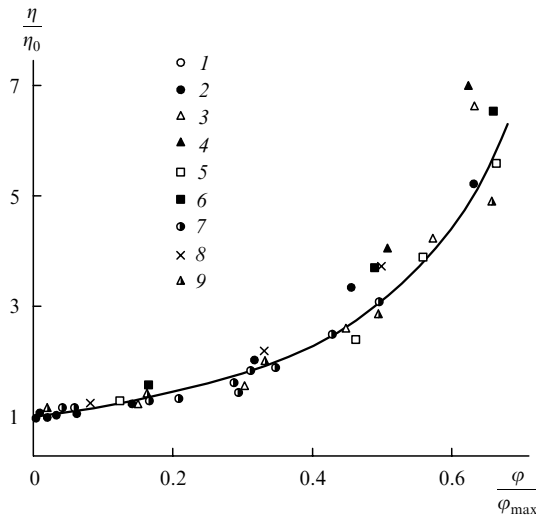


Figure 25. Theoretical data (curve) and data from computer simulations (points) of the suspension viscosity vs. the concentration. (1, 2) Lattice Boltzman method (2D);^{135, 145} (3, 4) Stokes dynamics (2D);^{140, 141} (5) lattice gas method;¹⁴⁴ (6) experiment;³⁰ (7, 8) Stokes dynamics (3D);^{142, 143} (9) lattice Boltzman method (3D).¹³⁵

the properties of disperse systems. The results of computer simulations were obtained at $Re = 0.1$ by the Stokesian dynamics,^{140–143} the lattice gas method¹⁴⁴ and the lattice Boltzmann method^{135, 145} for two- (2D) and three-dimensional (3D) systems. The maximum particle concentrations were taken equal to 0.785 and 0.605 for 2D and 3D systems, respectively.

The results of computer simulation of a system of ellipsoidal particles by dissipative particle dynamics are presented in Fig. 26.¹⁴⁶ The particles with the aspect ratio $f = 5$ were considered. The suspension viscosity was calculated from the equation

$$\eta = -\frac{\sigma_{xy}}{\dot{\epsilon}},$$

where σ_{xy} is the xy -component of the stress tensor, which is calculated in each time step. For dilute suspensions, the effective viscosity can be written as a first-order power series expansion in terms of the concentration of the solid phase φ

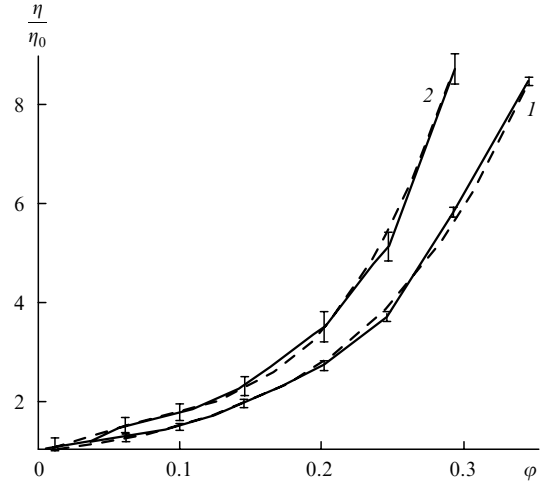


Figure 26. Relative viscosity of a suspension of ellipsoidal particles with the shape coefficient $f = 5$ vs. the concentration of the solid phase at dimensionless shear rates of 10^{-4} (1) and 10^{-5} (2).¹⁴⁶ Results of computer simulation were obtained by dissipative particle dynamics.

$$\frac{\eta}{\eta_0} = 1 + [\eta]\varphi.$$

According to the results of the investigation,¹⁴⁷ the degree of entanglement of rod-like particles increases with increasing concentration of a suspension, and the viscosity becomes proportional to the third power of the parameter φ . The results of simulations were approximated by third-order polynomials (see Fig. 26). The coefficient at the linear term $[\eta]$, which was obtained by approximation and interpreted as the ‘intrinsic’ viscosity of the system (5.67), is similar to the calculated value (5.78¹⁴⁶) for ellipsoids with $f = 5$.

The results of computer simulations of disperse systems considered in the present review confirm many experimentally observed and theoretically substantiated data on the dynamic and rheological properties of dispersions. Analysis of these results shows the ‘history’ of the appearance and development of some phenomena and provides an insight into their mechanisms, which is not only of theoretical interest but also of practical importance because it offers additional possibilities for searching new ways of controlling the properties of disperse systems.

IV. Conclusion

The development of procedures for controlling the dynamic state of disperse systems is tightly associated with the development of theories and models that describe the behaviour of disperse systems under dynamic conditions. The main rheological theories of solid phase–liquid disperse systems in flows are reviewed. Emphasis is given to the problems associated with the description of the properties of aggregated and non-aggregated suspensions, because the degree and character of structure formation are responsible for the bulk rheological properties of disperse systems. The theoretical views on the causes and conditions of the appearance of discontinuities, *viz.*, macroscopic inhomogeneities under structural deformation, are covered. The mechanism of the appearance of microinhomogeneities as discontinuities and the conditions of their healing were characterised for the first time by computer simulation methods. In a wide range of deformation rates, the evolution and elimination of inhomogeneities under vibrations are considered. The results of computer simulations of dynamics of disperse systems confirm many experimentally observed and theoretically substantiated features of the behaviour of disperse systems under dynamic conditions. Studies of these

features are of considerable importance not only because they provide the basis for the determination of the fundamental macroscopic and microrheological characteristics of these systems and elucidation of the relationship between these characteristics, but also because it is the controlled fluidity that is the most important factor for performing various heterogeneous chemical engineering processes (stirring, hydrotransport, catalysis, etc.).

Investigations of the dynamic state of disperse systems can help in revealing ways for providing dynamic aggregation stability and complete deaggregation of particles as the main condition for achieving the maximum fluidity of disperse systems with a decrease in the viscosity up to 8–11 orders of magnitude.

In studies of the ways and procedures for creating the maximum fluidity, it is necessary to use a combination of macro- and microrheological simulations taking into account intermolecular interactions, inertial and hydrodynamic effects under conditions of both continuous shear stress and a combination of this deformation with orthogonal oscillations and the addition of surfactants creating a structural-mechanical barrier on the particle surface. The parameters and conditions of the appearance of the latter require a theoretical description.

We thank E A Naumenko for help in performing computer simulations of disperse systems.

This review has been written with the financial support of the Russian Foundation for Basic Research (Project No. 03-03-32237).

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^d — *Theor. Found. Chem. Eng. (Engl. Transl.)*

Crystalline water ices

E A Zheligovskaya, G G Malenkov

Contents

I. Introduction	57
II. General remarks	57
III. Recent data on the structures and proton ordering of crystalline water ices. Phase transitions between crystalline ices	58
IV. Inelastic neutron scattering spectroscopy of water ices	69
V. Computer simulations of crystalline ices	70
VI. Occurrence of high-pressure ices in nature	73
VII. Appendix	73

Abstract. Recent publications on the structures of crystalline water ices are surveyed. Interconversions of crystalline and amorphous ices are considered. Some hypotheses concerning the occurrence of high-pressure ices in nature are outlined. The bibliography includes 149 references.

I. Introduction

The properties of crystalline and amorphous water ices have been attracting steady interest of researchers for several reasons. First, water plays the most important role in biological processes and thus the knowledge of typical structures formed by water molecules may help elucidating the structures of water bound to proteins or other biological macromolecules. Second, water is one of the most abundant substances in the universe and thus investigations into potential states that can be adopted by water in the interstellar space or other orbs are of great interest. Third, studies of water are of general theoretical importance since they give insights into the common regularities of structure and polymorphism of various substances featuring tetrahedral coordination of molecules or atoms, the reasons underlying the existence of several amorphous forms of a substance and the regularities of phase transitions between them, the nature of pressure-induced amorphisation of crystals and solid-state crystallisation from an amorphous state and many other issues.

The present review concerns structural studies of crystalline water ices. We survey the data on the structures of crystalline forms of ice and transitions between them published over the last 10–15 years and consider related topics, in particular, amorphisation of crystalline ices and their crystallisation from amorphous phases. Some earlier papers are cited where appropriate. A comprehensive review of studies published before 1974 can be found elsewhere.¹

E A Zheligovskaya, G G Malenkov 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) 955 44 21, e-mail: lmm@phycche.ac.ru

Received 24 May 2005

Uspekhi Khimii 75 (1) 64–85 (2006); translated by Ya V Zubavichus

II. General remarks

At present, thirteen reliably established crystalline modifications of water ices are known (Fig. 1 and Appendix, numbering of the crystalline phases reflects the order of their discovery). These

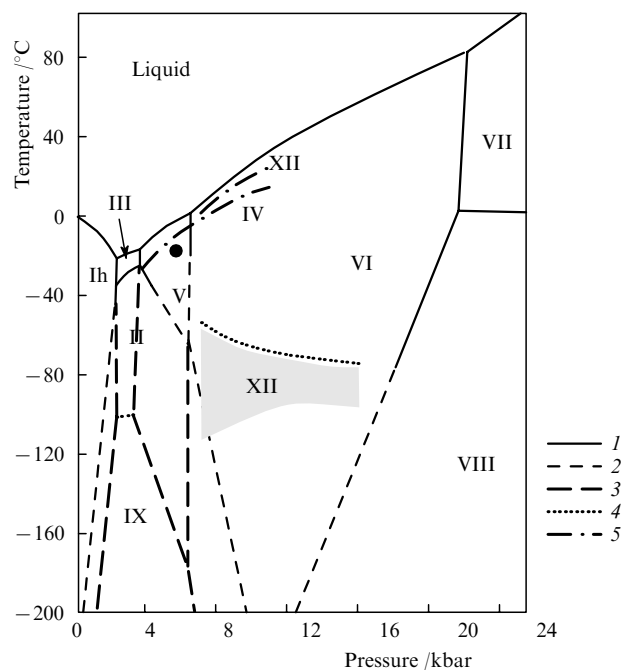


Figure 1. The low-temperature part of the water phase diagram at pressures up to 2.5 GPa.

(1) The experimentally determined lines of stable phase equilibria, (2) the calculated and extrapolated lines of stable phase equilibria, (3) the experimentally determined and calculated lines of metastable phase equilibria, (4) the experimental curve² for the maximum rate of the transformation of ice III into ice IX within the region of stability of ice II and the curve for the transformation³ of metastable ice XII into stable ice VI, (5) the experimentally determined melting curves of metastable ices IV⁴ and XII,⁵ the bold dot indicates the region where ice XII was prepared for the first time⁶ by crystallisation from liquid, the second area of the existence³ of ice XII prepared by crystallisation of high-density amorphous ice (HDA, see Section III.6) is marked grey.

forms of ice can be reproducibly prepared using *ad hoc* techniques, they have been thoroughly characterised by spectroscopy and their crystal structures have been determined using X-ray or neutron diffraction. Some of the known crystalline modifications of ice are characterised by specific regions of the stability in the water phase diagram, whereas others (*viz.*, Ic, IV, IX and XII) occur exclusively as metastable states. It is of note that the recently discovered metastable ice XII can occur in two separate regions of the phase diagram.

In the structures of all known crystalline ices, each water molecule forms four hydrogen bonds directed towards vertices of an ideal or slightly distorted tetrahedron with neighbouring molecules. In all cases except for ice X, the H₂O molecules retain their integrity and act as donors of hydrogen atoms for two out of the four hydrogen bonds and as acceptors for two other bonds.

The normal-pressure crystalline phases (Ih, Ic and XI) are characterised by nearly ideal tetrahedral closest environment of water molecules. Meanwhile, in high-pressure phases (II, III, IX, V, IV, XII and VI), the oxygen atoms of neighbouring molecules occupy vertices of a distorted tetrahedron. The framework of hydrogen bonds becomes self-entangled starting from a pressure of ~ 0.5 GPa (ices IV and V), which means that it represents an integral network where at least some elementary H-bond cycles appear hooked to each other. At higher pressure, phases composed of two independent interpenetrating frameworks of hydrogen bonds are formed (crystalline ices VI, VII and VIII). Unlike self-entangled frameworks, these ices contain two interpenetrating non-linked H-bond networks. At a pressure of the order of 2 GPa or higher, nearly ideal tetrahedral coordination of water molecules is recovered (ices VII and VIII). Finally, at even higher pressures, the oxygen sublattice of ices VII and VIII is preserved but the hydrogen atoms are shifted towards the centres of the O—H $\cdots$ O bonds. Consequently, starting from ~ 50 GPa, the hydrogen atoms become evenly shared between the two neighbouring oxygen atoms and the molecular structure is transformed in a framework structure in crystalline ice X. Such a structure is maintained at pressures of up to 200 GPa, which is the highest value explored to date.

Protons in the crystalline water ices occupy the respective positions near the oxygen atoms in a regular or random way. In proton-ordered ices, the two neighbouring molecules involved in donor-type H-bonding and those two involved in acceptor-type H-bonding are defined unambiguously (in other words, the orientation of water molecules with respect to their closest neighbours is known). Two of the four possible positions of the H atoms near an O atom have occupancies close to unity (they are equal to unity in the case of complete ordering), whereas two other positions have occupancies close to zero (they are equal to zero in the case of complete ordering). In the case of proton-disordered ices, each of the four hydrogen bonds formed by a water molecule can serve simultaneously as both the donor and the acceptor such that four possible hydrogen positions around the respective oxygen atom have equal occupancies of 0.5. In a sense, water molecules in these proton-disordered ice modifications adopt arbitrary orientations with respect to their closest neighbours in the crystal structure. The situation with the occupancies of some hydrogen positions significantly differing from 0, 0.5 or 1 is referred to as a partial (dis)order. Ices II and VIII are completely proton-ordered; ice IX is partially proton-ordered; the proton-ordered ice XI has been obtained only as nanocrystallites embedded into a matrix of ice Ih, thus the extent of its proton-ordering cannot be reliably analysed; other ices are completely or partially proton-disordered.

Since water molecules preserve their integrity and form exactly two donor and two acceptor H-bonds with neighbouring water molecules in all but ice X water ices, the disordering of proton positions in the crystal structures of proton-disordered ices obeys the so-called Bernal–Fowler rules:⁷ (i) exactly two H atoms are located around each oxygen atom at a distance of the covalent bond; (ii) each hydrogen bond accommodates exactly one hydrogen

atom. A violation of the first rule gives rise to ionic defects (*i.e.*, the occurrence of H₃O⁺ or OH[−] ions instead of H₂O molecules); a violation of the second rule results in the Bjerrum defects (*i.e.*, the coexistence of two hydrogen atoms or a hydrogen vacancy along a hydrogen bond, also referred to as D- and L-defects, respectively).

Among the known ice polymorphs, several pairs of crystalline modifications having identical oxygen sublattices but differing from each other in the extent of the proton ordering can be distinguished. These include proton-disordered ices Ih, III and VII with their proton-ordered counterparts, ices XI, IX and VIII, respectively. Since orientations of water molecules relative to their closest neighbours within these pairs are different, these phases have different dynamical characteristics and, as a consequence, vibrational spectra. These differences are manifested in the IR, Raman and inelastic neutron scattering (INS) spectra.

Several water ices have close structural analogues among other crystalline substances built up of tetrahedrally coordinated atoms. In particular, lonsdalite (hexagonal diamond modification), wurtzite (ZnS) and high-temperature tridymite (SiO₂) are isostructural to ice Ih; diamond, silicon, germanium, grey tin, high-temperature cristobalite (SiO₂) and sphalerite (ZnS) are isostructural to ice Ic; high-pressure germanium and keatite (SiO₂) are isostructural to ices III and IX; the aluminosilicate framework of edingtonite Ba(Al₂Si₃O₁₀) is isostructural to one of two identical independent interpenetrating frameworks of ice VI. Note that Zn and S atoms in the frameworks of wurtzite and sphalerite alternate in positions occupied by the oxygen atoms in the corresponding ices Ih and Ic. In SiO₂ polymorphs isostructural to crystalline ices, H-bonded oxygen sublattice is replaced by similar frameworks of silicon atoms linked by covalent Si—O—Si bonds.

The discovery of a new crystalline phase of water, namely, the metastable ice XII, is probably the most outstanding recent achievement in the studies of crystalline water ices. The crystal structure of this phase, which has no analogues among substances with the tetrahedral coordination of atoms, has been determined; two regions of its stability in the water phase diagram have been established and the parallel crystallisation of ices IV and XII from amorphous high-density ice has been observed. In addition, the presence and extent of proton ordering in various water ices, the boundaries of their stability and metastability in the phase diagram as well as their thermodynamical parameters were specified in studies of the last decade. Phase transitions between ice polymorphs have been investigated. IR, Raman and INS spectra have been collected for all known ice phases. In parallel, vibrational spectra of various ices have been calculated theoretically using the lattice dynamics method. Finally, the molecular dynamics has been applied to simulate the existing and hypothetical crystalline water ices. The results of these studies are considered below.

III. Recent data on the structures and proton ordering of crystalline water ices. Phase transitions between crystalline ices

1. Ices Ih, Ic and XI

Hexagonal ice Ih, its proton-ordered low-temperature analogue, ice XI, and metastable cubic ice Ic constitute the group of normal-pressure (1 bar) crystalline water ices. Among these modifications, ice Ih, which is formed upon freezing of water at a pressure from 0 to ~ 0.2 GPa, is studied the best. Metastable ice Ic with the structure relating to that of ice Ih in the same way as the structure of diamond relates to that of lonsdalite can be prepared by deposition of water vapour on a cold ($163 < T < 183$ K) metal support,⁸ rapid cooling of emulsions composed of water microdroplets down to $150 < T < 190$ K (at a cooling rate of 10^6 – 10^7 K s^{−1}),⁹ freezing of water in capillaries^{10,11} (see below in this Section) and heating of quenched high-pressure crystalline^{12–18} (see Section III.8) or amorphous^{19–21} (see Sec-

tion III.6) water ices at a pressure of 1 bar. Irrespective of the preparation method, annealing of ice Ic initiates its irreversible conversion into ice Ih. The temperature of this transition depends on the heating rate and prehistory of the sample and lies in the range from 140 to 230 K.

The unit cell parameters a and c of ices Ih(H₂O) and Ih(D₂O) were measured²² by powder X-ray diffraction using synchrotron radiation in a wide temperature range from 10 to 265 K at a constant pressure of 100 Torr. The unit cell parameters of ice Ih(D₂O) were slightly larger than those of ice Ih(H₂O) in the whole temperature range. The a/c ratio was virtually independent of temperature indicating that the thermal expansion of ice Ih can be considered isotropic. The linear thermal expansion coefficients (α) of both ices Ih(H₂O) and Ih(D₂O) are negative below 75 K, which means that these phases expand upon cooling. Such a behaviour is also typical of other substances with the tetrahedral coordination of atoms.²² Below 100 K, the coefficients $\alpha_{\text{H}_2\text{O}}$ and $\alpha_{\text{D}_2\text{O}}$ are the same but the increase in $\alpha_{\text{D}_2\text{O}}$ above 100 K occurs faster than that of $\alpha_{\text{H}_2\text{O}}$.

The linear thermal expansion coefficients of ices Ih and Ic were also calculated theoretically using the TIP4P intermolecular interaction potential²³ with averaging over a large ensemble of possible proton configurations.²⁴ These calculations confirmed that the coefficients α for both ices Ic and Ih should become negative at low temperature. Similar calculations²⁵ for ices Ic and VII based on the Carravetta–Clementi potential²⁶ showed that $\alpha < 0$ for ice Ic at low temperature, whereas the linear thermal expansion coefficient is always positive for ice VII, which represents two independent interposed frameworks of ice Ic.

It is known that ice Ih is proton-disordered and this positional proton disorder persists upon cooling down to 0 K.⁷ Meanwhile, according to the third law of thermodynamics, only one thermodynamically stable structure with a specific arrangement of protons should exist at 0 K at any given pressure. Such a transition to the equilibrium structure cannot be realised for chemically pure water due to the vanishingly low orientational mobility of H₂O molecules in the crystal structure of ice Ih. Introduction of a minute amount of hydroxide anions into water results in the formation of defects distorting the framework of H-bonds, which facilitates the phase transition of the crystalline ice Ih to the proton-ordered state. Such a transition has indeed been observed at 72 K in calorimetric experiments and measurements of dielectric properties.²⁷ This new phase representing a proton-ordered low-temperature analogue of ice Ih was entitled²⁷ ice XI, since phases II–X had already been known to that moment.

The crystal structure of heavy ice XI(D₂O) doped with KOD was investigated using powder neutron diffraction.²⁸ High-resolution powder neutron diffraction was also applied to elucidate the structure of normal ice XI(H₂O) doped with KOH.²⁹ The results obtained were consistent with the orthorhombic structure corresponding to the space group $Cmc2_1$ with the protons ordered into a ferroelectric phase. It has to be mentioned that the same structure was predicted earlier based on a theoretical analysis.^{28,29} Nevertheless, the fraction of the ordered phase as revealed in the neutron diffraction studies^{28,29} was low, and the major structural information in these measurements related to disordered ice Ih. Thus, the cited studies left open the question on the structure of ice XI. Furthermore, a series of theoretical studies of the ordered structures with a framework of water molecules based on ice Ih^{30–32} claimed a structure corresponding to the space group $Pna2_1$ with the antiferroelectric ordering of protons and eight water molecules per unit cell to be the most stable. Therefore, the results of neutron diffraction studies^{28,29} were contested and thus the character of the proton ordering in the crystal structure of ice XI remained a subject of debate for a long time.

Recently, Jackson and Whitworth,^{33,34} using a newly developed method of temperature-stimulated depolarisation, which is based on the generation of an electric current pulse in the transition of a polarised ice into the disordered state upon heating,

have shown that the proton ordering in the structure of ice XI corresponds to a ferroelectric with a non-zero dipole moment along the c axis and the zero dipole moment in the ab plane. Further investigations into the structure of ice XI(D₂O) using high-resolution powder neutron diffraction³⁵ and of ice XI(H₂O) using neutron diffraction on a quasi-single crystal³⁶ obtained from ice Ih that underwent the phase transition Ih $\rightarrow$ XI and contained about 37% of ice XI, also confirmed the orthorhombic structure of ice XI with the space group $Cmc2_1$. Neighbouring hexagonal layers in this structure are somewhat shifted with respect to each other, which probably plays the decisive role in the stabilisation of the ferroelectric structure. It has been shown that the diffraction pattern of ice XI manifests the (131) reflection, which is forbidden for ice Ih (in the corresponding orthorhombic setting).

The formation of ice XI from a single crystal of Ih(D₂O) grown from a 0.1 M KOD solution kept for 520 h at 62 K and for 88 h at 68 K was also studied by neutron diffraction.³⁷ [The temperature of transition to ice XI for KOD-doped Ih(D₂O) was 76 K.] The extent of conversion was monitored by the intensity of the (131) reflection, which first increased and then reached a plateau. The degree of conversion of ice as a function of time and the ultimate degree of conversion at $t \rightarrow \infty$ (i.e., 38.2% at 62 K and 47.9% at 68 K for the 0.1 M KOD solution in D₂O used to grow the single crystal of Ih) were determined. The results obtained can be explained by the emergence of numerous nucleation sites of ice XI inside the single crystal of Ih (most probably, around the OD[−] ions) followed by growth of ordered domains of ice XI around these sites. The characteristic size of ice XI domains depending on temperature, duration of storage and KOD concentration in the solution did not exceed³⁷ 60 Å under the conditions used. However, it remains unclear, why the transition stopped very far from the complete conversion of the samples into ice XI with randomly oriented contacting domains. It is of note that storage of the KOD-doped ice Ih for 40 h at 51 K yielded no detectable amounts of ice XI.

The crystal structure of ice Ih has two different mutual orientations of H-bonded water molecules lying in adjacent hexagonal layers (Fig. 2*a,b*) and two different orientations of H-bonded water molecules within the same hexagonal layer (Fig. 2*c,d*). Due to the electrostatic repulsion, the energy of the molecular pairs depicted in Figs 2*b* and 2*d* is higher than that of the pairs depicted in Figs 2*a* and 2*c*, respectively. Within a model³⁸ proposed for ices Ih and Ic, the latter type of bonds is

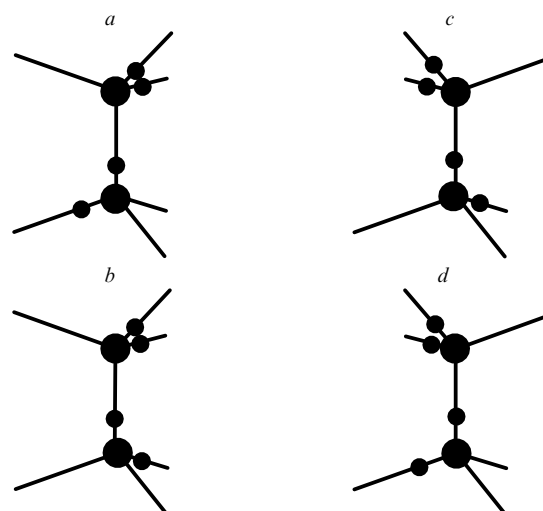


Figure 2. Types of hydrogen bonds in ices Ih and Ic: strong (*a*) and weak (*b*) hydrogen bonds between the hexagonal layers of ice Ih; strong (*c*) and weak (*d*) hydrogen bonds within a hexagonal layer in ices Ih and Ic.³⁸

referred to as strong bonds, whereas the former type of bonds is referred to as weak bonds with the respective difference in the force constants used for their description. The application of this model to the interpretation of INS spectra of various crystalline ices is discussed in Section IV.

Within the model of two force constants, a structure with the maximum fraction of strong H-bonds has to be the most stable at a given geometry of the oxygen framework. Kirov³⁹ suggested a proton distribution over the structure of ice Ih containing only strong H-bonds. In this structure, the positions of protons are disordered in the hexagonal layer but are ordered along the *c* axis.³⁹ Analogous models comprising only strong H-bonds have also been suggested for ice Ic.^{40, 41} One of them is disordered along the direction [111] of the cubic lattice but contains ordered layers; another represents a defectless axial twin with a step-like proton ordering. However, it has to be noted that the proton-ordered ice Ic, even if observed, existed only as partially polarised thin films⁴² on a support inducing this polarisation (see below in this Section), and the real proton-ordered crystal structure of ice XI comprises three weak H-bonds per strong H-bond. Thus, as mentioned above, it is the change in the geometrical parameters, in particular, relative shifts of hexagonal layers, that plays the decisive role in the stabilisation of the proton-ordered structure of ice XI rather than the fraction of strong bonds (calculated within the model of two force constants).^{35, 36}

It has been shown that partial proton ordering in an ice structure leading to its polarisation can be caused by surface effects. In particular, proton ordering resulting in a polarised structure was observed in thin films of ice Ih (1–80 monolayers) prepared by vacuum deposition of water vapour on a Pt(111) support at 137 K.⁴³ The strains occurring in the first monolayer due to mismatch between the cell parameters of platinum and ice Ih are relieved already at the fifth monolayer. The preferred orientation of the first H₂O monolayer lying on the Pt(111) crystal face induces the polarised ordering in subsequent layers. The extent of the orientation order decreases with an increase in the distance to the platinum surface (by a factor of ~ 2.7 at a distance of 30 monolayers).

Iedema *et al.*⁴² reported partial polarisation of thin films of ice Ic (with thicknesses of 2000 to 100 000 monolayers) prepared similarly by the deposition of water vapour on a Pt(111) support at temperatures from 135 to 145 K. The degree of ordering in the films was 0.2% but it was independent of the distance to the support, in contrast to the data cited above.⁴³ The oxygen atoms of the H₂O molecules were directed away from the support. In both studies^{42, 43} it was considered that the partial ordering during ice crystal growth emerged due to interactions between the water molecules at the interface with the support or with the surface of the growing crystal.

Recently, the process of water freezing in narrow pores of glassy silicates, which is strongly affected by hydrophilic pore walls, has been elucidated. It was found¹⁰ that water can be overcooled down to –18 and –27 °C in completely filled pores with diameter of 50 Å and in half-filled pores (which corresponded roughly to three molecular layers adsorbed on the pore walls), respectively. Remarkably, no indication of crystallisation down to –196 °C was observed in quarter-filled pores, which corresponded to an H₂O monolayer on the wall. The temperature of nucleation of the crystalline phase depends on both the degree of pore coverage with water and the pore size: it decreases with a decrease in the pore size, *i.e.*, water can be overcooled to a lower temperature in a narrower pore.¹¹ In addition, in sufficiently narrow pores, ice Ih crystallises in the case of partial filling, whereas ice Ic crystallises in the case of complete filling.^{10, 11}

2. Ice II. Phase transition Ih → II

The formation of crystalline water ices II–X and XII requires elevated pressures, therefore, these phases are referred to as high-pressure ices.

Many of the high-pressure ices can be retained in the metastable state even at 1 bar. To this end, an ice sample prepared at the corresponding high pressure should be cooled to liquid nitrogen temperature and this temperature should be kept during the pressure release down to atmospheric pressure. Such metastable states of water are referred to as quenched ices. It is for recovered forms at atmospheric pressure that the crystal structures of various high-pressure ices have been determined. However, these measurements give no information on the changes in structural parameters (such as the extent of proton ordering, volume compressibility, tensor of elasticity constants, *etc.*) as a function of pressure and temperature. Recently, the structures of various crystalline ice phases have been studied at different pressures and temperatures within the regions of their thermodynamic stability and/or metastability.

The crystal structure of ice II was determined for the first time by Kamb⁴⁴ in 1964 using single-crystal X-ray diffraction on a recovered sample at atmospheric pressure. Ice II possesses a rhombohedral structure with hexagonal columns composed of alternating six-membered rings in the chair conformation differing from each other in the degree of flattening (Fig. 3) along the *c* axis of the hexagonal unit cell or along the direction [111] in the rhombohedral unit cell as the main structural elements. The more corrugated rings comprise water molecules with the O(1) atoms, whereas more flattened rings are composed of the water molecules with the O(2) atoms. Each column is surrounded by six other columns of the same type going parallel but shifted by 1/3 translation along the *c* axis. The cavity inside the columns has a diameter of about 3 Å, which thus can accommodate helium or neon atoms or hydrogen molecules.⁴⁵ The resultant non-stoichiometric solid solutions of inert gases or hydrogen in ice II matrix can also be considered as host–guest hydrates with the framework of ice II as the host and gas molecules as guests.

The presence of a dissolved gas changes substantially the thermodynamic parameters of ice. For instance, crystallisation of ice from water at a hydrostatic pressure of 0.28–0.50 GPa in an atmosphere of helium upon cooling to the freezing point of 250–270 K gives rise to ice II-based helium hydrates rather than to ices III and V, which are thermodynamically stable in this region of the phase diagram (see Fig. 1).^{45–47} The crystal structure of the helium hydrate with ice II-derived water framework, which

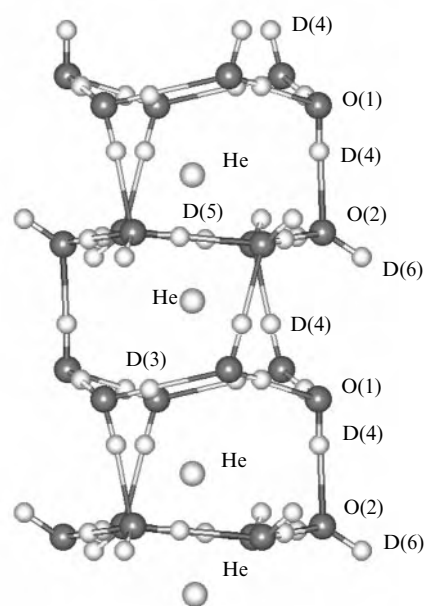


Figure 3. A hexagonal layer in ice II (the projection perpendicular to the *c* axis). Helium atoms that can penetrate into the hexagonal channels in ice II structure are also shown.

is formed under the above conditions, has been determined using powder neutron diffraction.⁴⁷ Like ice II, this helium hydrate is proton-ordered and this is the only known case when a proton-ordered crystalline framework of water molecules is formed directly from the liquid phase. The crystal structure of the gas-free ice II in the region of its thermodynamical stability has been determined for the first time by Lobban *et al.*⁴⁸ also using powder neutron diffraction; the results obtained made it possible to analyse the influence of absorbed gas on the geometry of the water framework of ice II.

Helium atoms in the hexagonal channels of ice II experience repulsion from the deuterium atoms D(4) at the oxygen atoms O(1) constituting the corrugated rings (see Fig. 3). As a result, helium atoms occupy positions closer to the flattened ring rather than exactly in the centre between the flattened and the corrugated rings within the unit cell of the respective hydrate (see Fig. 3).⁴⁷ The repulsion of the He atoms from the O(2) atoms of the flattened rings results in the increase in the diameter of these rings as compared to the structure of helium-free ice II.⁴⁸ Meanwhile, the diameter of the corrugated rings remains virtually unchanged. The inclusion of helium atoms into ice II structure results in the opposite changes in the unit cell parameters a and c .⁴⁸ The distance between walls of adjacent channels in the structure of the hydrate decreases due to the increase in the diameter of the flattened rings. Meanwhile, the distance between the axes of the channels somewhat increases upon inclusion of He, which results in the increase in the parameter a . In contrast, the parameter c somewhat decreases since the increase in the diameter of channels should be accompanied by the reduction in their lengths.

Upon an increase in pressure, the diameter of the flattened hexagonal rings changes insignificantly, whereas that of the corrugated rings decreases in both the structures of helium-free ice II and ice II-derived helium hydrate.⁴⁸ Upon an increase in pressure from 0.28 GPa to 0.48 GPa, the distance between the axes of the channels decreases. As anticipated, the volume compressibility of He-containing ice II is smaller than that of its helium-free prototype. An estimate⁴⁸ of the isothermal volume compressibility of pure ice (D_2O) at 200 K (14.8 GPa) is in good agreement with the value of 14.4 GPa obtained earlier⁴⁹ based on acoustic measurements for ice II(H_2O) at 237.5 K.

The structure of the water framework in ice II (free of dissolved helium) was simulated within the density functional theory using the PW91 functional at different temperatures and pressures.⁵⁰ The calculated values of density, volume compressibility, unit cell parameters and atomic coordinates were in good agreement with the experimental results.^{44, 48, 49} The same simulations showed that the decrease in the density of ice II upon an increase in pressure is due to a decrease in the distance between the axes of the hexagonal channels, which is also in accord with the experimental observations.⁴⁸

In an earlier study on the structure determination of quenched ice II, Kamb⁴⁴ noted that this structure can be derived from that of ice Ih by preserving some of the hexagonal channels of ice Ih while rearranging the system of H-bonds between them. This is accompanied by certain increase in the diameter of the hexagonal rings with a concomitant decrease in the distance between the axes of these channels, which gives rise to an increase in the density of the resultant framework. A scheme of such a conversion from the structure of ice Ih to that of ice II is depicted in Fig. 4.⁵¹

The transition of ice Ih to ice II under hydrostatic compression in an atmosphere of helium was studied experimentally using neutron diffraction.⁵² The incorporation of helium atoms into ice Ih starts at 120 K at a pressure interval from 0.25 GPa to 0.31 GPa. This results in an expansion of the crystal lattice around the inserted helium atoms, which manifests itself in an increase in the distance between the (h h 0) planes. Heating of the sample to 180 K at 0.31 GPa is accompanied by an abrupt phase transition of ice Ih with dissolved helium into ice II-based helium hydrate. Due to the large difference in densities of ices Ih and II, a single crystal of Ih converts into polycrystalline powder of ice II-based

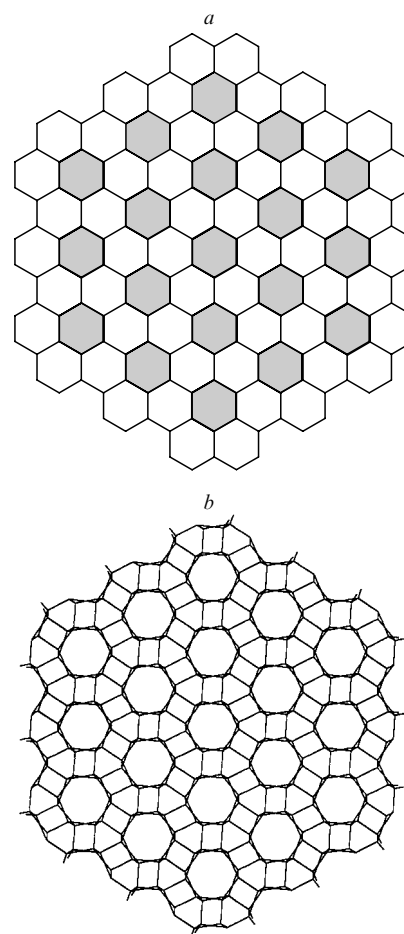


Figure 4. Rearrangement of the framework of hydrogen bonds of ice Ih (a) to ice II (b). In both cases, projections along the c axes of the hexagonal lattices are given. The hexagonal channels in ice Ih that are retained upon the transition Ih $\rightarrow$ II are marked grey.

helium hydrate. It is of note that the positional proton disorder in the structure of ice Ih is preserved until completion of the transition into He-containing ice II.

3. Ices III and IX. Transition III $\rightarrow$ IX

The structures of ices III and IX at pressures from 0.28 to 0.30 were first determined by Londono *et al.*⁵³ using powder neutron diffraction. Later, powder neutron diffraction was applied to refine the structure of ice III in different points in the region of its thermodynamical stability.⁵⁴ Ices III and IX possess identical oxygen frameworks but differ from each other in the extent of proton ordering (Fig. 5). Gradual ordering of proton positions upon cooling of ice III compressed to 0.23 GPa in a temperature range from 208.0 to 164.5 K was established back in 1968 by dielectric susceptibility measurements.² The maximum change in the dielectric susceptibility as a function of temperature (which corresponded to the maximum ordering) was observed at ~ 173 K. Meanwhile, there was no indication of any changes in the oxygen framework. Thus, ice IX represents a low-temperature proton-ordered analogue of ice III.² It is of note that quenched ice III cannot be recovered at atmospheric pressure using the standard method since it always undergoes a phase transition to ice IX upon cooling. In the crystal structure of recovered ice IX determined⁵⁵ at atmospheric pressure using single-crystal neutron diffraction, the mean occupancy of the least occupied hydrogen position was as low as 4%. The change in entropy due to the phase transition III $\rightarrow$ IX was found⁵⁶ to be $1.34 \pm 0.29 \text{ J K}^{-1} \text{ mol}^{-1}$. Meanwhile, the theoretical value of the entropy change assuming the complete proton disorder in ice III and complete order in ice

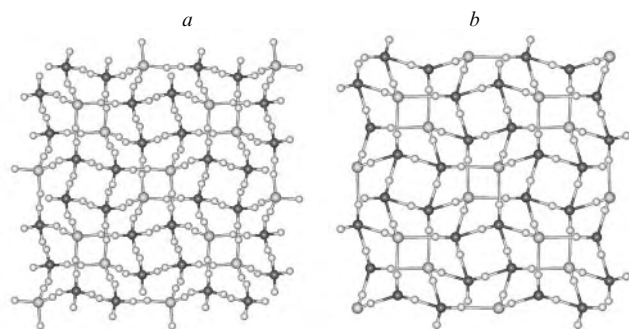


Figure 5. The structures of proton-disordered ice III (a) and its proton-ordered analogue, ice IX (b). The projection is along the c axis. All possible positions of the hydrogen atoms in ice III are shown; their occupancies are close to 0.5. The atoms O(1) forming helices along the c axis are marked black, whereas the atoms O(2) linking the helices into a united framework are marked grey.

IX should be $3.37 \text{ J K}^{-1} \text{ mol}^{-1}$ (Ref. 54), which is 2.5 times larger than the above experimental value (see Ref. 56). This large discrepancy cannot be explained solely by a partial proton disorder of ice IX, therefore, it was suggested that the structure of ice III is partially proton-ordered. The correctness of this suggestion was confirmed experimentally by crystallographic studies of ice III.^{53, 54}

The mean occupancies of the least occupied proton position in the crystal structure of ice IX at 0.28 GPa and at atmospheric pressure are nearly the same (4%).⁵³ No substantial changes in the extent of positional proton order of ice III within the region of its thermodynamical stability were observed (the occupancy of the least occupied position was slightly larger than 40%).⁵⁴ However, the change in the configurational entropy due to the transition III $\rightarrow$ IX estimated from the occupancies of the proton positions in ices III and IX also exceeds the experimental value. Therefore, ΔS corresponding to this phase transition is not governed exclusively by the change in the configurational entropy due to different proton ordering in these phases, some other factors are also involved.⁵⁴

In addition to the proton ordering, cooling of ice III is accompanied by changes in the unit cell parameters a and c and, consequently, the unit volume. It is of note that the relative decrease in the volume of ice due to the transition III $\rightarrow$ IX is an order of magnitude larger than that due to analogous transitions into proton-ordered phases with the conservation of the oxygen framework, *i.e.*, Ih $\rightarrow$ XI and VII $\rightarrow$ VIII.⁵³ The c/a ratio in ice III is larger than that in ice IX.^{53, 54} Although the unit cell parameters a and c do not depend on the sample prehistory, both a decrease in temperature and an increase in pressure, on the whole, result in the anisotropic compression of ices III and IX with the parameter c decreasing faster than a . In addition, ice IX anisotropically expands upon pressure release to atmospheric pressure. In the crystal structures of ices III and IX, water molecules with the oxygen atoms O(1) form helices along the c axis, whereas water molecules with the oxygen atoms O(2) link the adjacent helices into a united framework (see Fig. 5). The ease of compression and stretching of the helices along their axes explains the lower rigidity of the parameter c .⁵⁴

4. Ice V

In contrast to the transition of proton-disordered ice III into nearly completely proton-ordered ice IX, which does not violate any symmetry operations and thus preserves the space group $P4_12_12$, the proton ordering in the structure of ice V has to result in lower space symmetry of the crystal structure. According to structural studies of ice V at different temperatures and pressures (in particular, within the region of its thermodynamical stability)

performed for the first time by Lobban *et al.*,⁵⁴ the degree of proton ordering in ice V generally increases upon cooling or compression. Nevertheless, no complete ordering is achieved. Thus, neither the aforementioned lowering of the space symmetry occurs, nor consequently changes in the space group are observed.⁵⁴ The crystal structure of recovered ice V at atmospheric pressure⁵⁷ corresponds to the same space group $A2/a$ as at 0.4–0.5 GPa.⁵⁴

The $\text{O} \cdots \text{O} \cdots \text{O}$ angles in the crystal structure of ice V (from 86° to 132°) deviate strongly from the bond angle $\text{H} - \text{O} - \text{H}$ of a free water molecule (*ca.* 105°), which results in bending of the $\text{O} - \text{H} \cdots \text{O}$ hydrogen bonds. Straight hydrogen bonds are energetically more favourable than bent ones. Therefore, the fraction of H_2O molecules occupying unfavourable positions with strongly bent H-bonds in the crystal should decrease upon cooling thus increasing the degree of the orientational order of the structure.

On the one hand, an increase in pressure deforms the water framework (further distortion of the hydrogen bonds), while, on the other hand, the density of the phase increases, *i.e.*, the volume per water molecule in the crystal structure diminishes. The latter factor enhances the contribution of van der Waals repulsion, which tends to orient adjacent molecules that are not linked through H-bonds. Apparently, this factor is responsible for the proton ordering upon an increase in pressure, since the energy change due to the former factor is insignificant, as evidenced by theoretical estimates.⁵⁴

The dielectric relaxation spectra⁵⁸ of ice V agree well with the observed proton ordering. The increase in the dielectric susceptibility of ice V upon cooling from 266 to 133 K amounts to 77% of the value calculated from the decrease in both volume and internal energy. Johari and Whalley⁵⁸ assign this difference to partial orientational ordering of H_2O molecules upon cooling.

Specific endothermic effects observed in the differential scanning calorimetry (DSC) curves (heating rate, 30 K min^{-1} at atmospheric pressure) for samples of metastable ice V subjected and not subjected to annealing at sufficiently high temperature can also be interpreted as a kinetic activation of the orientational transition proton order–disorder.⁵⁹ When ice V is cooled at a certain rate (say, 30 K min^{-1}), the orientational relaxation time required to achieve the equilibrium state becomes, starting from a specific threshold temperature, longer than the duration of the experiment. This results in kinetic freezing of the excessive proton positional disorder at low temperature. In subsequent heating at the same rate, the response of the system to heating is somewhat delayed since the orientational mobility of water molecules is initially too low, *i.e.*, at any given temperature T , the extent of proton disorder in the system is higher than the equilibrium value. With a further increase in temperature, the orientational mobility of molecules increases and, starting from a certain temperature, becomes sufficient to enable complete relaxation to the equilibrium degree of disorder. This is equivalent to the reactivation of the transition order–disorder related to the positions of protons in the structure of ice V.

The actuation of the orientational relaxation to the thermodynamic equilibrium is manifested in the DSC curves⁵⁹ registered at a heating rate of 30 K min^{-1} as an endothermic effect with a leading edge at 130 K and a width of 20 K for samples of ice V not subjected to annealing at sufficiently high temperature or with a leading edge at 125 K and a width of also around 20 K for preannealed samples or samples being heated for the second time. The orientational relaxation times τ for the structure of ice V at atmospheric pressure estimated from the DSC curves⁵⁹ are about 70 s and 7 s at 130 K and 140 K, respectively. These values are in accord with other estimates of τ for ice V at pressures of 0.50 GPa⁵⁴ and 0.61 GPa.⁵⁸

5. Ices VI, VII, VIII and X and transitions between them

General features of the crystal structures of ices VI, VII and VIII (including the extents of the proton ordering therein) in the

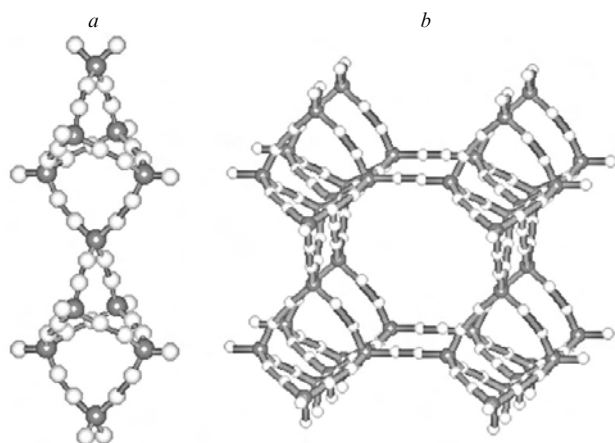


Figure 6. The structure of one of two identical independent interpenetrating frameworks of ice VI.

(a) The chain of water molecules stretched along the c axis representing the main structural unit in ice VI, (b) the pattern of assembly of the chains into the united framework.

Chains forming the second framework (not shown here) pass through the cavities of the first framework. All possible positions of the hydrogen atoms are shown; the occupancies are equal to 0.5.

regions of their thermodynamical stabilities were determined in the mid-1980s.^{60–62} Ice VI is composed of two identical independent interpenetrating water frameworks that represent structural analogues of the aluminosilicate framework $(\text{Al},\text{Si})\text{O}_2$ found in the mineral eddingtonite (Fig. 6).^{60,63} According to the available data,⁶⁰ the structure of ice VI is completely proton-disordered throughout the region of its thermodynamical stability, no indication of any proton ordering has been revealed upon cooling. The crystal structures of ices VII and VIII can be described as two interposed frameworks of ice Ic. As a first approximation, one can consider that the oxygen atoms occupy the sites of a body-centred cubic (bcc) lattice of ice VII. Ice VII is completely proton-disordered,^{60,61} whereas, in contrast, ice VIII is completely proton-ordered.^{60,62} In the structure of ice VIII, the dipole moments of all molecules of the two independent frameworks of ice Ic are oriented along the directions $[001]$ and $[00\bar{1}]$ of the tetragonal lattice. This results in the compensation of the dipole moments of both the independent frameworks in any unit cell of ice VIII. The interaction of molecules with oppositely oriented dipole moments gives rise to a relative shift of the frameworks along the c axis by $0.27 \text{ \AA}$, which slightly distorts the bcc packing of oxygen atoms. Due to the shift, two distances between any oxygen atom and its four non-H-bonded neighbours appear longer ($3.32 \text{ \AA}$) and two appear shorter ($2.74 \text{ \AA}$) than the other four distances with the H-bonded O atoms ($2.89 \text{ \AA}$).^{60,62} Ices VI, VII and VIII can be considered as self-clathrates owing to the presence of two interpenetrating water frameworks with no common hydrogen bonds in their structures.

In contrast to the transition III $\rightarrow$ IX (see Section III.3), the transition between ices VII and VIII is clear and reversible, the conversion VII $\rightarrow$ VIII occurring at a temperature about 10 K lower than the reverse conversion VIII $\rightarrow$ VII.^{60,64} Densities of ices VII and VIII at identical temperatures in the region of the transition are very similar.⁶⁰

According to data from powder neutron diffraction,^{60,62} the O–D covalent bond lengths and D–O–D bond angles in water molecules constituting ice VIII ($0.97 \text{ \AA}$ and $\sim 105^\circ$, respectively) are close to those in a free molecule¹ ($0.958 \text{ \AA}$ and 104.5° , respectively). At the same time, refinement of the structure of ice VII using the neutron diffraction data under assumption of oxygen atoms occupying sites of the bcc lattice yields unrealisti-

cally short O–D distances of 0.89 or $0.943 \text{ \AA}$ (see Refs 60, 61) and unrealistically large D–O–D angles of 109.5° . This was rationalised as disordering of the equilibrium positions of either oxygen atoms around the sites of the bcc lattice with a deviation $\delta(\text{O})$ ⁶⁰ or deuterium atoms around the positions (x,x,x) ⁶¹ with a deviation $\gamma(\text{D})$. Refinement of these models afforded more realistic O–D bond lengths and D–O–D bond angles; however the best-fit deviations $\delta(\text{O})$ and $\gamma(\text{D})$ did not exceed the respective thermal vibration amplitudes.^{60,61} Therefore, several new attempts aimed at the redetermination of the crystal structures of ices VII and VIII have been undertaken.

Nelmes *et al.*⁶⁵ elucidated the structures of ices VII and VIII at identical P and T with pressures ranging from 3.3 to 20.6 GPa and in temperature intervals lying between the transitions VII $\rightarrow$ VIII and VIII $\rightarrow$ VII (*i.e.*, under the conditions admitting the coexistence of both phases) using neutron diffraction. For ice VII, the atomic parameters were refined within three different models of deviations of O atoms from the sites of the bcc lattice: (i) six possible positions for a deviation along the family of symmetrically related directions $\langle 100 \rangle$, (ii) twelve positions for a deviation along the family of directions $\langle 110 \rangle$ and (iii) two sets of four positions forming a regular tetrahedron for a family of directions $\langle 111 \rangle$ or $\langle \bar{1}\bar{1}\bar{1} \rangle$. For the D atoms, three different models of deviations from the equilibrium positions perpendicular to the directions $\langle 111 \rangle$ were also considered: (i) three positions $(x+u, x, x)$, $(x, x+u, x)$ and $(x, x, x+u)$, where $u = \gamma/\sqrt{2}a$; (ii) three positions $(x-u, x, x)$, *etc.* and (iii) six positions $(x+v, x-v, x)$, *etc.*, where $v = \gamma/\sqrt{6}a$, a is the cubic lattice parameter. After the refinement of atomic positions, those combinations of possible O and D sites were chosen that gave the O–D distance and D–O–D angle closest to the mean values for ice VIII at the same P and T . The model of disordering of O atoms around the sites of the bcc lattice along the directions $\langle 111 \rangle$ and of D atoms over three positions $(x+u, x, x)$, *etc.* provided the maximum likelihood. Within this model, the mean O–D bond length [$0.977(7) \text{ \AA}$] and the D–O–D bond angle [$107(1)^\circ$] in the structure of ice VII at 5.1 GPa appeared very similar to the respective values in the structure of ice VIII ($0.97 \text{ \AA}$ and 107.3° , respectively). Due to the deviations of O positions from the sites of the bcc lattice, the structure of ice VII reveals two types of hydrogen bonds with lengths of ~ 2.75 and $\sim 2.93 \text{ \AA}$.⁶⁵ With an increase in pressure to 20.6 GPa , the O–D bond lengthens to $0.98 \text{ \AA}$ (ice VIII, $230\text{--}250 \text{ K}$) and $0.99 \text{ \AA}$ (ice VII, $260\text{--}280 \text{ K}$).⁶⁵

Systematic investigations into the structure of ice VIII using powder neutron diffraction at a pressure ranged from 2 GPa to 10 GPa at 265 K confirmed^{66,67} the tetragonal crystal structure with one independent oxygen and one deuterium atoms in the positions $(0, 1/4, z)$ and $(0, y, z)$, respectively. Furthermore, it was found that the O–D covalent bond linearly elongates with an increase in pressure and the relative shift ε between the two independent frameworks of hydrogen bonds decreases with an increase in pressure (rapidly and non-linearly in the range from 2 GPa to 3 GPa and linearly in the range from 3 GPa to 10 GPa).

Ice VIII is thermodynamically stable above 2 GPa . However, at temperatures below 125 K , the ice VIII structure is retained with pressure release. It was established that many properties of this phase (in particular, positions of bands in the Raman spectra⁶⁸) change non-linearly in the pressure range from 2 GPa to atmospheric pressure. The same is true for the frequencies of translational vibrations revealed in INS⁶⁸ and IR spectra.^{68,69} Neutron diffraction studies of ice VIII at 85 K at a pressure from 7 GPa to 0 GPa demonstrated⁶⁸ that this non-linearity was due to a drastic increase in the relative shift ε between the independent water frameworks in the structure of ice VIII with a decrease in pressure owing to a weakening of the electrostatic interaction between them. For a constant temperature of 85 K , the non-linear increase in ε with an increase in pressure starts at 7 GPa and ceases at $\sim 1 \text{ GPa}$.⁶⁸ As mentioned above, at 265 K , this transition starts

between 3 GPa and 2 GPa but is interrupted at a lower pressure by the subsequent transition VIII $\rightarrow$ VI.^{66, 67} Besson *et al.*⁶⁸ explained this abrupt weakening of the electrostatic interactions between the independent water frameworks in the structure of ice VIII with a decrease in pressure by a respective drastic change in the charges on the O and D atoms, which should give rise to strengthening of the covalent O–D bond and, respectively, to its shortening. Indeed, according to the available experimental data, the O–D bond length in the structure of ice VIII decreases with a reduction of pressure.⁶⁸

In contrast to ice VIII, the quenched form of ice VII (like that of ice III) cannot be recovered at atmospheric pressure by the standard methods, since it always transforms into the ordered ice VIII upon cooling. This transition occurs at about 273 K at a pressure from 2 GPa to 15 GPa. Notwithstanding, a new low-temperature metastable form of ice VII existing within the region of stability of ice VIII has recently been discovered; this can be prepared by isothermal compression of various crystalline ices or high-density amorphous ice (HDA) below 150 K. Quenched ice VII can be recovered at atmospheric pressure from this form by pressure release at low temperature.

This low-temperature metastable form of ice VII is often referred to as ice VII'. This form has been prepared for the first time by isothermal compression of ice Ih at 77 K (see Ref. 70). First, the transition Ih $\rightarrow$ HDA occurs at 1.0 GPa (it is considered in detail below in Section III.6 devoted to amorphous ices), then HDA converts into ice VII' at $\sim$ 4 GPa. Ice VII' transforms into ice VIII upon isobaric heating. Different ice phases were identified by Raman spectroscopy.

A transition of ice VI(D₂O) into ice VII' was also observed.¹² Ice VI was prepared by cooling liquid D₂O down to 300 K at 1.5 GPa. Then the temperature was further lowered to 95 K and ice VI was compressed to 5.4 GPa. During compression, an abrupt increase in pressure was observed at $P = 3.8$ GPa, which can be interpreted as a transition into a new phase. According to neutron diffraction data, this phase has a structure of ice VII, which is conserved after the isothermal (at 100 K) release of pressure down to atmospheric pressure. A neutron diffraction study of recovered ice VII' at $P = 1$ bar confirmed that this is identical with ice VII. Storage of ice sample at atmospheric pressure at 77 K did not result in any structural changes, as was also evidenced by neutron diffraction.¹²

The compression of ice II at low temperatures also affords a metastable phase with the structure of ice VII.⁷¹ In contrast to ice VII' prepared from ice VI, diffraction patterns of ice VII' samples prepared from other ices revealed some features not typical of pure ice VII. Meanwhile, the IR and Raman spectra of the differently prepared ice VII' samples were identical.^{70, 71}

Song *et al.*⁷¹ determined the boundaries of the metastability region of the low-temperature phase VII'. In that study, ice VII' was produced by isothermal compression of ices II and VI to 4–10 GPa below 120 K. Ice phases were identified by IR spectroscopy. The compression of ice VI in the temperature range of 200–273 K leads to a transition into ice VIII at 1.9–2.1 GPa. On the other hand, no conversion into ice VIII is observed upon isothermal compression of ice VI at $T < 150$ K, which is near the boundary between the stability regions of ices VI and VIII as estimated by the extrapolation of its experimentally established high-temperature part. Further increase in pressure induces the transition into ice VII'. The pressure of the transition VI $\rightarrow$ VII' increases with a decrease in temperature: from 2.8 GPa at 120 K to 7.9 GPa at 40 K. Similar trends were also reported for the compression of ice II (see Ref. 71) and HDA.⁷⁰ Further increase in pressure at a temperature below 100 K results in the transformation of ice VII' prepared by the method described above into ice VIII at 30 GPa irrespective of temperature. The isobaric heating of ice VII' also induces the transition into ice VIII, the temperature range of this transition is from 10 to 20 K, and the temperatures of

the start and completion of this transition decrease with an increase in pressure. Thus, metastable ice VII' exists in the pressure range from 2.8 GPa to 30 GPa at temperatures below 180 K.

The temperature-induced transition of ice VII' into the ordered state proceeds⁷¹ due to the activation of the orientational mobility, which allows rearrangement of water molecules into ice VIII, *i.e.*, the phase with a higher thermodynamical stability. The VII' $\rightarrow$ VIII transition upon isothermal compression at temperatures below 100 K is due to rotational tunneling of water molecules, because their rotational mobility is frozen under the conditions indicated. The probability of a tunnelling jump is determined by the lengths of the hydrogen bonds, which strongly depend on pressure and are virtually independent of temperature under the conditions considered. Thus, the pressure of the transition VII' $\rightarrow$ VIII initiated by the isothermal compression at $T < 100$ K is also virtually independent of temperature.⁷¹

With an increase in pressure, the structures of ices VII and VIII gradually change, which finally results in the formation of a new crystalline framework phase, *viz.*, ice X, where the oxygen atoms form a bcc lattice (as in the structure of ice VII) with hydrogen atoms residing exactly in the middle between the respective oxygen atoms.

In the structures of ices VII and VIII, the distances between oxygen atoms both connected and not connected by H-bonds decrease with an increase in pressure. This impedes rotation of water molecules due to, first, strengthening of the H-bonds and, second, steric repulsion of non-H-bonded adjacent oxygen atoms. Therefore, an increase in pressure suppresses orientational mobility of water molecules as regards their rotation around the oxygen atoms. In parallel, another mechanism of proton positional disordering is becoming increasingly important. The approach of the oxygen atoms linked by the O–H $\cdots$ O bonds decreases the distance between two minima of the potential energy corresponding to two possible positions of an H atom along this bond. Simultaneously, the barrier height between them is decreased thus increasing the frequency of proton tunnelling transitions between these two minima. In the case of proton-ordered ice VIII, this should bring about disordering of proton positions, *i.e.*, to a transition into ice VII. In addition, such transitions lead to the dissociation of water molecules to form defects, such as H₃O⁺ and OH[–]. When the probability of occurrence of a proton exactly in the centre of the respective O $\cdots$ O bond becomes equal to those in the minima of the potential energy along this hydrogen bond, ice VII transforms into a new form with symmetric hydrogen bonds, *viz.*, ice X. With further shortening of the distance between the oxygen atoms, the probability density of the proton localisation in a given point will have a single maximum at the centre of the bond. Furthermore, the two potential energy minima along the O–H–O bond coalesce, which all the more retains the symmetry of the H-bond.

The idea that the O–H $\cdots$ O hydrogen bond should become symmetric with a single potential energy minimum at an elevated pressure was proposed more than 30 years ago.⁷² An alternative definition of the symmetric hydrogen bond was suggested: a hydrogen bond is considered symmetric provided that the distribution function of proton positions along the hydrogen bond has the only maximum exactly at its centre.⁷³ The structures with two potential energy minima but one maximum of the proton distribution function exactly at the centre of the O $\cdots$ O bond are referred to as proton-disordered symmetric ices, whereas those with the single potential energy minimum at the centre of the hydrogen bond are referred to as proton-ordered symmetric ice.⁷⁴

The sequence of structural changes occurring with ices VII and VIII with an increase in pressure described above was fully supported by quantum-chemical calculations.^{74–76} In the calculations, the molecular dynamics method was used with atomic nuclei treated within the quantum mechanical approximation.

The simulation box contained sixteen water molecules. The simulation was performed in the *NPT* ensemble.[†] No dimensionality reduction or other approximations, including quasiclassical and quasiharmonical, apart from the neglect of exchange between identical species were applied in the calculation of the path integrals. For each specific configuration, the forces experienced by nuclei were calculated within the Born–Oppenheimer approximation based on the electronic structures determined within the density functional theory. The simulation admitted cleavage and reformation of chemical bonds.

The following sequence of transitions as a function of increasing pressure was revealed for 100 K: ice VIII–ice VII (owing to tunnelling translational transitions of protons along the hydrogen bonds)–proton-disordered ice X–proton-ordered ice X.⁷⁴ The pressure required for the transition of ice VII(H₂O) into the structure with two potential energy minima for a proton along the hydrogen bond and a single maximum of the proton distribution function located in the centre of the bond was estimated⁷⁶ to be 55 GPa at 300 K. The pressure of the next transition into ice with a single potential energy minimum in the centre of the hydrogen bond was estimated to be 110 GPa at the same temperature.⁷⁶

The implementation of diamond anvil cells over the last decades has made it possible to generate ultrahigh pressures and characterise samples subjected to extreme conditions by various spectroscopic techniques and X-ray diffraction. In particular, Hemley *et al.*⁷⁷ used X-ray diffraction with synchrotron radiation (SR) to show that oxygen atoms still occupy the sites of the bcc lattice up to a pressure as high as at least 128 GPa. A more recent SR-based single-crystal X-ray diffraction study of ice VII(H₂O) at 300 K and pressures up to 170 GPa demonstrated⁷⁸ that the oxygen framework of ice VII is preserved under these conditions and the hydrogen bonds become symmetric in the pressure range from 60 GPa to 150 GPa. Although the localisation of hydrogen atoms based on X-ray data is challenging, the proton ordering in the cited study was monitored by the intensity of reflection (111) and its symmetry equivalents, which are forbidden in the ideal bcc structure with fully disordered proton positions. With an increase in pressure, the intensities of these reflections first increased, then reached a plateau at 60 GPa and then again started to increase rapidly after 150 GPa. This is in agreement with two theoretically predicted^{74–76} transitions of ice VII first to the proton-disordered and then to the proton-ordered ice X, for which these reflections are allowed.

More direct evidence for the symmetrisation of the hydrogen bonds can in principle be provided by neutron diffraction, which can reliably locate positions of deuterium atoms. However, these experiments under ultrahigh pressures are presently not feasible since they require relatively bulky samples taking into account the low neutron-scattering cross-section. As mentioned above, neutron diffraction studies on the structures of heavy ices VII(D₂O) and VIII(D₂O) in the pressure range up to 20 GPa revealed some increase in the length of the O–D covalent bonds.^{66,67} This experimental observation is also supported by the results of quantum-chemical calculations.⁷⁶

The transitions of ices VII and VIII into the form with the symmetric hydrogen bonds can also be monitored by means of vibrational spectroscopy, since three types of bands corresponding to the three types of vibrations of a water molecule in a molecular crystal should be transformed into two types of bands typical of a framework crystal. According to the IR studies of ice VII(H₂O) at room temperature in the pressure range up to

110 GPa, the symmetrisation of the hydrogen bonds occurs between 59.5 GPa and 64.7 GPa.⁷⁹ In a more detailed IR study⁸⁰ of ices VII and VIII (both H₂O and D₂O) at temperatures between 85 K and 300 K in the pressure range up to 210 GPa, the transition to the symmetrically H-bonded structure was found to occur at 60 GPa (H₂O) and 70 GPa (D₂O). In both cases, the transitions afforded proton-disordered ice X and the experimentally measured transition pressures agreed well with the respective theoretical estimates.⁷⁶ In addition, Goncharov *et al.*⁸⁰ reported changes in the IR spectra at a pressure between 150 GPa to 160 GPa, which suggests the subsequent structural transition to the proton-ordered ice X devoid of proton tunnelling transitions between the two potential energy minima.

According to Raman studies⁸¹ of ices VII, VIII and X at pressures up to 100 GPa, the transition from ice VII to ice VIII occurs at 273 K at pressures lower than 12 GPa, and the transition temperature rapidly decreases with an increase in pressure approaching 0 K at about 60 GPa. In another Raman study by Goncharov *et al.*,⁸² the phase diagram of H₂O was determined in the regions of the transitions VII–VIII–X. The authors found that the transition into the proton-ordered ice X with the symmetric H-bonds occurs at $P > 100$ GPa.

The phase diagrams of ices H₂O and D₂O in the regions of the transitions VII–VIII, VII–X and VIII–X were also systematically elucidated by Song *et al.*⁸³ using IR spectroscopy. The transition to the proton-disordered ice X with the symmetric H-bonds was monitored in the temperature range of 12–298 K and pressure range of 2–100 GPa. The transition VII–VIII occurred at about 273 K for H₂O (at 277 K for D₂O) at a pressure of ~ 15 GPa, and the transition temperature decreased nearly linearly as a function of pressure down to ~ 100 K at 62 GPa (H₂O) and 75 GPa (D₂O). The values of pressure where the transitions VII–X and VIII–X occurred depended little on temperature: in the case of H₂O, the transition pressure increased only from 60 GPa to 62 GPa on going from 300 K down to 12 K; in the case of D₂O, the transition pressure increased from 72 GPa to 77 GPa on going from 298 K down to 16 K. The determined⁸³ temperatures and pressures of the transitions VII–VIII–X were in good agreement with the respective values obtained earlier using IR^{79,80} and Raman^{81,82} spectroscopy. The triple point VII–VIII–X was located at 100 K and 62 GPa for H₂O and at 100 K and 75 GPa for D₂O.⁸³ According to theoretical predictions,^{74–76} the isothermal compression of ice VIII between 100 K and 273 K should first initiate the transition to ice VII and then to ice X.

Schwager *et al.*⁸⁴ determined the melting curve of ices VII(H₂O) and X(H₂O) in the pressure range from 20 GPa to 90 GPa. The curve revealed a kink around 43 GPa supposedly attributed to the triple point VII–X–liquid (at 43 GPa and 1600 K). The dissociation of H₂O molecules in the liquid phase became significant only at temperatures above the melting point by 200–400 K.⁸⁴

It is of note that the symmetrisation of hydrogen bonds upon the transition VII $\rightarrow$ X switches the mechanism of proton diffusion in the crystal. In the structure of ordinary ice, the diffusion proceeds in two steps (a proton can move to the adjacent energy minimum along the H-bond or jump to a different bond) but in the case of ice with the symmetric H-bonds, the diffusion can be accomplished only by jumps between the bonds. Thus, it might be expected that the proton diffusion coefficient of ice X is higher than that of ice VII. Furthermore, compression of ice VII increases the concentration of ionic defects, which should also lead to an increase in the proton diffusion coefficient with an increase in pressure. However, direct measurements of the proton diffusion coefficient for ice VII at pressures ranged from 10.2 GPa to 63 GPa at 400 K (which lies in the region of its thermodynamic stability) showed⁸⁵ that under these conditions the proton diffusion coefficient decreases from $10^{-15} \text{ m}^2 \text{ s}^{-1}$ to $10^{-17} \text{ m}^2 \text{ s}^{-1}$ with an increase in pressure.

[†] *NPT* ensemble is a thermodynamical ensemble in which the total number of particles N , pressure P and temperature T remain constant; other thermodynamical ensembles, *e.g.*, *NVE* (with the constant total number of particles N , volume V and total energy E) and *NVT* (with the constant total number of particles N , volume V and temperature T) will be referred further in the text.

6. Kinds of amorphous ices. Pressure-induced amorphisation of crystalline ices and crystallisation of different ices from amorphous water phases on heating

As has been mentioned above, the isothermal compression of ice Ih affords HDA, which in turn transforms into crystalline ice VII' upon further compression. This example of interconversions of amorphous and crystalline ices is not unique. The kinds of amorphous ice known to date are considered in this section in their relation to crystalline ices.

Amorphous ice has been prepared for the first time by deposition of water vapour onto a copper support cooled to a temperature below 163 K (see Ref. 8). The density of amorphous ice produced in this way⁸⁶ was 0.94 g cm^{-3} . Sometimes, this type of amorphous ice is referred to as amorphous solid water (ASW). Rapid cooling of water emulsions composed of water droplets with sizes of the order of a few micrometers at a rate of more than 10^5 K s^{-1} affords amorphous ice of a similar density.¹⁹ This form is typically referred to as hyperquenched glassy water (HGW). The thermodynamical properties of ASW and HGW are much alike and thus they can be considered as the same phase.⁵⁹ Upon heating, ASW and HGW convert into ice Ic, which in turn converts into ice Ih at higher temperature.

A detailed study of phases prepared by deposition of water vapour on a cold metal support has shown⁸⁶ that the type of the phase formed depended on the temperature and deposition rate. In particular, the deposition at a rate of 10 mg h^{-1} onto a support kept at 77 K affords amorphous ice with a density of 0.94 g cm^{-3} , whereas the deposition at a rate of 4 mg h^{-1} onto a support at 10 K yields another form of amorphous ice with a density of 1.1 g cm^{-3} . For the former case, according to wide-angle X-ray scattering, the local structure is characterised by nearly ideal tetrahedral environment of water molecules with the $\text{O}\cdots\text{O}\cdots\text{O}$ angle close to 109° and the mean distance between the oxygen atoms of $2.76 \text{ \AA}$. In the latter case, the mean closest distance between the oxygen atoms is also about $2.76 \text{ \AA}$; however the overall local structure is more complicated than in the former phase. Therefore, the very slow deposition onto a very cold support (kept at a temperature below 55 K) affords amorphous ice other than ASW, which is characterised by higher density and distinct structural and thermodynamical characteristics.⁸⁶

Mishima *et al.*²⁰ developed another method for the preparation of amorphous ice by isothermal (at 77 K) compression of ice Ih. Upon compression to $\sim 1.0 \text{ GPa}$, the volume of the samples gradually decreased, the decrease became abrupt in the pressure range from 1.0 GPa to 1.5 GPa and again smooth with a further increase in pressure to 1.6 GPa . When the pressure was isothermally (at 77 K) released to the atmospheric value, the sample expanded elastically, this was accompanied by a gradual increase in its volume. The densities of the sample were 1.31 g cm^{-3} and 1.17 g cm^{-3} at 1.0 GPa and atmospheric pressure, respectively. Ice sample prepared in this way proved amorphous, as evidenced by powder X-ray diffraction. Subsequent annealing of the sample at atmospheric pressure afforded another amorphous phase with a density of 0.94 g cm^{-3} . The heavier amorphous phase was referred to as HDA (see previous Section) and the lighter one to as low-density amorphous ice (LDA). Thermodynamical properties of LDA differ from those of ASW and HGW.^{20, 59} LDA transforms into cubic ice Ic upon annealing, similar to ASW and HGW. Presently, there is no consensus on the equivalency of ASW and HGW on the one hand and LDA on the other.^{59, 87} The relation of HDA to amorphous ice with a density of 1.1 g cm^{-3} produced⁸⁶ by the slow deposition on a cold support also remains a subject of debate.

Like ice Ih, LDA converts into HDA upon isothermal compression at 77 K, albeit the transition $\text{LDA} \rightarrow \text{HDA}$ starts at lower pressure (*ca.* 0.6 GPa)²¹ than the transition $\text{Ih} \rightarrow \text{HDA}$. It is of note that the transitions $\text{Ih} \rightarrow \text{HDA}$ and $\text{LDA} \rightarrow \text{HDA}$ are irreversible but have some common features with first-order phase transitions as regards stepwise changes in certain parameters.^{20, 21}

The compression of ice Ic also yields HDA.⁸⁸ Therefore, the following closed loop of transitions can be realised: (i) $\text{Ic} \rightarrow \text{HDA}$ upon isothermal (at 77 K) compression to 0.8 GPa , (ii) elastic expansion of HDA by isothermal (77 K) pressure release down to atmospheric pressure, (iii) $\text{HDA} \rightarrow \text{LDA}$ by annealing at atmospheric pressure, (iv) $\text{LDA} \rightarrow \text{Ic}$ by annealing at higher temperature at atmospheric pressure.⁸⁸

As has been mentioned in the previous section, HDA transforms into ice VII' upon isothermal (at 77 K) compression to 4 GPa .⁷⁰ Meanwhile, the isothermal compression at higher temperature (*ca.* 140 K) initiates the transition of HDA into ice VIII. Upon isobaric heating, HDA can convert into various crystalline ices, depending on the pressure and heating rate. For instance, the transition of HDA into ices Ih (through the intermediate steps of LDA and Ic), VI and VIII at $T \leq 160 \text{ K}$ was reported.⁷⁰ Systematic studies of conversions of HDA in the course of isobaric heating at different pressures revealed that HDA transforms into LDA at $P \approx 0.2 \text{ GPa}$ ⁸⁹ and, at higher pressures, subsequently into crystalline ice III' ($\sim 0.2\text{--}0.3 \text{ GPa}$), a mixture of ices IV, V and XII ($\sim 0.4\text{--}0.7 \text{ GPa}$) and a mixture of ices VI and XII ($\sim 1.0\text{--}1.2 \text{ GPa}$).⁹⁰ The aforementioned crystalline ice III' represents ice III with a higher degree of proton ordering, which transforms first into ice IX and then to ice II upon isobaric heating at $\sim 0.2\text{--}0.3 \text{ GPa}$. Some features of the transition⁹¹ of HDA to ices IV and XII upon isobaric heating are discussed in more detail below.

The density of HDA increases in the course of isobaric heating at 1.1 or 1.9 GPa . If the heating of HDA is stopped before the start of crystallisation of ices IV or XII, a new amorphous ice phase with a density of 1.25 g cm^{-3} different from the phases described above can be recovered at atmospheric pressure by cooling the sample down to 77 K followed by pressure release at this temperature.⁹² This phase is referred to as very high-density amorphous ice (VHDA). Upon heating at atmospheric pressure, VHDA is transformed directly to LDA without intermediate formation of HDA.⁹² It is of note that the structures of HDA and VHDA determined at similar densities are very similar, therefore, VHDA probably should not be considered as an independent amorphous phase.⁹³

Section III.8 considers yet another type of transitions between crystalline and amorphous ices, *viz.*, temperature-induced transformation of quenched ices VII' and VIII into LDA.¹²

At present, the investigations into amorphous ices are focused on the following issues.

1. How different are the known amorphous water phases and what properties are the most indicative of this difference? In particular, what is the difference between the local structures of amorphous ices? What is the fundamental reason for water polyamorphism?

2. Which of the aforementioned amorphous phases can be considered as a thermodynamic extension of supercooled liquid water to the region of lower temperatures?

3. What are the thermodynamic characteristics of the transitions between amorphous ices? In particular, does the second critical point of water exist, which corresponds to the experimentally observed first-order $\text{LDA} \rightarrow \text{HDA}$ transition, and what are its P , T coordinates?

4. What is the mechanism of the pressure-induced amorphisation of ices Ih and Ic and whether such amorphisation is possible for other crystalline ices?

5. What is the mechanism of the solid-state crystallisation of amorphous ices upon annealing at $150\text{--}170 \text{ K}$?

A discussion of the above issues can be found elsewhere.^{87, 94, 95} Ponyatovsky *et al.*⁹⁶ proposed a new method (alternative to the adopted method by Mishima and Stanley⁹⁴) for the determination of the coordinates of the second critical point of water and applied it⁹⁷ to elucidate non-equilibrium phase diagrams of substances other than water. Non-equilibrium transitions between crystalline and amorphous water phases in the low-temperature part of the phase diagram were studied in detail

by Gromnitskaya *et al.*⁹⁸ and by Lyapin *et al.*⁹⁹ Very recently, Brazhkin and Lyapin¹⁰⁰ surveyed the experimental data on the transitions between disordered condensed phases (either liquid or solid) of various compounds and modern theoretical approaches to their description.

7. Ices IV and XII

Let us resume the discussion of properties of crystalline ices and transitions between them.

Some properties of ices Ic and IX, which have no specific regions of thermodynamic stability in the water phase diagram, have already been discussed above. In addition to these two forms, two more modifications, *viz.*, ices IV and XII, are also known to exist only in metastable state within the regions of stability of other ices.

The existence of metastable crystalline ice IV has already been mentioned in the very first studies^{101, 102} of the water phase diagram. It was established that ice IV exists within the region of stability of ice V and can be prepared by overcooling liquid water in a certain pressure range.^{4, 102} The structure of quenched ice IV recovered at atmospheric pressure at 10 K was determined by Engelhardt and Kamb¹⁰³ (Fig. 7). Structural parameters of ice IV were also reported for 210 K and 0.7 GPa, which lies within the region of its metastable existence.⁹⁰

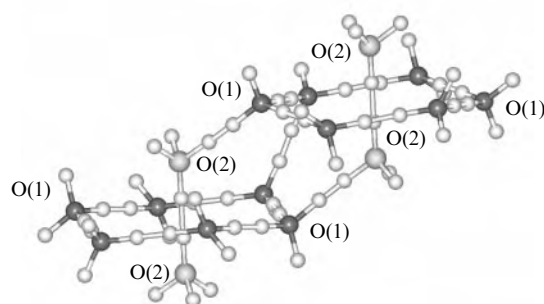


Figure 7. Two identical fragments of the structural motif of ice IV linked to each other. All possible positions of the H atoms (with the occupancies of 0.5) are shown.

Note that ice IV persisted at 248 K only for a short period from a few seconds to several minutes before spontaneous transformation into a more stable phase in a study⁴ aimed at determining transition lines IV–VI and liquid–ice IV and the triple point liquid–IV–VI. In the study of the transition liquid–ice IV within the region of stability of ice V, the formation of other metastable crystalline ices was detected as well but it appeared impossible to reliably characterise them since the probability of their formation was even lower and their conversion into the stable phase proceeded even faster than for ice IV.⁴

A reproducible method for the preparation of one of these metastable crystalline phases, ice XII, was developed quite recently.⁶ It consists of slow cooling of liquid D₂O in an argon atmosphere at 0.55 GPa and 260 K, *i.e.*, again within the region of stability of ice V. Under these conditions, the crystal structure of ice XII was determined (Fig. 8) and its density was measured, which appeared rather close to that of ice IV and somewhat higher than that of ice V.

Later on, the same phase was prepared¹⁰⁴ in a totally different region of the water phase diagram by isothermal compression of ice Ih to 1.8 GPa at $T < 150$ K, albeit it is HDA rather than crystalline ice that was produced under nearly the same conditions in previous studies.^{20, 70} The reasons for the formation of ice XII instead of HDA remained unclear. Further investigations revealed¹⁰⁵ that the compression of Ih yields ice XII always through the intermediate formation of HDA. Ice XII crystallises only from LDA rather than directly from ice Ih and only at a

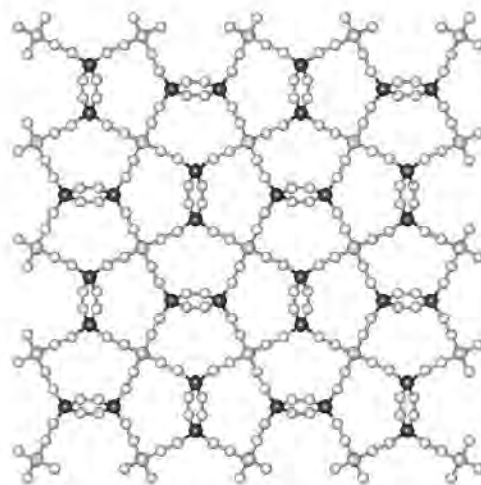


Figure 8. The structure of ice XII (the projection along the *c* axis). The occupancies of H positions are close to 0.5.

sufficiently high pressure and temperature. In particular, Koza *et al.*¹⁰⁴ found that ice XII was produced by the compression of ice Ih to $P > 1.1$ GPa at 77 K only in the case of imperfect mechanics operation giving rise to pressure drops, whereas no ice XII was formed in the case of smooth pressure trends. Likely, pressure drops result in acoustic pulses and consequent local heating of the sample up to 260 K, which actuates nucleation and growth of ice XII crystallites.¹⁰⁵ From the standpoint of these results, boundaries of the region of existence of ice XII determined by Koza *et al.*¹⁰⁴ required verification accounting for the pressure drops.

According to the study³ of the transition HDA → XII → stable crystalline ice upon isobaric heating of HDA prepared by smooth compression of ice Ih at various pressures, the refined second region of existence of metastable ice XII lies within the region of stability of ice VI and extends from 158 to 212 K and from 0.7 to 1.5 GPa. Interestingly, the two regions of metastability of ice XII are disconnected, *i.e.*, there is no direct path to pass from one region to another avoiding phase transitions. In particular, ice XII prepared from liquid water at 260 K transforms⁶ into stable ice V upon cooling, whereas ice XII prepared from HDA transforms³ into ice VI upon heating above 212 K. It is of note that the temperature-induced transition of HDA to ice XII is much faster than the subsequent transition of ice XII to ice VI. Presumably,³ the structure of HDA intrinsically contains crystallisation nuclei of ice XII.

Further analysis of properties of ice XII in comparison with those of ice V using DSC suggested⁵⁹ that some features of the DSC curves of ices XII and V can be explained by kinetic activation of the proton transition order–disorder resulting in partial proton ordering therein due to prolonged storage at 110–115 K. At the same time, the available neutron diffraction data^{6, 104} strongly suggest the complete proton disorder in the structure of ice XII. Salzmann *et al.*⁵⁹ proposed the following explanation of this discrepancy. In one of the neutron diffraction studies,⁶ the structure of ice XII was determined at 260 K, which is above the suggested transition order–disorder. In the second study,¹⁰⁴ ice XII was prepared at low temperature under the action of pressure drops. Rapid quenching of the sample heated by an acoustic pulse can in this case be responsible for the freezing of the positional proton disorder.

The measured³ lower boundary of the region of existence of ice XII prepared from HDA is determined by kinetics of the transition HDA → XII and this type of ice XII can in principle be cooled down to extremely low temperatures. In particular, the structure of ice XII was determined at 1.5 K and atmospheric pressure.¹⁰⁴ (Those samples were produced from HDA at different

pressures; then the pressure was released to atmospheric pressure while the samples were cooled to 77 K, and finally the samples were cooled down to 1.5 K.) It was even suggested³ that ice XII prepared by heating of HDA and existing within the region of stability of ice VI can become thermodynamically more stable than ice VI at low temperature. However, Johari¹⁰⁶ showed that the Gibbs free energy of ice XII at 1.1 GPa and 100 K is higher than that of ice VI thus confirming that ice VI is the stable phase.

In several cases, some amounts of ice IV formed upon annealing of HDA in addition to ice XII.³ A more detailed study⁹¹ of the crystallisation of HDA upon isobaric heating at $P = 0.81$ GPa up to 195 K at variable rates confirmed the possibility of the formation of ice IV. Under the conditions used, HDA converted into ices XII and IV simultaneously with the relative yields depending on the heating rate.⁹¹ Pure D₂O ice IV and nearly pure H₂O ice IV were formed on slow heating at a rate of 15 K min⁻¹. Mixtures of ices IV and XII were obtained at intermediate heating rates. This means that both entirely metastable high-pressure ice phases, ices IV and XII, exist within approximately identical regions of the phase diagram and can be prepared by either crystallisation of supercooled liquid or temperature-induced crystallisation of metastable LDA.

It is of note that very soon after the publication of the neutron diffraction study of ice XII,⁶ an independent report on the preparation of a new ice phase, unknown for that moment and crystallising from liquid water within the regions of stability of ices V and VI, appeared.⁵ The authors determined the melting curve of the phase, described typical crystal morphology and measured Raman spectra but failed to assign it to ice XII, since very limited information on this modification was then available. Recently measured¹⁰⁷ Raman spectra of ice XII manifest pronounced similarity to the spectra of that unidentified phase⁵ thus strongly suggesting that it was indeed ice XII.

Salzmann *et al.*¹⁰⁸ performed a comparative analysis of the thermodynamical properties of metastable ices IV and XII. In particular, the triple point for the metastable equilibria IV–XII–liquid were located at 0.5–0.6 GPa and ~267 K in the intersection of melting curves of ices IV (see Ref. 4) and XII (see Ref. 5). Since both ices IV and XII are completely proton-disordered,^{6,90,103,104} they should be characterised by a nearly zero entropy difference. Based on the Clapeyron–Clausius equilibrium, this means that the boundary between the phases IV and XII should be nearly parallel to the temperature axis. Ice IV is more stable at $P < 0.5–0.6$ GPa, since its melting curve lies above that of ice XII under these conditions.¹⁰⁸ In contrast, ice XII becomes more stable above this threshold pressure. Surprisingly, the temperature-induced transition XII → IV was observed experimentally⁹⁰ at 0.6–0.7 GPa, *i.e.*, in the region of the higher stability of ice XII according to the above thermodynamic arguments. Salzmann *et al.*¹⁰⁸ noted that the accuracy of the experimental measurement of pressure⁹⁰ was of the order of 0.1 GPa, which can explain the apparent discrepancy: likely, the pressure of the transition XII → IV was actually lower than the reported value⁹⁰ of 0.6–0.7 GPa, *i.e.*, it lied in the region of higher stability of ice IV.

8. Transformations of quenched high-pressure ices upon heating at atmospheric pressure

As was established quite a long time ago, many high-pressure ices recovered at atmospheric pressure in their metastable quenched forms readily transform into ice Ic upon annealing. In particular, annealing of quenched ices II, IX, V and VI at $P = 1$ bar yields metastable ice Ic, which converts into thermodynamically stable ice Ih at higher temperature.^{13,14,109} The rates of these transitions depend on temperature and thermal prehistory of the sample under study. These processes can be utilised for the production of ice Ic in large quantities.¹³

However, not all quenched high-pressure ices transform into ice Ic upon annealing at atmospheric pressure. For instance, quenched ice VIII first converts into LDA and only then the

subsequent transitions LDA → Ic and further Ic → Ih occur.¹⁵ Like in the previous case, the temperature and rate of the transition depend on the heating rate. In particular, at a heating rate of 10 K h⁻¹, the transitions VIII → LDA, LDA → Ic and Ic → Ih are revealed in thermograms as peaks centred at 136 K, 148 K and 210 K, respectively.¹⁵

Quenched ice VII' prepared by compression of ice VI first to 3.8 GPa and then to 5.4 GPa at 95 K followed by pressure release to atmospheric pressure at a temperature of 100 K undergoes similar thermal transformations.¹² In this case, a slow temperature increase to 115 K initiates gradual ordering of ice VII' into ice VIII, then the transformation of ices VII' and VIII into LDA starts at $T = 125$ K, which is completed after annealing of the sample at 138 K for 1.5 h. The neutron diffraction pattern of the sample heated to 152 K is fully consistent with that of Ic.¹²

There have been several reports^{16,17} that quenched ice VIII converts into LDA and HDA simultaneously upon heating to 130–135 K at a rate of 1 K min⁻¹. This conclusion was derived on the basis of neutron diffraction data. In a more recent study,¹² similar neutron diffraction patterns were obtained but the conclusion^{16,17} on the formation of HDA was questioned. Klotz *et al.*¹² argued that the peak observed in the neutron diffraction patterns previously attributed^{16,17} to HDA was too narrow for an amorphous phase and thus its appearance should rather be explained by an admixture of an unidentified crystalline phase. Furthermore, it is known²¹ that HDA irreversibly converts into LDA above 125 K. Therefore, we may conclude with a high level of confidence that the temperature-induced conversion of quenched ice VIII into LDA is not accompanied by the concomitant formation of HDA.

In summary, heating of quenched ices VII' and VIII brings about their transformation into LDA, which in turn converts into Ic and further to Ih. Although both phases VII' and VIII behave similarly, ice VII' undergoes partial ordering to ice VIII and the transition VII' → LDA starts at lower temperature than the respective transition VIII → LDA.

According to the most recent data,^{18,104,107} quenched ice XII also transforms into ice Ic upon heating at atmospheric pressure. We would like to remind that it is ice XII, which is crystallised within its low-temperature metastability region from HDA during heating, that can be quenched. The conversion of quenched ice XII first prepared at atmospheric pressure by Koza *et al.*¹⁰⁴ into ice Ic upon heating to $T > 135$ K was reported. More recently, the thermal transition of quenched ice XII into ice Ic at $P = 1$ bar was studied in more detail.¹⁸ In this study, samples of ice XII were repeatedly heated to a specific (ever increasing) temperature ranged from 113 K to 183 K, maintained at this temperature for 5 min and cooled down to 93 K to register the X-ray diffraction pattern.¹⁸ The diffraction pattern obtained fully corresponded to the transition XII → Ic revealing no evidence of any amorphous phase.

Based on the high rate of the crystallisation of ice XII from HDA, a close relation between the structures of these two phases was suggested³ (see Section III.7). With this respect, Tulk and Klug¹¹⁰ proposed, disregarding the X-ray diffraction results,¹⁸ that quenched ice XII should behave in a way similar to HDA upon heating, *i.e.*, transform first into LDA and only then into ice Ic. They recorded Raman spectra¹¹⁰ of a sample of ice XII maintained at 12 K, heated to 120 K at a rate of 10 K min⁻¹, maintained at this temperature for several minutes, heated to 130 K at the same rate and maintained at this temperature for 15 min. The spectra registered at 12 and 130 K were ascribed to the crystalline phases XII and Ic, respectively, whereas a broad peak revealed in the spectrum measured at 120 K was attributed¹¹⁰ to LDA. Thus, based on the Raman spectra they concluded that quenched ice XII indeed behaves analogously to ices VII' and VIII: upon annealing at atmospheric pressure it transforms first into LDA, which in turn converts further into ice Ic.

Salzmann *et al.*¹⁰⁷ also recorded Raman spectra in ice XII during heating from 80 K to 150 K at a rate of 2 K min⁻¹. They observed that the positions of bands typical of ice XII drifted slightly with an increase in temperature; new bands typical of ice Ic emerged at 140 K, the bands of ice XII disappeared at about 150 K indicating that the transition XII → Ic was complete. No evidence of the intermediate formation of an amorphous phase was observed in agreement with the X-ray diffraction study cited above.¹⁸ Rationalising the discrepancy with the previous Raman study,¹¹⁰ Salzmann *et al.*¹⁰⁷ speculated that the initial sample in the study by Tulk *et al.*¹¹⁰ could be some phase other than ice XII. At least, that sample was not attested with diffraction methods, while its reported Raman spectrum¹¹⁰ differed from that of crystallographically characterised ice XII.¹⁰⁷

We may thus state with a high level of confidence that ice XII, like ices II, IX, V and VI transforms upon heating at atmospheric pressure directly to ice Ic, which in turn converts into ice Ih with a further increase in temperature. For ice IV, this sequence of transitions was also confirmed¹¹¹ using Raman spectroscopy for the temperature range of 80 < *T* < 145 K (at a heating rate of 2 K min⁻¹). It is of note that ices Ic and Ih cannot be distinguished by their Raman spectra and thus the formation of Ic was suggested^{107,111} only by analogy with the behaviour of other quenched ices.

Summarising all the experimental evidence discussed above, the annealing of quenched high-pressure ices II, IX, V, VI, IV and XII at *P* = 1 bar induces their transformation directly to Ic, whereas ice VII' and VIII first convert into LDA and only then the subsequent transition LDA → Ic occurs. Ice Ic converts into ice Ih upon further heating. Ice XI is stable at atmospheric pressure, it converts into ice Ih upon heating to 72–74 K.^{33,34} Ice III cannot be recovered at atmospheric pressure in the quenched form by the standard cooling at high pressure due to the inevitable transition III → IX. At the same time, no information is available on the thermal transformations at *P* = 1 bar of quenched low-temperature ice III' prepared⁹⁰ by the isobaric heating of HDA at 0.2–0.3 GPa. Ice X has not yet been obtained in the quenched form due to its transition into ice VIII upon pressure release.

IV. Inelastic neutron scattering spectroscopy of water ices

Vibrational spectroscopy can provide valuable information on the potential of the interactions between water molecules in various condensed phases since vibrational frequencies of a molecule are determined by the shape of the corresponding potential well. However, the interpretation of low-frequency part of conventional IR and Raman spectra of water phases is challenging due to the complex pattern of vibrational motions of H-bonded water molecules including acoustic, translational optical and libration modes. The parameters of molecular vibrations can be retrieved in the most straightforward way from inelastic neutron scattering, since INS spectra relate to the density of vibrational states of water molecules in a relatively simple manner.^{38,112} The INS spectra of quenched ices Ih, Ic, II, IX, V, VI, VII, VIII and XI, as well as of LDA and HDA (for both H₂O and D₂O) measured at atmospheric pressure at 15 K have been comprehensively analysed.¹¹²

The INS spectra of ices Ih and Ic are virtually identical.¹¹² This can be explained by the fact that vibrational spectra of condensed water phases are primarily determined by the interactions of water molecules with their proximate rather than long-range environment and the local environments of H₂O molecules in these two proton-disordered ices are identical: the closest oxygen neighbours reside in the vertices of a nearly ideal tetrahedron at distances of ~2.75–2.76 Å. The INS spectrum of LDA that features a local structure very similar to the structures of Ih and Ic (see Section III.6) also looks similar to those of Ih and Ic.

The INS spectra of ices Ih and Ic reveal two peaks at 28 meV[‡] and 37 meV with an integral intensity ratio of ~1 : 2 in the region of translational optical vibrations. These two peaks are located at nearly the same positions for H₂O and D₂O; they are observed in the spectra of both polycrystalline powders and single crystals (irrespective of their orientation).¹¹² Lattice dynamics and molecular dynamics simulations using traditional interaction potentials for water molecules failed to reproduce these two features in the low-frequency region.^{38,112} In 1993, Li and Ross suggested³⁸ that the split band of translational vibrations can be due to the presence of two types of hydrogen bonds (*viz.*, strong and weak one) in the structures of these ices, which become inequivalent due to different mutual orientations of adjacent molecules (see Fig. 2).

Since only bonding configurations depicted in Figs 2*c* and 2*d* are possible in the crystal structure of Ic, the number of former configurations should be twice as that of latter configurations in the case of a random distribution of protons obeying the Bernal–Fowler rules. With this respect, a model for the simulation of vibrational spectra of ices Ic and Ih was developed,³⁸ which assumed that two types of H-bonds, *viz.*, strong and weak ones, described by different force constants are present in the crystal structures of ices Ih and Ic in a ratio of 2 : 1.

It is of note that the above ratio of strong and weak H-bonds valid for the structure of Ic should be different in the case of ice Ih, since only one third of the hydrogen bonds between the hexagonal layers can adopt the configuration depicted in Fig. 2*a* from mere geometrical considerations. Nevertheless, the model assumed^{38,112} that the structure of Ih also features two strong H-bonds per weak one. A simulation within the lattice dynamics approach for a simulation box composed of eight unit cells of ice Ih with a random distribution of strong and weak bonds (in a ratio of 2 : 1) with the optimised force constants provided good agreement between the theoretical and experimental spectra; in particular, the peaks at 28 and 37 meV were quantitatively reproduced.^{38,112} The best-fit values for the force constants were 2.1 and 1.1 eV Å⁻² for the strong and weak H-bonds, respectively. It is of note that the empirically optimised ratio between the force constants, *i.e.*, 2.1 : 1.1, significantly exceeds the value that can be estimated based on the electrostatic repulsion of protons. In order to explain this discrepancy, the authors of the model^{38,112} speculated that the electron density distribution for a specific water molecule is highly sensitive to the orientations of surrounding molecules.

For the crystal structure of proton-ordered ice VIII, this model predicts the presence of only weak H-bonds (see Fig. 2*b*). The feature corresponding to strong bonds should thus be absent in the vibrational spectra of ice VIII. This fully agrees with the experimental INS spectrum of ice VIII.¹¹² Furthermore, the spectrum of proton-disordered ice VII should reveal the band of strong H-bonds, which again agrees with the experiment.¹¹² Meanwhile, the INS spectrum of proton-disordered ice XI (which includes both strong and weak H-bonds in a ratio of 3 : 1) simulated within the model of two force constants appeared drastically different from the experimental spectrum in the region of translational vibrations, which was rather similar to the spectrum of ice Ih.^{112,113} Likely, the model of two force constants for the hydrogen bonds represents merely a convenient empirical model, which well reproduces the spectra of ices Ih and Ic, since it was parametrised (as regards the values of force constants and the relative number of strong and weak bonds) just for this case but is not always applicable to the description of spectra of other water ices.

A comparison of INS spectra of ices Ih and XI, on the one hand, and of ices VII and VIII, on the other hand, demonstrates¹¹² that the spectra of proton-ordered phases reveal distinct narrow peaks, whereas the spectra of related proton-disordered phases are significantly smoother. The same is also true for IR and

[‡] 1 meV = 8.066 cm⁻¹.

Raman spectra. This is due to the fact that water molecules in the structures of proton-ordered ices with only one crystallographic type of oxygen atoms have identical environments thus occupying potential wells with identical shapes. Meanwhile, the shapes of potential wells, which depend on both local and long-range environment, in the proton-disordered ices somewhat differ even for identically oriented water molecules with the oxygen atoms of the same crystallographic type. This gives rise to broadening of peaks in the vibrational spectra of proton-disordered ices and their general smoothing as compared to the respective spectra of proton-ordered ices.

The model of two force constants^{38,112} was extended to the case of ice II.¹¹⁴ The translational region of its INS spectrum was reproduced to a high accuracy within a model that considered water molecules as points. Five force constants were introduced for the description of intermolecular interactions, two of them were selected to be identical and equal to that of the strong H-bond ($2.1 \text{ eV } \text{\AA}^{-2}$) from the respective model^{38,112} of ice Ih. The representation of molecules as points becomes insufficient for the calculation of librations, which required introduction of nine force constants. The simulations enabled an assignment of the peaks observed in the low-frequency part of the experimental INS spectrum to specific types of translational vibrations of water molecules in the crystal structure of ice II. A splitting of the libration band to a well-resolved sharp maximum at 68 meV and two broader bands, which resembles the respective region in the spectra of ice Ih, is characteristic of the INS spectrum of ice II.¹¹⁴

The lower-frequency boundary of the libration region in the INS spectra shifts towards lower energies in the series Ih–IX–II–V–VI–VIII.¹¹² This shift reaches the maximum value of about 12 meV for ices VI and VIII. The spectrum of LDA (H_2O) is characterised by a similar shift (13 meV). The INS spectrum of ice VI has other common features with that of HDA (both for H_2O ¹¹⁵ and D_2O ¹¹⁶), which allowed Kolesnikov *et al.*^{115,116} to suggest that similar dynamical properties of water molecules in HDA and ice VI are due to similar local environments of water molecules in these structures, which gives rise to potential wells with similar shapes. In particular, they proposed^{115,116} that domains of two interpenetrating but not interlinked frameworks of hydrogen bonds observed in the structure of ice VI are also characteristic of HDA. Note that the libration band in the INS spectrum of ice VI, like that of ice II, can be subdivided into three regions, including a well-resolved peak, which is however somewhat broader than the corresponding peak at *ca.* 60 meV in the spectrum of proton-ordered ice II. No similar peak was observed in the libration band of the INS spectrum of HDA.

The shift in the libration band boundary in INS spectra towards lower energies correlates with an elongation of mean $\text{O}\cdots\text{O}$ distances along the series I–IX–II–V–VI–VIII.¹¹⁷ This regularity is of common character. For instance, according to pressure-dependent INS spectroscopy of ice II, the lower-frequency boundary of the libration band shifts towards higher frequencies with an increase in pressure, which results in shortening of mean $\text{O}\cdots\text{O}$ distances.¹¹⁷ Furthermore, the lower-frequency boundary of the libration band in the INS spectrum of ice II-based helium clathrate hydrate (which is, in overall, quite similar to that of helium-free ice II) is shifted towards lower frequencies in agreement with somewhat elongated mean $\text{O}\cdots\text{O}$ distances.⁴⁶

An introduction of a small amount of H_2O into D_2O results in the incorporation of HOD molecules into the crystal structure, which violates periodicity. Vibrations of such impurity molecules give rise to narrow localised defect modes at frequencies differing from the vibrations of the whole lattice. Three defect modes characteristic of an HOD molecule can be attributed to different shifts of its H atom within the D_2O lattice. The μ_3 mode corresponds to shifts of the H atom along the hydrogen bond; the μ_2 mode emerges due to vibrations within the HOD plane perpendicular to the hydrogen bond; and the third defect mode, μ_1 , corresponds to vibrations in the direction orthogonal to the

first two. This type of vibrations of H atoms within HOD molecules was elucidated for quenched D_2O ices Ih, II, VIII and HDA at atmospheric pressure using INS.¹¹⁸

The peak corresponding to the low-frequency μ_1 mode shifts towards lower frequencies in the series Ih–II–VIII–HDA. The μ_1 band of ice VIII has a regular Gaussian profile, whereas in the case of ice Ih, it can be well approximated only with two Gaussians, which is in agreement with the model of two force constants. The peak corresponding to the high-frequency μ_3 mode shifts towards higher frequencies along the same series. Meanwhile, there is virtually no difference between frequencies corresponding to the μ_2 mode for various ice phases. It is of note that the shape of the μ_1 band can be also explained without recourse to the model of two force constants.¹¹⁹

Therefore, inelastic neutron scattering provides essential information on the vibrational spectrum of water molecules constituting various ice phases, which makes it possible to analyse the character of the intermolecular interactions therein.

V. Computer simulations of crystalline ices

Molecular dynamics (MD) represents yet another powerful tool that makes it possible to evaluate dynamical properties of water molecules in various condensed phases.¹²⁰ This is a general method for the numerical simulation of possible states adopted by a many-particle system, which is based on the integration of the Newton equations for all atoms constituting the system under study. The MD method can be applied to water systems only provided that the potentials of interactions between all atoms from both the same and different water molecules are known. Presently, a number of different potentials applicable to the simulation of water systems have been elaborated, however their comprehensive survey lies beyond the scope of the present review. Some advantages and disadvantages of several most common potentials are discussed elsewhere.^{121–123}

Molecular dynamics can be applied to direct computational problems aimed at the prediction of specific numerical values of desired parameters and to model problems pursuing the exploration of possible qualitative trends in the system behaviour irrespective of exact values. The first type of problems include, for instance, calculations of the equations of states for various ice phases. In this case, the resultant numerical values usually strongly depend on the potential selected. The second type of problems are diverse and numerous; among them, the following can be mentioned: verification of the stability of a real or hypothetical crystalline phase at a given interaction potential, elucidation of the character of motion of separate atoms or the whole molecule, monitoring of structural transitions at the molecular or atomic level, *etc.* In contrast to the first type of problems, specific parameters of the interparticle interactions are often not essential in such simulations, since in the case of a reasonably selected potential, the qualitative simulation results much less depend on its exact parameters. Below we consider some recent works on MD simulation of condensed water phases, including the problems of both types.

Borzsák and Cummings¹²⁴ elucidated the structural stability of a hypothetical proton-ordered analogue of ice XII as a function of proton configuration. The model structure had the same oxygen sublattice and unit cell as ice XII. For such a unit cell, ninety different proton configurations conserving the periodicity of the structure are possible with exactly one proton on every hydrogen bond and exactly two protons covalently bound to every oxygen atom.¹²⁴ All these possible configurations were simulated using molecular dynamics with the TIP4P potential²³ for a runtime of 100 ps. Only twenty-one configurations proved stable, whereas the remaining structures (both polarised and non-polarised) collapsed during the simulation. The most stable proton configuration in the proton-ordered ice XII analogue corresponded to a structure polarised along the *c* axis.¹²⁴ Note that after publication of these computational results, partial proton

ordering in ice XII upon prolonged storage at 110–115 K was suggested based on the experimental DSC data, although the character of this ordering was not clarified⁵⁹ (see Section III.7).

Ayala and Tchijov¹²⁵ calculated specific volumes v of ices III and V as a function of pressure at a specific temperature (246 K for ice III and 238 K for ice V) and as a function of temperature at a specific pressure (0.25 GPa for ice III and 0.5 GPa for ice V). They used molecular dynamics within the NPT ensemble with the TIP4P and TIP5P interaction potentials (see Ref. 126). In this computer experiment, the studied ice phases did not melt at pressures and temperatures lying within their regions of stability. Nevertheless, ice V did melt around the point $T = 268$ K, $P = 0.5$ GPa with the TIP4P potential, whereas the TIP5P showed no melting. For both ice phases, the two potentials afforded differently looking functions $v_T(P)$, *i.e.*, specific volume *vs.* pressure at constant temperature. More specifically, the curve $v_T(P)$ obtained with the TIP5P potential was located lower than that obtained with the TIP4P potential and both curves were lower than the respective curve $v_T(P)$ estimated from the experimental data.⁴⁹ As for the function $v_P(T)$, the TIP5P potential again yielded lower values of specific volume for both ice phases considered.

Báez and Clancy¹²⁷ calculated various parameters of the transitions liquid–crystal for a number of real and hypothetical ices at atmospheric pressure. The simulation was performed using the non-equilibrium molecular dynamics with the SPC/E potential (see Ref. 128). In contrast to the case of real water, the SPC/E-based simulation predicted that it is ice B,¹²⁷ a novel phase with a density higher than that of ice Ih, which was not observed experimentally, rather than ice Ih that should be the most stable crystalline phase at 100 Pa. The authors also attempted to grow various crystalline ices from the melt (*i.e.*, liquid water) at the respective ice–melt interface in the course of the simulation. In the case of ice II–melt interface, they observed a growth of ice II on some parts of the interface and partial melting on other areas in the same computer experiment, thus it was impossible to decisively conclude on the possibility of growth of ice II crystals in the model system. Meanwhile, in the case of the hypothetical ice B–melt interface, stable growth of ice B crystals was clearly observed. Furthermore, the phase B spontaneously formed from another hypothetical ice A (which has the structure of ice IX with a modified proton arrangement) in a simulation of ice A–liquid interface.¹²⁷ It is of note however that since the SPC/E potential rather poorly reproduces experimental properties of water and water ices, these results are mainly of methodical significance.

Zheligovskaya *et al.*¹²⁹ utilised MD to elucidate the dynamical properties of H₂O molecules in ices II and IX. The interactions between water molecules was described using the Poltev–Malenkov (PM) potential;^{130,131} the simulation was performed within the NVE ensemble for two values of the total energy of the system corresponding to temperatures of 82 and 201 K for ice II and of 87 and 203 K for ice IX. According to the direct visual control and a hydrogen bond analysis, the structures of these ices survived the simulation at the temperatures used.

The crystal structures of ices II and IX are proton-ordered and include two crystallographically different H₂O molecules. The following characteristics were calculated for the whole system: the mean-square displacement of the centre of gravity of water molecules as a function of time

$$\langle r^2(t) \rangle = \frac{1}{N} \sum_{i=1}^N [r_i(t) - r_i(0)]^2$$

[$r_i(t)$ is the radius-vector to the centre of gravity of the i th molecule at a time moment t ; the summation is performed over all N molecules in the system], the autocorrelation function of velocities of centres of gravity of water molecules

$$c(t) = \frac{\frac{1}{N} \sum_{i=1}^N [v_i(t)v_i(0)]}{\frac{1}{N} \sum_{i=1}^N [v_i(0)v_i(0)]}$$

[$v_i(t)$ is the velocity vector of the gravity centre of the i th water molecule at a time moment t] and the autocorrelation function of velocities of hydrogen atoms $c_H(t)$ (given by a similar formula). These parameters were also calculated separately for each of the two subsystems of crystallographically equivalent water molecules.

Different local environments of crystallographically non-equivalent water molecules lead to the respective difference in their dynamical characteristics. In particular, the amplitude of translational vibrations of the water molecules H₂O(1) constituting corrugated six-membered rings in the crystal structure of ice II appeared somewhat larger than that of the molecules H₂O(2) that constitute flattened rings (see Fig. 3). Similarly, in the case of ice IX, the amplitude of translational vibrations of the water molecules H₂O(1) constituting helices was smaller than that of the water molecules H₂O(2) that link the helices into the united framework (see Fig. 5b). Based on the autocorrelation function of velocities of centres of gravity of water molecules, the density of translational vibrational states was calculated, whereas the density of librational vibrational states was derived from the autocorrelation function of velocities of hydrogen atoms. The derived densities of librational and translational vibrational states were slightly different for crystallographically non-equivalent water molecules for the structures of both ices II and IX. A comparison of the theoretical density of librational vibrational states with the experimental INS spectra indicates¹³² that the use of the PM potential underestimates the position of the libration band with respect to that in the experimental spectrum.

As has been mentioned above, in the case of proton-disordered ices, dynamical characteristics differ even for both crystallographically independent molecules and molecules with crystallographically identical O atoms even those possessing O–H bonds with the same orientation. The effects of the proton order on the dynamical characteristics of water molecules in crystalline ices were elucidated with proton-disordered ice III and its proton-ordered counterpart, ice IX, as examples.¹³³ As in the previous case,¹²⁹ ices III and IX were simulated using MD with the PM potential within the NVE ensemble. The same parameters as listed above¹²⁹ were calculated for all water molecules in the model, separately for the crystallographically non-equivalent molecules H₂O(1) and H₂O(2) and, in the case of ice III, additionally for all water molecules with specifically oriented protons. According to the results obtained, the difference between the dynamical characteristics of the molecules H₂O(1) and H₂O(2) was significantly larger in ice IX than in its proton-disordered analogue, ice III. Furthermore, the theoretical spectrum of librational vibrations of ice III was more smeared as compared to that of ice IX. This is due to the presence of ten different types of orientations of water molecules [six orientation for H₂O(1) and four more orientations for H₂O(2)] in ice III instead of only two possible orientations in ice IX. Moreover, both local and long-range environments of water molecules can be different even for identically oriented molecules. Therefore, the spectrum of ice IX formally represents a superposition of two spectra, whereas the spectrum of ice III represents a superposition of a significantly larger number of spectra corresponding to molecules in different environments, which gives rise to its apparent smoothing.

The PM potential was also employed¹³⁴ in simulations of proton-disordered metastable ices IV and XII. As in the two studies cited above,^{129,133} the MD simulation was performed within the NVE ensemble. The mean temperature was fixed at about 70 K. The structure of ice IV partially collapsed during the simulation, whereas ice XII survived the simulation and preserved its integrity. The self-entangled framework of hydrogen bonds in ice IV contains, as the main structural unit, rings built up of six

water molecules with the oxygen atom O(1) pierced by a ‘needle’ composed of two H-bonded water molecules with the oxygen atom O(2) (see Fig. 7). The O(2)⋯O(2) hydrogen bonds in ice IV are elongated to 2.916 Å; each oxygen atom O(2) has short contacts of only 3.14–3.29 Å with six O(1) atoms forming no H-bonds with it.¹⁰³ Therefore, the collapse of the structure of ice IV started with the cleavage of the long O(2)⋯O(2) hydrogen bond followed by the formation of initially absent O(2)⋯O(1) hydrogen bonds.

The six-membered rings initially present in ice IV were mainly preserved after such a transformation and thus they survived the simulation. The metastable ice XII survived the simulation, which made it possible to calculate dynamical characteristics (the same as discussed above^{129,133} for ices II, IX and III) of the constituent water molecules. As expected, the theoretical parameters of the crystallographically non-equivalent water molecules H₂O(1) and H₂O(2) in the structure of ice XII proved somewhat different.

According to the recent calculations by Henry¹³⁵ using the DFT-based method PACHA (Partial Atomic Charges and Hardnesses Analysis), ice IV is indeed characterised by the most strained structure among all known water ices. Based on the computational results obtained, Henry proposed¹³⁵ a corrected structural model for ice IV without the elongated O(2)⋯O(2) hydrogen bonds. (It has to be however stressed that the reported¹⁰³ crystal structure of ice IV is correct since it was confirmed in a more recent study.⁹⁰) Difficulties in the experimental preparation of ice IV and its rapid spontaneous conversion into more stable phases at 250 K consistently indicate the relatively low stability of this structure.⁴ From this standpoint, its collapse during the computer experiment¹³⁴ does not look surprising.

The diffusion of noble-gas atoms and surplus water molecules not incorporated into the crystal structure through the frameworks of crystalline water ices was a subject of several studies. For example, an MD study on the diffusion of water molecules and helium atoms through the crystals of Ih showed¹³⁶ that the mechanisms of the diffusion of He atoms and surplus H₂O molecules through the framework of Ih are different in principle. Helium atoms migrate by jumps from one stable position in a cavity of the framework of Ih to another cavity, which makes virtually no effects on vibrations of water molecules forming the framework. In contrast, surplus water molecules not incorporated into the crystalline framework form short-lived hydrogen bonds with the molecules of the framework and thus their diffusion should be accompanied by cleavage and formation of new H-bonds.

Another MD study¹³⁷ of dynamical characteristics of Ar and He atoms in the water framework of ice II showed that Ar atoms diffuse in ice II neither along the hexagonal channels, nor through their walls. At the same time, in the case of He atoms filling a part of cavities inside the channels, single jumps of helium atoms to adjacent cavities within the same channel were detected.

Finally, Matsumoto *et al.*¹³⁸ reported the first observation of crystallisation of ice from the bulk of liquid water in a molecular dynamics experiment. They simulated a system composed of 512 water molecules within the *NVT* ensemble using the TIP4P potential. The crystallisation process in the system was initiated at a time moment $t = 0$ by an abrupt temperature decrease to 230 K after a prolonged preliminary thermalisation at 400 K.

The process of crystallisation of ice from the bulk of liquid water in this simulation proceeded in four distinct steps. In the first step, there were no stable nuclei of a crystalline phase in the system. This step was characterised by a relatively high and nearly constant potential energy of the system. The fluctuating network of hydrogen bonds involved five-, six- and seven-membered rings in nearly constant proportions. The first step completed at a time moment $t \approx 256$ ns with the spontaneous generation of a local stable polyhedral structure of long-lived hydrogen bonds with strengths above the system average.

In the second step of the crystallisation process, the polyhedral structure was slowly growing up while migrating through the system with gradual decrease in the potential energy. The nucleus of a crystalline phase settled at a certain place to a time moment $t \approx 290$ ns and its rapid growth started, which corresponded to the third crystallisation step. The network of hydrogen bonds within the growing nucleus included predominantly six-membered rings. The energy of the system was rapidly decreasing. At the end of the process, *i.e.*, at the moment of about $t \approx 320$ ns, the nucleus already encompassed the entire volume of the model system. This started the fourth crystallisation step. During this step, the network of hydrogen bonds was gradually approaching the regular structure of ice Ih, which gave only insignificant gain in the potential energy.

Matsumoto *et al.*¹³⁸ did not specify the overall duration of the computer experiment (*i.e.*, the CPU runtime expended), but it is evident that the experiment lasted for many months. This fact together with the stochastic nature of the wait time before the generation of a crystalline nucleus make this study unique and difficult to reproduce.

We would like to emphasise that this was the very first MD-based computer experiment¹³⁸ that clearly tracked the spontaneous crystallisation from the bulk of liquid at the molecular level. Previously, the crystallisation from a liquid phase was observed in computer experiments only in the presence of a predefined crystalline surface¹²⁷ or under external electric field (see Ref. 139).

Computer experiments related to water crystallisation under an external impact or boundary conditions can be illustrated by another example, *viz.*, an MD simulation of the crystallisation of water in a narrow slit between two hydrophobic walls.¹⁴⁰ The model included 960 water molecules confined between two planar hydrophobic walls at a distance adjusted to < 1 nm so as to accommodate two molecular layers. The interactions between water molecules were described with the TIP4P potential, whereas the interactions between water molecules and the walls were described with the 9-3 Lennard-Jones-type potential. The simulation was performed within the *NPT* ensemble. According to the simulation, a bilayer amorphous phase was gradually formed from the initial confined liquid water volume upon a decrease in temperature. The layers constituting the amorphous phase were nearly planar and included five-, six- and seven-membered rings. The two layers were related to each other to within a high accuracy by a symmetry plane going in the middle of the gap parallel to the walls. Each water molecule in the bilayer amorphous phase formed four hydrogen bonds (three bonds with the molecules from the same layer and an additional bond with its mirror image from the second layer). Upon further decrease in temperature, this amorphous phase started to crystallise into a bilayer crystalline phase composed of two hexagonal layers arranged one above another and linked by vertical hydrogen bonds. In contrast to the Ih structure comprised of corrugated hexagonal layers with one hydrogen bond to the upper layer and one to the lower layer per a six-membered ring, the resultant bilayer structure¹⁴⁰ consists of nearly flat hexagonal layers with two hydrogen bonds to the bottom layer per a six-membered ring of the upper layer. This result implies that the confinement effects can give rise to the formation of water structures non-typical of bulk phases, *e.g.*, in hydrophobic nanopores.

The formation of unusual structures upon cooling of water incorporated in nanopores even in the case of wettable walls was observed in yet another computer experiment.¹⁴¹ It is known that carbon nanotubes are wetted with water and thus water can penetrate inside due to the capillary effect. According to the MD simulation¹⁴¹ of the behaviour of water inside carbon nanotubes with an internal diameter ranged from 1.1 nm to 1.4 nm, water molecules can assemble at sufficiently low temperatures into nanotubes with square, pentagonal, hexagonal or heptagonal cross-sections, depending on the diameter of the carbon nanotube. Note that experimental investigations^{10,11} into the crystallisation

of water within small pores of silicate materials also demonstrated that this process differs from bulk water crystallisation and thus can lead to another outcome.

VI. Occurrence of high-pressure ices in nature

Under terrestrial conditions, the pressure in ice strata never exceeds a few hundred atmospheres and the temperature never goes below 180 K. Therefore, high-pressure ices do not occur on Earth. Typically, frozen water occurs on Earth as hexagonal ice Ih or as a component of gas hydrates, a detailed consideration of which is beyond the scope of the present review.

Ice strata in Antarctica and Greenland have been maintained at low temperature for a long period. Fukazawa *et al.*¹⁴² suggested that this could have resulted in at least partial positional proton ordering, *i.e.*, the transition to proton-ordered ice XI could have started. In order to verify this hypothesis, several ice probes retrieved from depths of 200 m (temperature of 213 K and age of 8000 years) and 350 m (temperature of 214 K and age of 15000 years) of an Antarctica's ice shelf were studied by means of INS.¹⁴² The spectra obtained manifested some features typical of the INS spectra of ice XI, which suggested that the studied samples of ice from the Antarctica's ice shelves have indeed transformed into ice XI.¹⁴² However, the INS spectra of analogous ices retrieved from depths ranged from 200 m (age of 1000 years) to 5500 m (age of more than 10⁶ years) of Greenland's ice shelves were fully consistent¹⁴³ with the respective spectra of ordinary ice Ih. The authors of the latter study¹⁴³ argued that ice samples analysed in the former study¹⁴² also represented ordinary ice Ih and the INS features were misinterpreted due to the insufficient signal-to-noise ratio and low resolution.

Bina and Navrotsky proposed a model¹⁴⁴ of geological processes proceeding upon subduction of the oceanic lithosphere that considered the formation and accumulation of ice VII in large quantities as a possible consequence of the oceanic bed lowering. It is of note however that this is only one of many hypotheses concerning geological processes in the Earth's mantle.

Water ices can also occur in the Earth's atmosphere. Many types of halos around Moon and Sun and other related optical

phenomena can be explained by refraction of light upon propagation through crystals of ice Ih suspended in atmosphere. A rare type of such a halo due to the light deflection by 28° have been observed several times, which cannot be explained by the refraction in crystals of ice Ih.¹⁴⁵ This halo can be rationalised under the assumption of emergence of small octahedral crystals of ice Ic in the atmosphere, since light refraction in such crystals can result in the deflection exactly by 27.4° (see Ref. 145). The shape of several types of snow-flakes with ice Ih crystals twinned at 70° is another evidence of the formation of small crystals of ice Ic in the Earth's atmosphere. Such a twinning can be explained by the epitaxy of the (0001) planes of hexagonal ice Ih on the family of symmetry related {111} planes of octahedral crystallites of ice Ic acting as nuclei for the growth of the snow-flake.¹⁴⁶

Therefore, only occurrence of Ih in the Earth's mantle is reliably established, although there is serious experimental evidence that both ice Ih and Ic can form in the Earth's atmosphere as small crystals.

There are 18 orbs with radii more than 100 km composed to a large extent of water ices within the Solar system.¹⁴⁷ These are the largest Jupiter's satellites, *viz.*, Europa, Io, Ganymede and Callisto, Saturn's satellites, *viz.*, Mimas, Enceladus, Tethys, Dione, Rhea, Titan, Hyperion and Iapetus, Uranus' satellites, *viz.*, Ariel, Umbriel, Titania and Oberon, a Neptune's satellite, Triton, and the Pluto–Charon system. Observations of these orbs were performed from the Earth and, in some cases, from the spacecrafts passing by. Among them, the Jupiter's and Saturn's satellites are the best studied.

The presence of water ices on a surface of an orb can be suggested based on the results of IR photometry or reflectometry. A low mean density of an orb is another indicator of a large water fraction in its interior. The densities of the orbs listed above except for Europa (with $\rho = 3.0 \text{ g cm}^{-3}$) do not exceed 2 g cm^{-3} , whereas all known rocks have densities more than 2.5 g cm^{-3} .

For the four largest Jupiter's satellites, Ganymede, Europa, Callisto and Io, spherically symmetrical density distributions were simulated to be consistent with the available data on their radii, mean densities and moments of inertia.¹⁴⁸ Based on the densities obtained, the composition of mantle-forming rocks and the

VII. Appendix

Table. Crystallographic parameters of the structures of crystalline ices.

Ice	Space group	T, P^a	Unit cell parameters	Z^b	$\rho / \text{g cm}^{-3}$	Degree of proton ordering	Ref.
Ih(H ₂ O)	$P6_3/mmc$	98 K, 1 bar	$a = 4.48 \text{ \AA}, c = 7.31 \text{ \AA}$	4	0.92	completely disordered	63
Ic(H ₂ O)	$Fd\bar{3}m$	98 K, 1 bar	$a = 6.350 \text{ \AA}$	8	0.92	the same	63
II(H ₂ O)	$R\bar{3}$	123 K, 1 bar	$a = 7.78 \text{ \AA}, \alpha = 113.1^\circ$	12	1.17	completely ordered	44
III(D ₂ O)	$P4_12_12$	240 K, 0.25 GPa	$a = 6.67 \text{ \AA}, c = 6.96 \text{ \AA}$	12	1.286	disordered	54
IV(D ₂ O)	$R\bar{3}c$	110 K, 1 bar	$a = 7.60 \text{ \AA}, \alpha = 70.1^\circ$	16	1.272	completely disordered	103
V(H ₂ O)	$A2/a$	98 K, 1 bar	$a = 9.22 \text{ \AA}, b = 7.54 \text{ \AA},$ $c = 10.35 \text{ \AA}, \beta = 109.2^\circ$	28	1.231	disordered	57
V(D ₂ O)	$A2/a$	234 K, 0.5 GPa	$a = 9.0926 \text{ \AA}, b = 7.5409 \text{ \AA},$ $c = 10.2547 \text{ \AA}, \beta = 109.14^\circ$	28	1.400	the same	54
VI(H ₂ O)	$P4_2/nmc$	98 K, 1 bar	$a = 6.27 \text{ \AA}, c = 5.79 \text{ \AA}$	10	1.31	completely disordered	63
VI(D ₂ O)	$P4_2/nmc$	225 K, 1.1 GPa	$a = 6.1812 \text{ \AA}, c = 5.6980 \text{ \AA}$	10	1.526	the same	60
VII(D ₂ O)	$Pn\bar{3}m$	295 K, 2.4 GPa	$a = 3.344 \text{ \AA}$	2	1.778	"	60
VIII(D ₂ O)	$I4_1/amd$	10 K, 2.4 GPa	$a = 4.656 \text{ \AA}, c = 6.775 \text{ \AA}$	8	1.810	completely ordered	60
IX(D ₂ O)	$P4_12_12$	110 K, 1 bar	$a = 6.73 \text{ \AA}, c = 6.83 \text{ \AA}$	12	1.13	ordered	55
X(H ₂ O, D ₂ O)	$Pn\bar{3}m$	—	—	2	—	the protons reside in the middle of the O...O bonds	
XI(D ₂ O)	$Cmc2_1$	5 K, 1 bar	$a = 4.502 \text{ \AA}, b = 7.798 \text{ \AA},$ $c = 7.328 \text{ \AA}$	8	0.93	ordered	28
XII(D ₂ O)	$I\bar{4}2d$	260 K, 0.50 GPa	$a = 8.304 \text{ \AA}, c = 4.024 \text{ \AA}$	12	1.4365	disordered	6
XII(D ₂ O)	$I\bar{4}2d$	1.5 K, 1 bar	$a = 8.2816 \text{ \AA}, c = 4.0361 \text{ \AA}$	12	1.4397	the same	104

^a Temperature and pressure at which the structure was determined; ^b the number of water molecules (the number of formula units for ice X) per unit cell.

possible thicknesses of the outer crusts from water ices were estimated. For Ganymede and Callisto, the models were further refined according to the data on the surface heat radiation, presumed intensity of heat generation in their cores due to the radioactive decay, heat conductivity of mantle components and of the outer ice crust to predict the depth distributions of densities, temperatures and pressures. Based on these data altogether, the occurrence of high-pressure ices therein was concluded. The results of measurements of the magnetic fields around the satellites were also utilised, which can support either the presence or absence of an iron core creating an own magnetic field around the satellite or the presence of an internal conductive ocean from liquid water with dissolved salts, which affects the magnetic field induced by Jupiter.

The following conclusions were derived based on these calculations.¹⁴⁸ Io is composed of a core (mostly from Fe and FeS) with a radius of 38% to 53% of its total radius (1821.6 km) surrounded by an outer shell of olivine rocks. No water is present in Io. The radius of the central core of Europa (composed of pure or FeS-contaminated iron) amounts 10% to 45% of the total radius of this satellite (1565 km), its mantle is composed of olivine rocks, the outermost shell represents a crust from water ices with a thickness from 120 to 170 km. Ganymede has a core with a radius of 1/4 to 1/3 of its total radius (2634 km), the mantle is also dominantly composed of olivine rocks, whereas its outer ice crust with a thickness of 900 km is subdivided into concentric shells of ices VI, V, III and I. Water ices and rocks are probably at least partly spatially separated also in Callisto (with a radius of 2410.3 km); among ice forms, ices VI, V, III and I can occur there.

As for the investigated Saturn's satellites, the density of Titan is 1.9 g cm^{-3} , densities of other satellites range from 1.4 g cm^{-3} to 1.0 g cm^{-3} . This strongly suggests that the composition of all the investigated Saturn's satellites but Titan is dominated by water ices. According to simulations of the structure of Titan's interior, the Titan's core is either composed of only silicate rocks or represents a core-shell structure with a central core from molten iron and an outer shell of silicate rocks.¹⁴⁹ The core is surrounded by a mantle composed of several layers, including ice VI, other high-pressure ices and clathrate hydrates, then liquid water and the outermost layer of ice Ih.¹⁴⁹

Therefore, there is serious evidence that crystalline high-pressure ices indeed occur in some satellites of larger planets in the Solar system.

* * *

Solid water phases have remained in the focus of interest of researchers over the last 15 years. A new crystalline modification, ice XII, has been discovered; transitions between crystalline ices, amorphisation of crystalline ices and crystallisation of amorphous ices have been elucidated in detail. The data obtained clearly demonstrate that water polymorphism is truly multi-faceted and no other substance can compete with water in the diversity of forms. We believe that the nearest future will witness more striking investigations into water, especially, its non-equilibrium forms and transitions between them.

The present review has been written with a partial financial support of the Russian Foundation for Basic Research (Project No. 03-03-32227).

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^a — *J. Exp. Theor. Phys. Lett. (Engl. Transl.)*

^b — *J. Struct. Chem. (Engl. Transl.)*

^c — *Mendeleev Chem. J. (Engl. Transl.)*

^d — *J. Exp. Theor. Phys. (Engl. Transl.)*

^e — *Russ. J. Phys. Chem. (Engl. Transl.)*

Magnetic properties of bismuth(III) oxy compounds

E A Kravchenko, V G Orlov, M P Shlykov

Contents

I. Introduction	77
II. Splitting of the ^{209}Bi NQR spectra of bismuth(III) oxy compounds in internal magnetic fields	78
III. ^{209}Bi NQR experiments on $\text{Bi}_4\text{Ge}_3\text{O}_{12}$ and $\text{Bi}_3\text{B}_5\text{O}_{12}$ single crystals in external magnetic fields	79
IV. Studies of local magnetic fields by analysis of the quadrupole spin echo envelope	83
V. The results of magnetisation measurements and magnetoelectric effect in the $\alpha\text{-Bi}_2\text{O}_3$ single crystal	86
VI. On the probable origin of anomalies in magnetic properties of bismuth oxy compounds	89
VII. Conclusion	90
VIII. Appendix. The calculation of the nuclear quadrupole spin echo	90

Abstract. Nuclear quadrupole resonance and SQUID-magneto-metric studies on magnetic properties of bismuth(III) oxy compounds comprising neither d- nor f-elements are surveyed and systematised. The magnetic properties, not conventionally expected in the Main Group element substances, were found to exist in most of the compounds discussed. The results of the analysis of the zero-field ^{209}Bi NQR line shapes, the Zeeman-perturbed patterns in external fields of various orientations with respect to the crystal axes, and the spin-echo envelopes suggest the existence in $\alpha\text{-Bi}_2\text{O}_3$, $\text{Bi}_3\text{O}_4\text{Br}$, $\text{Bi}_2\text{Al}_4\text{O}_9$, $\text{Bi}_2\text{Ge}_3\text{O}_9$, $\text{Bi}_4\text{Ge}_3\text{O}_{12}$ and BaBiO_2Cl , of ordered magnetic fields ranging from 30 to 250 G, which notably exceed the dipole nuclear magnetic fields. The magnetoelectric effect was observed in the $\alpha\text{-Bi}_2\text{O}_3$ single crystal, and the paramagnetism depending on the thermal prehistory of the crystal was found using a SQUID-technique. The questions concerning the origin of unusual magnetic and electronic properties of the title compounds are discussed. The bibliography includes 49 references.

I. Introduction

Bismuth oxide $\alpha\text{-Bi}_2\text{O}_3$ and related compounds are parent substances for the preparation of high-temperature superconductors and ferroelectrics, and some of them are materials exhibiting valuable electroacoustic, piezoelectric and nonlinear optical properties. However, in spite of the interest of researchers, the magnetic properties of these compounds have not been explored adequately. The ^{209}Bi nuclear quadrupole resonance (NQR) spectra suggest that $\alpha\text{-Bi}_2\text{O}_3$, $\text{Bi}_3\text{O}_4\text{Br}$, $\text{Bi}_2\text{Al}_4\text{O}_9$, $\text{Bi}_2\text{Ge}_3\text{O}_9$, $\text{Bi}_4\text{Ge}_3\text{O}_{12}$, BaBiO_2Cl and $\text{Bi}_3\text{B}_5\text{O}_{12}$ comprising no magnetism

carriers, *i.e.*, atoms of d- or f-elements, are not diamagnets in the conventional sense. Local ordered magnetic fields (H_{loc}) up to 250 G in these compounds cause, in some of them, typical Zeeman splittings of the ^{209}Bi NQR lines in the absence of external magnetic fields (see Refs 1–4 and references cited therein). Their NQR spectra reveal an extraordinarily high sensitivity of the electronic characteristics to weak ($H_e < 500$ Oe) external magnetic fields, which suggests a strong coupling between the magnetic and electronic subsystems of the substances. This, in principle, points to a possibility of governing the functional properties of the corresponding materials by applying weak magnetic fields. For instance, a dramatic increase in the line intensity was observed in the ^{209}Bi NQR spectrum of $\text{Bi}_4\text{Ge}_3\text{O}_{12}$ upon applying an external magnetic field, which is not described within the conventional theory of the Zeeman NQR spectroscopy.

The NQR spectroscopy is recognised as a direct, most efficient and precise method of detecting and studying the nuclear quadrupole interactions, because the quadrupolar Hamiltonian is determined by interactions between the nuclear electric quadrupole moment Q (all the nuclei with spin $I > 1/2$ have such a moment) and the electric field gradient (EFG)

$$q_{ij} = \frac{\partial E_i}{\partial j} = -\frac{\partial^2 U}{\partial ij},$$

where E is the strength of the electrostatic field, U is the electrostatic potential at the nuclear site and $i, j = x, y, z$. The quadrupole coupling constant

$$QCC = \frac{eQq_{zz}}{h}$$

and the EFG asymmetry parameter

$$\eta = \frac{q_{xx} - q_{yy}}{q_{zz}}$$

are the parameters that are measured.

Their values are directly related to the electron density distribution around the nucleus studied. As a result, any weak disturbance of the electron density is clearly and adequately reflected in the NQR spectra. The NQR spectroscopy may be used for studies of a wide variety of phenomena accompanied by changes in the electric fields in the vicinity of the resonance nuclei, and NQR was used as the basic method of investigating the problems discussed. The physical principles of the NQR phenom-

E A Kravchenko N S Kurnakov Institute of General and Inorganic Chemistry, Russian Academy of Sciences, Leninsky prosp. 31, 119991 Moscow, Russian Federation. Fax (7-495) 954 12 79, tel. (7-495) 955 48 22, e-mail: ekravchenko@igic.ras.ru
V G Orlov, M P Shlykov Russian Research Centre 'Kurchatov Institute', pl. Kurchatova 1, 123182 Moscow, Russian Federation. Fax (7-495) 196 18 70, tel. (7-495) 196 95 19, e-mail: orlov@mbslab.kiae.ru (V G Orlov), shlykov@mbslab.kiae.ru (M P Shlykov)

Received 5 August 2005

Uspekhi Khimii 75 (1) 86–104 (2006); translated by E A Kravchenko

enon, the scope and limitations of NQR spectroscopy in application to problems of inorganic chemistry have been reviewed.^{5,6}

The results of investigations showed that the methods based on measurement of nuclear quadrupole interactions are highly sensitive to the presence of a magnetic field in a substance. The experiments discussed in the present review involved studies of the zero-field ^{209}Bi NQR line shapes in crystalline powders and single crystals, analysis of splittings in the spectra of single crystals in external magnetic fields (H_e) of various orientations with respect to the crystal axes (the Zeeman experiment) and examination of the shapes of the quadrupole spin-echo envelopes (SEE). The experiments recording the SEE in the spectra of crystalline powders enable one to detect small (within the line width) splittings observed as modulations of the SEE curves. Subsequent mathematical processing and computer simulation of either the Zeeman splittings or the SEE shape give the quantitative characteristics of the internal source of splittings, namely, the strength and orientation of the local magnetic field.

The ^{209}Bi NQR Zeeman spectra of the majority of compounds discussed in this review displayed multiplicities, which points to the magnetic non-equivalence of bismuth positions. Therefore, the computer simulation required analysis of the symmetry properties of the EFG tensor. This analysis was based on the crystal-field potential model developed by Orlov.⁷

II. Splitting of the ^{209}Bi NQR spectra of bismuth(III) oxy compounds in internal magnetic fields

The zero-field ^{209}Bi NQR spectrum (the ^{209}Bi nuclear spin is $9/2$) comprises a set of four transitions between five doubly degenerate energy levels $|\pm m\rangle$; their frequencies, assuming the simplest case of magnetic equivalence of the bismuth sites and $\eta = 0$, are determined as

$$\nu_k = \frac{3keQq_{zz}}{2I(2I-1)h},$$

where $k = 1, \dots, 4$.

Figure 1 shows the diagram of the ^{209}Bi NQR spectra of a single crystal in zero and non-zero external magnetic field of arbitrary orientation with respect to the EFG axes. A perturbing static magnetic field H_e removes the double degeneracy $\pm m$ of the quadrupole energy levels, because the energy of interaction of the nuclear magnetic moment with this field becomes different for the orientations of the nuclear spin projection along and opposite the H_e direction. In this case, each singlet, assigned to the resonance transition $\pm m \rightarrow \pm(m+1)$, at $m > 1/2$ is split into a doublet with the separation between the components

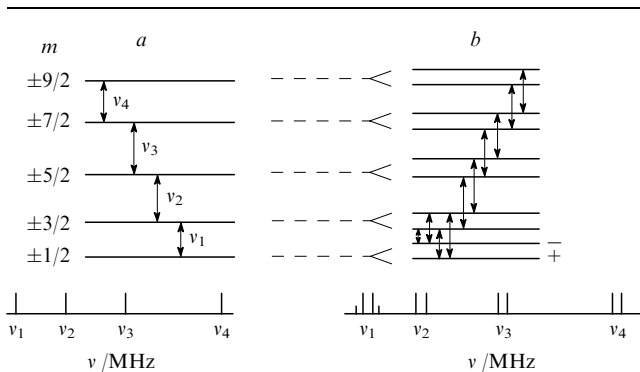


Figure 1. Diagrams of quadrupole energy levels and transitions between them for the ^{209}Bi nucleus (spin $9/2$) in zero (a) and Zeeman (b) magnetic fields.

$$\Delta\nu = 2\gamma H_e \cos\theta, \quad (1)$$

where γ is the gyromagnetic ratio for the quadrupole nucleus and θ is the angle between the EFG q_{zz} axis and H_e . The doublet components are symmetrical about the original non-split NQR frequency ν_m , and their total intensity is equal to that of the initial non-split line.⁸ The lowest levels $m = \pm 1/2$ mix in external magnetic field to produce new states ψ_+ and ψ_- and hence a quadruplet, centred at the frequency of the unperturbed transition $\nu_{\pm 1/2} \rightarrow \nu_{\pm 3/2}$

$$\nu_\alpha = \frac{6A}{h} - \frac{1}{2}(3-f)\gamma H_e \cos\theta, \quad (2)$$

$$\nu_\beta = \frac{6A}{h} - \frac{1}{2}(3+f)\gamma H_e \cos\theta,$$

$$\nu'_\alpha = \frac{6A}{h} + \frac{1}{2}(3-f)\gamma H_e \cos\theta,$$

$$\nu'_\beta = \frac{6A}{h} + \frac{1}{2}(3+f)\gamma H_e \cos\theta,$$

where

$$A = \frac{eQq_{zz}}{4I(2I-1)},$$

$$f = \left[1 + \left(I + \frac{1}{2} \right)^2 \tan^2\theta \right]^{1/2}.$$

The quadruplet components are also symmetrical about the frequency of the unperturbed transition.⁸

Thus, the presence in the spectrum of a quartet of lines assigned to the lowest transition ν_1 ($\Delta m = 1/2 - 3/2$) and doublets to the remaining transitions ($\nu_2, \dots, \nu_n$) points to the magnetic nature of the splittings, hence excluding the crystallographic non-equivalence of atomic positions as the cause for the splittings. The separations between the doublet components $\nu_\alpha(\nu'_\alpha)$ and $\nu_\beta(\nu'_\beta)$ are evidently determined by equations

$$\Delta\nu_\alpha = (3-f)\gamma H_e \cos\theta, \quad (3)$$

$$\Delta\nu_\beta = (3+f)\gamma H_e \cos\theta.$$

which show that the number of components (multiplicity) and their frequencies depend on the strength and orientation of the Zeeman field H_e with respect to the EFG axes of a single crystal.

Figure 2 demonstrates the ^{209}Bi NQR line shapes recorded in zero applied field for $\alpha\text{-Bi}_2\text{O}_3$ and $\text{Bi}_3\text{O}_4\text{Br}$. One can see that both

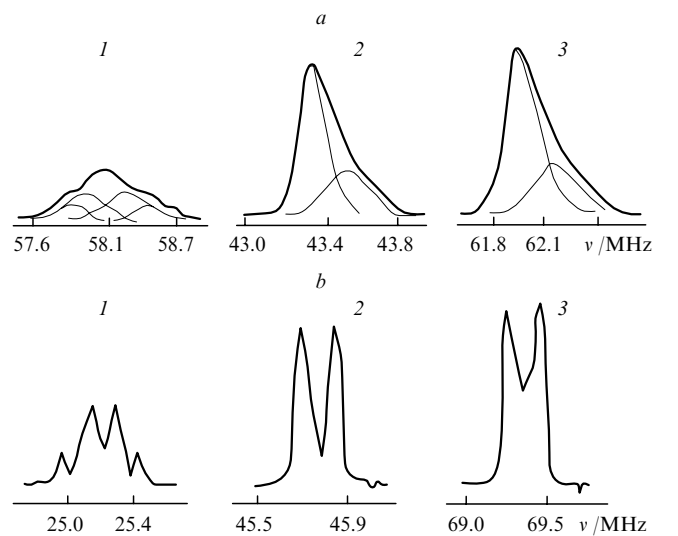


Figure 2. The ^{209}Bi NQR spectral lines assigned to the transitions ν_1 (1), ν_2 (2), ν_3 (3) (see Table 1) in $\text{Bi}_3\text{O}_4\text{Br}$ (a) and $\alpha\text{-Bi}_2\text{O}_3$ (b).

Table 1. The zero-field ^{209}Bi NQR spectra and values of H_{loc} in bismuth oxy compounds (the frequencies are averaged over splittings).^{2,4}

Compound	T/K	Transition frequencies (MHz) $\nu_n = m_i \rightarrow m_{i+1}$				$eQq/h/\text{MHz}$	$\eta(\%)$	H_{loc}/G
		ν_1	ν_2	ν_3	ν_4			
$\alpha\text{-Bi}_2\text{O}_3$								
Bi(1)	77	25.2	45.8	69.4	92.8	556.7	0.13	171
Bi(2)		39.3	37.2	58.3	79.4	482.6	0.40	136
$\text{Bi}_3\text{O}_4\text{Br}$								
Bi(1)	77	21.6	25.1	39.6	53.3	322.6	0.31	—
Bi(2)		58.0	43.4	61.9	86.6	536.9	0.62	250 ± 10
$\text{Bi}_2\text{Al}_4\text{O}_9$	77	33.15	50.5	78.0	104.1	626.4	0.19	150 ± 10
$\text{Bi}_4\text{Ge}_3\text{O}_{12}$	300	20.4	40.9	61.3	81.7	490.3	0.0	25 ± 5
$\text{Bi}_2\text{Ge}_3\text{O}_9$	77	25.7	51.6	77.35	103.2	618.8	0.0	60 ± 10
	300	25.25	50.5	75.7	101.0	605.9	0.0	—

splitting patterns appear as typical Zeeman-perturbed NQR patterns for nuclei having spin $I > 3/2$: the lowest line ν_1 ($\Delta m = 1/2 - 3/2$) is split into a quadruplet, and the lines of higher frequency transitions ν_2, ν_3 , into doublets. This evidences that an internal source of the line splittings exists in these compounds, namely, a local ordered magnetic field H_{loc} , which has a fixed orientation with respect to the nuclear spin direction. This is supported by the observation of the zero-field splittings not only in single crystals, but also in powders. Each crystallite in a powder sample is a single crystal for the local magnetic field, so the observation of the zero-field Zeeman splittings in powder samples rules out the suggestion that an impurity may be the cause for the splittings.

The zero-field splittings were later observed in the ^{209}Bi NQR spectra of several other bismuth oxy compounds, $\text{Bi}_2\text{Al}_4\text{O}_9$, $\text{Bi}_4\text{Ge}_3\text{O}_{12}$ and $\text{Bi}_2\text{Ge}_3\text{O}_9$,^{3,4} although the X-ray data^{9–11} show that the bismuth sites are crystallographically equivalent in their structures. This also excludes the crystallographic non-equivalence as the cause for the spectroscopic splittings. Analysis of the splittings showed that they are consistent with local ordered magnetic fields of 25–250 G notably exceeding the dipole nuclear magnetic fields (about several G). Therefore, the electronic system solely can be the source of the fields in the compounds in question. On the other hand, the values of H_{loc} are several orders of magnitude smaller than those in conventional ferro- and anti-ferromagnets, which is indicative of a new phenomenon. The ^{209}Bi NQR spectra of the compounds mentioned and the values of H_{loc} estimated from the zero-field splittings are listed in Table 1.

III. ^{209}Bi NQR experiments on $\text{Bi}_4\text{Ge}_3\text{O}_{12}$ and $\text{Bi}_3\text{B}_5\text{O}_{12}$ single crystals in external magnetic fields

Small values of splittings and low intensities of some of the transitions made difficult further studies of magnetic properties in the zero field. They were continued in weak external magnetic fields with a view to study the Zeeman splittings in the ^{209}Bi NQR spectra of single crystals. This approach appeared to be efficient because the Zeeman spectra of single crystals exhibited some specific features most clearly revealed on the change in the orientation of external magnetic fields with respect to the crystal axes. The single crystals of $\text{Bi}_4\text{Ge}_3\text{O}_{12}$ and $\text{Bi}_3\text{B}_5\text{O}_{12}$ were studied extensively.^{12–15}

The Zeeman fields H_e from 0 to 500 Oe were applied either parallel or perpendicularly to the direction of the radiofrequency field (H_{rf}). The crystals were turned in the rf-coil about the H_{rf} direction at a definite angle α , which changed the orientation of H_e with respect to the crystallographic axes of the samples. This procedure allowed detailed studies on the shapes, intensities and multiplicities of the resonance lines as functions of mutual orientation of the fields disturbing the bismuth nuclear magnetic moments. A pulse NQR spectrometer, which enabled continuous

scanning through the frequency range required, was used for the experiments.

The $\text{Bi}_4\text{Ge}_3\text{O}_{12}$ single crystal had a shape of parallelepiped ($6 \times 9 \times 25$ mm) with a (100) crystallographic plane perpendicular to the radiofrequency coil axis that coincided with the H_{rf} direction. On successive variation of the strength and orientation of H_e during the experiment, the ^{209}Bi NQR lines of the $\nu_1 - \nu_3$ transitions were recorded at several positions of the crystal in the coil.¹²

If the spin system is simultaneously disturbed by both local and external magnetic fields, the Zeeman spectrum shown in Fig. 1b is expected to become more complicated. As was mentioned above, this is chiefly determined by the crystal symmetry of the compound studied. The number of components (multiplicity), their frequencies and intensities depend also on the strength and orientation of the fields H_e and H_{loc} . Therefore, a theoretical modelling that takes into account the crystal symmetry is necessary for the interpretation of the spectra.

The package of programs¹² for the modelling of the Zeeman splittings in the ^{209}Bi NQR spectra of single crystal included no approximate analytical expressions for the nuclear spin energy levels or transition probabilities. The calculation of these parameters by diagonalisation of the quadrupolar Hamiltonian was carried out numerically with any desired accuracy. After that, the evolution of the spectroscopic splittings was simulated for the given strength and orientation of H_e with respect to the crystal axes. By comparing the simulated and observed splittings, the strength of H_{loc} and angular parameters specifying the field orientation with respect to the EFG axes at the bismuth sites, were derived. The basic stages of the simulation of the ^{209}Bi NQR Zeeman spectra of the $\text{Bi}_4\text{Ge}_3\text{O}_{12}$ single crystal¹² are briefly described below and summarised in the Appendix.

According to X-ray diffraction data,^{9,10} all the sixteen bismuth atoms in the unit cell of the eulitine-type structure (space group $I\bar{4}3d$), to which $\text{Bi}_4\text{Ge}_3\text{O}_{12}$ belongs, occupy the c -type sites in the threefold rotation axis. These positions are characterised by four magnetically non-equivalent EFG tensors. The direction of the maximum component $q_{zz'}$ for each EFG tensor (x', y', z' are the EFG principal axes) with respect to the crystallographic system (x, y, z) is found by diagonalisation of the tensors. This direction is determined by the Euler angles θ and φ connecting the co-ordinate systems (x, y, z) and (x', y', z') (Fig. 3). The third Euler angle ψ , which specifies the direction of the axes x' and y' in the plane perpendicular to the z' -axis, remains arbitrary in consistence with the zero EFG asymmetry parameter at the bismuth sites in the eulitine structure. The angle ψ does not affect line splittings in the NQR spectra in a magnetic field, influencing only line intensity. With the symmetry properties of the lattice contribution to the EFG tensor taken into account, the relationship between the angular parameters of the principal axes $q_{zz'}$ was derived for all the four EFG tensors.¹²

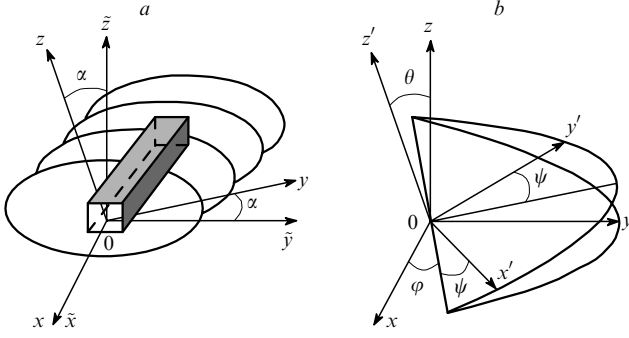


Figure 3. Mutual orientation of the Cartesian coordinate systems: the laboratory frame ($\tilde{x}, \tilde{y}, \tilde{z}$) and the system referred to the crystallographic axes (x, y, z) (a); the system referred to the crystallographic axes and to the EFG principal axes (x', y', z') (b).

$$\theta, \varphi; \pi - \theta, \varphi; \theta, \pi - \varphi; \pi - \theta, \pi - \varphi. \quad (4)$$

Hence, one has to find the angular parameters θ and φ for the principal axes of only one EFG tensor, those for three remaining ones being determined by the relationships (4).

In the absence of local and external magnetic fields and at $\eta = 0$, the energy of the nuclear spin levels E_j ($j = 1, 2, \dots, 10$) and the appropriate eigenfunctions Y_j are calculated by diagonalisation of the simplest quadrupolar Hamiltonian:

$$\hat{H}_Q = \frac{eQq}{4I(2I-1)} [3I_z^2 - I(I+1)], \quad (5)$$

where $eQq/h = 490.3$ MHz (see Table 1). The frequencies of transitions between the appropriate quadrupole levels are the same for all the four EFG tensors, because the Hamiltonian (5) does not depend on the parameters (4). In other words, in the absence of magnetic fields, all the bismuth sites in the eulitine structure are equivalent and the NQR spectra are indistinguishable. The observed singlets assigned to each of the four transitions ($k = 1, \dots, 4$, see Fig. 1a) represent superposition of four lines with identical frequencies and intensities. An external magnetic field directed at different angles to the four EFG principal axes systems makes the bismuth positions in the eulitine structure magnetically non-equivalent. In general, the NQR line can split into a maximum of 16 components (four quadruplets) for the transition $\Delta m = 1/2 - 3/2$ and 8 (4 doublets), for all the remaining transitions, the EFG symmetry properties (4) being taken into account. The angles θ and φ can be determined from the measured splittings of the Zeeman spectra of the oriented single crystal. The orientation of the laboratory system ($\tilde{x}, \tilde{y}, \tilde{z}$) is determined by the field directions as $\tilde{x} \parallel \mathbf{H}_{rf}$ and $\tilde{z} \parallel \mathbf{H}_e$ (see Fig. 3). Because the quadrupole Hamiltonian (5) was determined in the system of the EFG principal axes, a projection of vector $\mathbf{H}_e$ onto the axes (x', y', z') is to be used in the Hamiltonian of interaction of the nuclear magnetic moment with external magnetic field $\hat{H}_e$. This procedure is performed using a rotation matrix D , whose particular form is determined by orientation of the single crystal axes with respect to the laboratory system. Hence, the matrix D depends on the angle of sample turn in the rf-coil from the initial position ($\alpha = -45^\circ$) and from the Euler angles θ, φ and ψ . It is to be reminded that in the reported experiments,¹² the $\text{Bi}_4\text{Ge}_3\text{O}_{12}$ single crystal was placed in the rf-coil so that its longer axis [100] was parallel to the coil axis. The direction of $\mathbf{H}_e$ in the initial position of the crystal was perpendicular to the plane (011).

If the spin system of a quadrupole nucleus is simultaneously disturbed by both local and external magnetic fields, the nuclear spin energy levels and their eigenfunctions are evaluated by diagonalisation of the Hamiltonian¹²

$$\hat{H} = \hat{H}_Q + \hat{H}_{loc} + \hat{H}_e, \quad (6)$$

where $\hat{H}_{loc}$ is the Hamiltonian of interaction of local magnetic field with the bismuth nuclear magnetic moment, $\hat{H}_e$ is the Hamiltonian of interaction of external magnetic field with the bismuth nuclear magnetic moment

$$\hat{H}_{loc} = -g_{\text{Bi}}\mu_{\text{B}}\mathbf{H}_{loc}\mathbf{I} = \quad (7)$$

$$= -g_{\text{Bi}}\mu_{\text{B}}H_{loc}(\sin\theta_{loc}\cos\varphi_{loc}I_{x'} + \sin\theta_{loc}\sin\varphi_{loc}I_{y'} + \cos\theta_{loc}I_{z'}),$$

$$\hat{H}_e = -g_{\text{Bi}}\mu_{\text{B}}\mathbf{H}_e\mathbf{I} = -g_{\text{Bi}}\mu_{\text{B}}H_e(D_{13}I_{x'} + D_{23}I_{y'} + D_{33}I_{z'}). \quad (8)$$

Here $g_{\text{Bi}} = \mu_{\text{Bi}}/I\mu_{\text{B}}$, $\mu_{\text{Bi}} = 4.0797\mu_{\text{B}}$ is the magnetic moment of the bismuth nucleus and angles θ_{loc} and φ_{loc} determine the direction of $\mathbf{H}_{loc}$ with respect to the EFG principal axes.¹²

In $\mathbf{H}_e \perp \mathbf{H}_{rf}$, the components of the matrix D are

$$\begin{aligned} D_{13} &= \cos\psi \sin\varphi \sin\alpha + \sin\psi (\cos\theta \cos\varphi \sin\alpha + \sin\theta \cos\alpha), \\ D_{23} &= -\sin\psi \sin\varphi \sin\alpha + \cos\psi (\cos\theta \cos\varphi \sin\alpha + \sin\theta \cos\alpha), \\ D_{33} &= -\sin\theta \cos\varphi \sin\alpha + \cos\theta \cos\alpha. \end{aligned} \quad (9)$$

Hence, in this case, the nuclear spin energy levels E_j ($j = 1, 2, \dots, 10$) are determined by the parameters eQq/h , H_{loc} , θ_{loc} , φ_{loc} , H_e , θ , φ and α .

In $H_{loc} = 0$ and $\eta = 0$, the typical Zeeman spectrum consists of a quadruplet assigned to the transition v_1 ($\Delta m = 1/2 - 3/2$) and doublets for the remaining transitions, provided that all the EFG tensors are magnetically equivalent (see, for instance, Fig. 4 in Ref. 12). As follows from Eqns (6), (8) and (9), the contribution of the external magnetic field ($\mathbf{H}_e \perp \mathbf{H}_{rf}$) to the splitting of the doublet components is determined as

$$\Delta_e = \frac{2g_{\text{Bi}}\mu_{\text{B}}}{h} H_e (-\sin\theta \cos\varphi \sin\alpha + \cos\theta \cos\alpha). \quad (10)$$

It can be shown that in $\mathbf{H}_e \parallel \mathbf{H}_{rf}$, the matrix D does not depend on α , and the above expression becomes

$$\Delta_e = \frac{2g_{\text{Bi}}\mu_{\text{B}}}{h} H_e \sin\theta \sin\varphi. \quad (11)$$

Using Eqns (10), (11) with relationships (4) taken into account, one can simulate the Zeeman-perturbed ^{208}Bi NQR spectra for the $\text{Bi}_4\text{Ge}_3\text{O}_{12}$ single crystal. The splittings of the selected lines in the Zeeman spectrum of this crystal are shown in Fig. 4. As follows from Eqn (11), the Zeeman-perturbed patterns assigned to the transition $\Delta m = 3/2 - 5/2$ and other higher transitions in $\mathbf{H}_e \parallel \mathbf{H}_{rf}$ are expected to be unit doublets, because the separations between the doublet components are identical according to relationships (4) for all the four EFG tensors. Meanwhile, it is clearly seen in Fig. 4c that each doublet component displays a weak additional splitting, which can be explained by the presence of H_{loc} in the compound $\text{Bi}_4\text{Ge}_3\text{O}_{12}$. The contribution of H_{loc} to the Zeeman splitting of the NQR spectra is described by the formula

$$\Delta_{loc} = \frac{2g_{\text{Bi}}\mu_{\text{B}}H_{loc}\cos\theta_{loc}}{h}. \quad (12)$$

The net splitting observed between the doublet components for the transitions $v_2 - v_4$ is evidently constituted by a superposition of the contributions described by Eqns (11) and (12):

$$\Delta = |\Delta_e + \Delta_{loc}|. \quad (13)$$

Analysis of the Zeeman-perturbed pattern for the line v_2 , carried out using Eqns (11)–(13), showed that the simulated pattern gives the best fit to the observed one (compare Figs 4c and f) if the local magnetic fields are added to relationships (4) for the angular parameters of the EFG principal axes as follows:

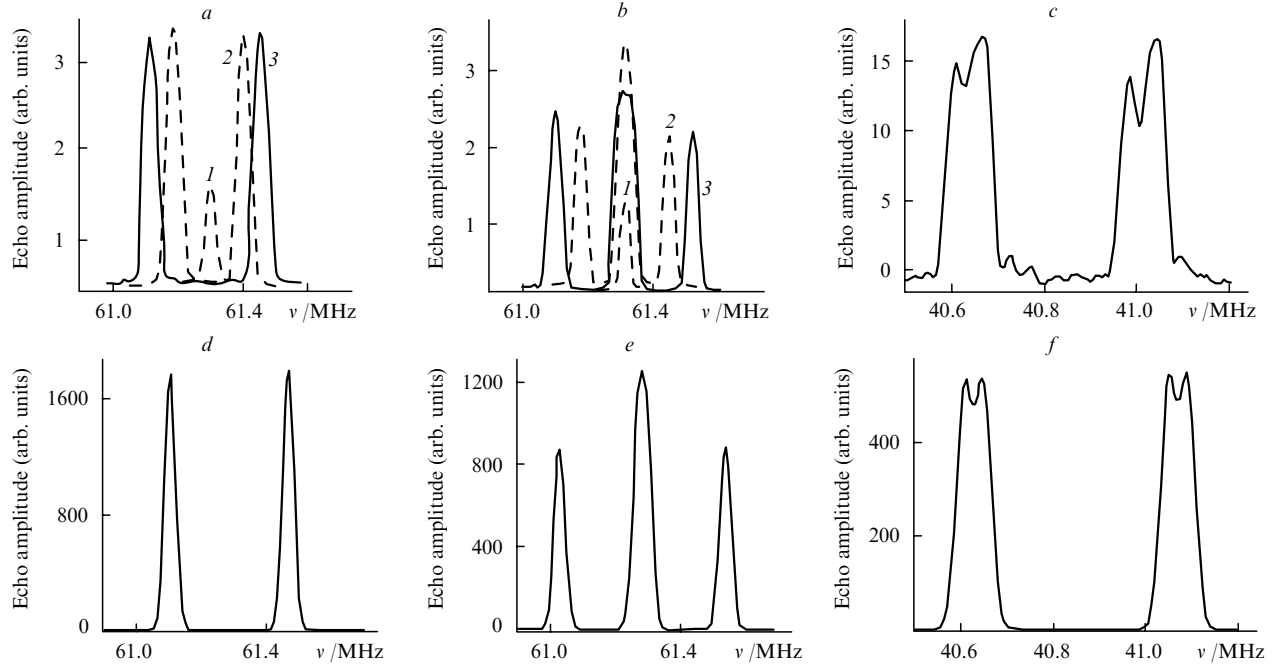


Figure 4. Recorded (*a–c*) and simulated (*d–f*) Zeeman-perturbed patterns in the ^{209}Bi NQR spectrum of the $\text{Bi}_4\text{Ge}_3\text{O}_{12}$ single crystal; (*a, d*) are the lines assigned to the transition ν_3 ($\Delta m = 5/2 - 7/2$) in the field $\mathbf{H}_e \perp \mathbf{H}_{\text{rf}}$ at the orientation of the crystal $\alpha = 0^\circ$ (see text); (*b, e*) $\alpha = 45^\circ$; (*c, f*) are the lines assigned to the transition ν_2 ($\Delta m = 3/2 - 5/2$) in the field $\mathbf{H}_e \parallel \mathbf{H}_{\text{rf}}$. H_e / G : (*a, b*) 0 (1), 300 (2), 480 (3); (*c, f*) 450; (*d, e*) 480.

$$\theta, \varphi, H_{\text{loc}} \cos \theta_{\text{loc}}; \quad \pi - \theta, \varphi, -H_{\text{loc}} \cos \theta_{\text{loc}}; \quad (14)$$

$$\theta, \pi - \varphi, H_{\text{loc}} \cos \theta_{\text{loc}}; \quad \pi - \theta, \pi - \varphi, -H_{\text{loc}} \cos \theta_{\text{loc}}.$$

This means that the local magnetic fields in the compound $\text{Bi}_4\text{Ge}_3\text{O}_{12}$ are ordered antiferromagnetically. The magnitude of projection $H_{\text{loc}} \cos \theta_{\text{loc}}$ of the local field vector onto the EFG principal axis z' , estimated from the additional splittings of the doublet components in $\mathbf{H}_e \parallel \mathbf{H}_{\text{rf}}$ (Fig. 4 *c*), was found to amount to 30 ± 3 G.

The angular parameters θ and φ can be found using Eqn (10) from the analysis of the Zeeman-perturbed line shapes observed upon rotation of the single crystal in the radiofrequency coil ($\mathbf{H}_e \perp \mathbf{H}_{\text{rf}}$) through various angles α . Thus, it follows from this equation that the Zeeman-perturbed pattern at $\alpha = 0^\circ$ is a doublet, which was confirmed experimentally (Fig. 4 *a*). Using Eqn (10) and the experimental data, the angle θ was found to amount to $61 \pm 3^\circ$.

It also follows from equation (10) that the Zeeman patterns should be identical at α equal to $+45^\circ$, -45° and -135° . The coincidence of the appropriate splittings has earlier been observed experimentally as well.¹² The angle $\varphi = 54 \pm 3^\circ$ was determined using Eqn (10) from the measured separation between the outer pair of lines in the Zeeman spectra (see Figs. 4 *a, b*). A more complicated modelling procedure¹² had to be performed because of slight deviation of the crystallographic axis of the sample from the $\mathbf{H}_{\text{rf}}$ direction due to the imperfect shape of the single crystal used for the experiment.

The probability of transitions between the nuclear spin energy levels Y_i is proportional to the squared matrix element

$$\Omega_{ij} = |\langle Y_i | \mathbf{H}_{\text{rf}} \mathbf{I} | Y_j \rangle|^2 = H_{\text{rf}}^2 \omega_{ij}, \quad (15)$$

where for both cases, $\mathbf{H}_e \parallel \mathbf{H}_{\text{rf}}$ and $\mathbf{H}_e \perp \mathbf{H}_{\text{rf}}$ the relationships

$$\omega_{ij} = |\langle Y_i | D_{11} I_x + D_{21} I_y + D_{31} I_z | Y_j \rangle|^2, \quad (16)$$

$$D_{11} = \cos \psi \cos \varphi - \sin \psi \cos \theta \sin \varphi,$$

$$D_{21} = -\sin \psi \cos \varphi - \cos \psi \cos \theta \sin \varphi,$$

$$D_{31} = \sin \theta \sin \varphi$$

hold true.

The line shape was modelled by a procedure described earlier⁴:

$$F_{ij} \propto v_{ij}^2 \omega_{ij} \int_{\tilde{\nu}_1}^{\tilde{\nu}_2} g(v - v_{ij}) dv. \quad (17)$$

Here $v_{ij} = (E_j - E_i)/h$ is transition frequency, ω_{ij} is defined by Eqn (16) and Gaussian $g(v - v_{ij})$ is described as

$$g(v - v_{ij}) = \frac{\sqrt{4 \ln 2}}{\sqrt{\pi} \sigma} \exp \left[-\frac{4 \ln 2 (v - v_{ij})^2}{\sigma^2} \right], \quad (18)$$

where σ denotes a line width at half maximum and simulates the effect of broadening due to EFG inhomogeneity.

The entire spectrum was simulated by summing the functions (17) over all the transitions with non-zero ω_{ij}

$$F = \sum_{i,j} F_{ij}. \quad (19)$$

As was said above, the observed splittings in Fig. 4 (see also Figs 1 and 2 in Ref. 12) represent a superposition of the Zeeman splittings giving rise to a complicated pattern that depends on the orientation of $\mathbf{H}_e$ with respect to the crystal axes (angle α) and direction of $\mathbf{H}_{\text{rf}}$. In $\mathbf{H}_e \parallel \mathbf{H}_{\text{rf}}$, the spectral pattern is independent of the position of a sample in a probe head and remains unchanged upon rotation of the crystal. In $\mathbf{H}_e \perp \mathbf{H}_{\text{rf}}$, the spectral patterns recorded at α equal to -135° and $\pm 45^\circ$ were similar to each other as well as those at 0 and -90° [here $(-)$ means clockwise and $(+)$, counterclockwise rotation].¹²

Therefore, based on the results of computer simulation of the Zeeman splittings in the ^{209}Bi NQR spectra of the $\text{Bi}_4\text{Ge}_3\text{O}_{12}$ single crystal, the conclusion was made that antiferromagnetically ordered local magnetic fields of the order of 30 G exist in the unit cell of this compound.¹²

Apart from the additional splittings caused by the local magnetic fields, the Zeeman spectra of $\text{Bi}_4\text{Ge}_3\text{O}_{12}$ exhibited yet another specific feature: a dramatic increase in the resonance intensity occurred in an external magnetic field (see Fig. 4). The resonance line intensity is known to be proportional to

$$I \approx \nu_{ij}^2 \omega_{ij},$$

where ν_{ij} is the frequency of transition between the quadrupole levels i and j , and ω_{ij} is the term that defines the angular dependence of the transition probability [see Eqn (16)]. This term seems to be the only factor that can vary considerably upon applying $\mathbf{H}_e$. Therefore, the angular dependence of the resonance intensity for the ν_2 – ν_4 transitions was analysed.¹² This is determined by the sum of the squared coefficients of I_x and I_y in Eqn (16) as

$$S = \cos^2\theta + \sin^2\theta \cos^2\varphi. \quad (20)$$

Assuming the angular dependence of the function S to be responsible for the observed increase in intensity, one has to admit that $\mathbf{H}_e$ is capable of influencing the spatial orientation of the EFG axes with respect to the crystallographic ones.¹²

As distinct from $\text{Bi}_4\text{Ge}_3\text{O}_{12}$, no splittings were observed in the zero-field ^{209}Bi NQR spectrum of the $\text{Bi}_3\text{B}_5\text{O}_{12}$ single crystal. However, the anomalies found in the intensity ratio of the spectroscopic lines suggested the presence of unusual magnetic properties in this compound as well.¹³ The $\text{Bi}_3\text{B}_5\text{O}_{12}$ single crystal used in the experiment was grown by the Czochralski method from a stoichiometric melt to have a long side (20 mm) parallel to the b -axis of the unit cell and a hexagonal cross-section ($D \cong 10$ mm). The plane parallel to the ab -plane of the crystal was polished. According to the X-ray data,^{16,17} the orthorhombic (space group $Pnma$) lattice of bismuth borate comprises two crystallographically independent bismuth sites [Bi(1) and Bi(2)] that form a triangle centred at the oxygen atom not bonded to boron atoms (Fig. 5). The occupancy of the Bi(2) position of the general type is evidently twice as high as that of Bi(1) lying in the symmetry element (the mirror plane). In agreement with the X-ray diffraction data, the ^{209}Bi NQR spectrum of $\text{Bi}_3\text{B}_5\text{O}_{12}$ also points to the presence of two crystallographically independent bismuth positions. The Bi(1) atom, located in the mirror plane, is characterised by lesser magnitude of the EFG asymmetry parameter than Bi(2) due to its higher local symmetry (Table 2). The double occupancy of the Bi(2) sites is expected to give, in the NQR spectrum, the line ν_2 of nearly double intensity as compared to ν_2 of Bi(1).

However, the experiment on a single crystal showed the inverse resonance intensity ratio: the intensity of the ν_2 line of Bi(1) lying in the mirror plane was at least twice as high as that assigned to Bi(2) in the general position (Fig. 6).

In order to calculate the dependence of the resonance intensities in a pure NQR spectrum of a single crystal on the orientation of the EFG axes with respect to the $\mathbf{H}_{\text{rf}}$ direction one has to find the orientation of these axes at both bismuth sites with respect to the crystal axes. For this, the zero-field resonance intensities were

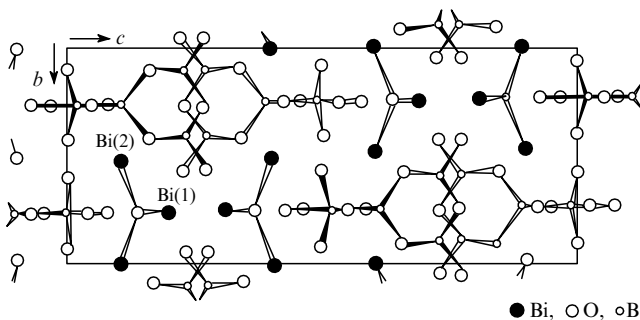


Figure 5. Projection of the $\text{Bi}_3\text{B}_5\text{O}_{12}$ crystal structure along the crystallographic axis a .¹⁷

Table 2. The zero-field ^{209}Bi NQR spectrum of $\text{Bi}_3\text{B}_5\text{O}_{12}$ at 300 K.¹⁸

Atom	Transition frequencies /MHz				eQq/h /MHz	η (%)
	ν_1	ν_2 (see ^a)	ν_3	ν_4		
Bi(1)	35.50	53.03 (0.55)	82.09	109.90	661.4	19.3
Bi(2)	71.60	52.20 (1)	72.20	101.50	632.7	65.7

^a The resonance intensities calculated on the basis of the X-ray diffraction data¹⁶ are parenthesised.

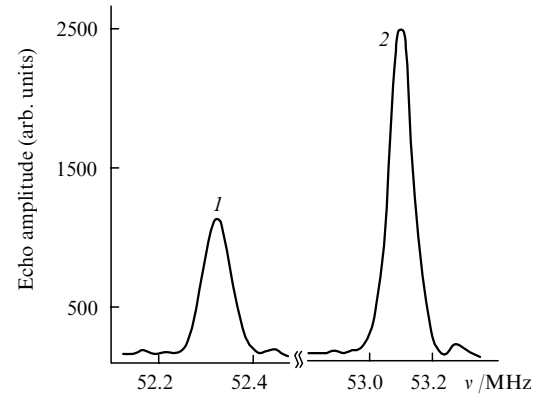


Figure 6. Zero-filed ν_2 resonances assigned to the sites Bi(2) (1) and Bi(1) (2) in the ^{209}Bi NQR spectrum of the $\text{Bi}_3\text{B}_5\text{O}_{12}$ single crystal ($\mathbf{H}_{\text{rf}} \parallel b$).

first analysed on rotation of the crystal about the b -axis in $\mathbf{H}_{\text{rf}} \perp b$ (Fig. 7) and then the Zeeman-perturbed NQR spectra were examined in the external magnetic field optimum for modelling

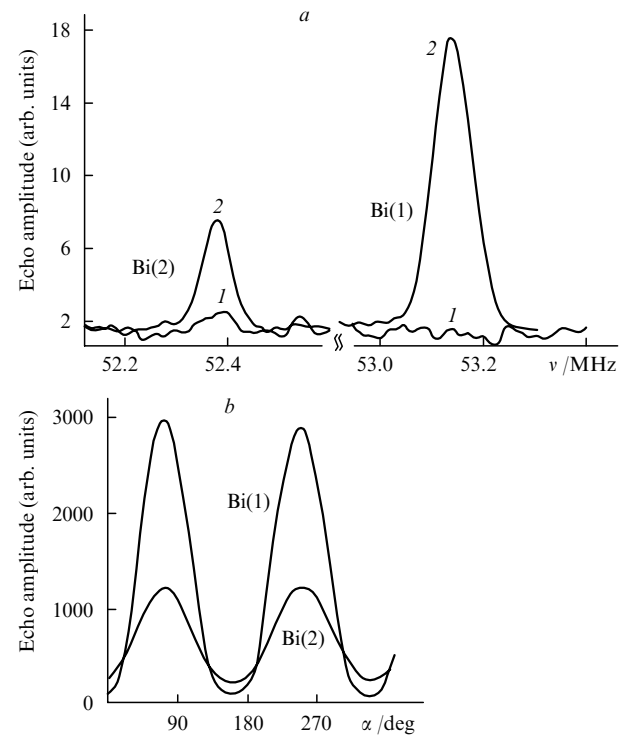


Figure 7. Zero-field ν_2 resonances assigned to the sites Bi(1) and Bi(2) in the ^{209}Bi NQR spectrum of the $\text{Bi}_3\text{B}_5\text{O}_{12}$ single crystal for the crystal orientation $\mathbf{H}_{\text{rf}} \perp b$, $\mathbf{H}_{\text{rf}} \parallel a$ (1) and $\mathbf{H}_{\text{rf}} \perp b$, $\mathbf{H}_{\text{rf}} \parallel c$ (2) (a) and the amplitude changes of these resonances over one-period rotation of the crystal about the crystallographic axis b ($\mathbf{H}_{\text{rf}} \perp b$) (b).

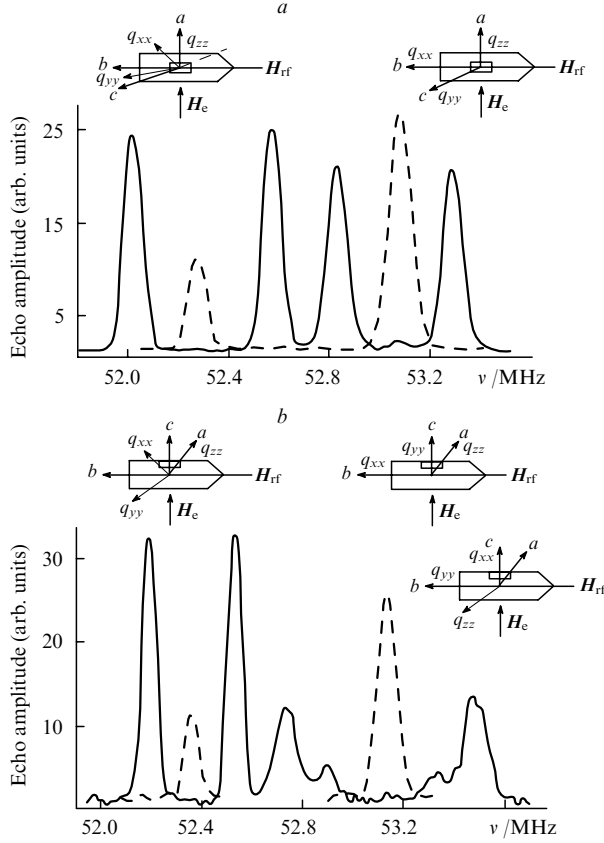


Figure 8. Zeeman-perturbed ($H_c \perp H_{rf}$, $H_c = 300$ G) ν_2 resonances (see Table 2) in the ^{209}Bi NQR spectrum of the $\text{Bi}_3\text{B}_5\text{O}_{12}$ single crystal (solid lines) as compared to those in zero magnetic field (dotted lines) for the crystal orientations $H_{rf} \parallel b$, $H_c \parallel q_{zz} \parallel a$ (a) and $H_{rf} \parallel b$, $H_c \parallel c$ (b). The orientations of the crystallographic and EFG principal axes of the single crystal as well as the directions of the H_c and H_{rf} fields are given for the Bi(1) and Bi(2) sites.

($H_c = 300$ G) at two orientations of the crystal with respect to the H_c direction (Fig. 8).¹³ In zero field, the rotation of the sample in the rf-coil about the b -axis was accompanied by a simultaneous amplitude change for both resonances: they practically vanished in $H_{rf} \parallel a$ and reached their maxima in $H_{rf} \parallel c$, whereas the intensity ratio

$$r = \frac{I_{\text{Bi}(1)}}{I_{\text{Bi}(2)}} \quad (21)$$

at its maximum remained the same ($r > 2$, see Fig. 7b). This means that on both bismuth sites, the EFG q_{zz} axes are parallel to the crystallographic axis a . The orientations of the q_{xx} and q_{yy} axes with respect to the crystal axes were found from the Zeeman experiment in $H_c = 300$ G ($H_c \perp H_{rf}$; $H_{rf} \parallel b$). The splittings ($\Delta\nu$) between the Zeeman components for both Bi(1) and Bi(2) atoms at various positions of the crystal in the probe head (see Fig. 8) are given by the formula

$$\Delta\nu = 2\gamma H_c \left\{ \left[A_m \cos^2\theta + \frac{1}{4} \sin^2\theta (B_m + 2C_m \cos 2\varphi) \right]^{1/2} - \left[A_{m'} \cos^2\theta + \frac{1}{4} \sin^2\theta (B_{m'} + 2C_{m'} \cos 2\varphi) \right]^{1/2} \right\}, \quad (22)$$

where $\pm m$ and $\pm m'$ denote the degenerate states $\pm 3/2$ and $\pm 5/2$, respectively, and the coefficients $A_m(m')$, $B_m(m')$, $C_m(m')$ are tabulated by Cohen for certain values of η .¹⁹ Good agreement of the observed and calculated splittings (Table 3) is reached assuming that at Bi(1), the EFG $q_{xx}(q_{yy})$ axis is parallel to the b -axis and

Table 3. The observed ($\Delta\nu_{\text{exp}}$) and calculated ($\Delta\nu_{\text{calc}}$) splittings of the ν_2 resonances in the ^{209}Bi NQR spectrum of the $\text{Bi}_3\text{B}_5\text{O}_{12}$ single crystal in $H_c = 300$ G (see Fig. 8).¹³

Atom	ν_2 / MHz	$\Delta\nu_{\text{exp}}$ / kHz	$\Delta\nu_{\text{calc}}$ / kHz
$H_c \parallel a$			
Bi(1)	53.03	466.0	487.0
Bi(2)	52.20	548.0	566.0
$H_c \parallel c$			
Bi(1)	53.03	548.0 (av.)	554.5 (av.)
Bi(2)	52.20	342.0	389.0

$q_{yy}(q_{xx})$, to the c -axis of the crystal. At Bi(2), q_{xx} lies in the bc -plane at an angle of 45° to the b -axis and q_{yy} , in the same plane at an angle of -45° to the b -axis. The additional splitting of the ν_2 Bi(1) line (see Fig. 8b) is caused by the magnetically non-equivalent Bi(1) positions in the lattice. With the orientation of the EFG principal axes found, one can calculate the expected resonance intensity ratio r in zero field, i.e., in a pure quadrupole spectrum of a single crystal. The transition probability W (and hence the line intensity) in a pure NQR spectrum is known to depend on the orientation of the EFG axes with respect to the H_{rf} direction as

$$W = 2D \cos^2\theta + \frac{1}{2} \sin^2\theta (G + 2J \cos 2\varphi). \quad (23)$$

Here θ and φ are the angles between the H_{rf} direction and the EFG principal axes; D , G and J are the coefficients depending on η and m .¹⁹ As the results of the calculation showed, the resonance intensity ratio r in a pure NQR spectrum is less than unity being different in the crystal orientations $H_{rf} \perp b$ and $H_{rf} \parallel b$. However, the experimental intensity ratio r exceeded 2 and was the same in both crystal orientations (see Figs 6 and 7). Hence, the observed zero-field NQR spectrum of the $\text{Bi}_3\text{B}_5\text{O}_{12}$ single crystal is not a pure quadrupole spectrum, which gives indirect evidence for the existence of unusual magnetism-related properties in this compound, in particular, local magnetic fields found earlier in $\alpha\text{-Bi}_2\text{O}_3$ and $\text{Bi}_4\text{Ge}_3\text{O}_{12}$. These fields are most likely weak, so that the appropriate zero-field splittings are masked by the effect of inhomogeneous line broadening and cannot be observed directly. The Zeeman fields $H_c = 300$ G optimal for modelling completely suppressed the spectroscopic manifestation of the local field ($H_c \gg H_{\text{loc}}$), resulting in no anomalies in the Zeeman splittings. Therefore, the evaluation of the local field strength and orientation with respect to the crystal axes from the Zeeman experiments appeared impossible.¹³

IV. Studies of local magnetic fields by analysis of the quadrupole spin echo envelope

A study of the problem was continued using an approach enabling detection of weak (within an inhomogeneous line broadening) spectroscopic splittings. Such splittings are known to be registered as low-frequency modulations of the spin echo envelope. The registering of SEE involves accumulation of the NQR signals upon continuous increase in pulse separation followed by data processing. A preliminary experiment showed that the SEE for the ν_2 Bi(1) line was modulated in zero field, pointing to the presence of line splitting. A detailed examination of this SEE curve revealed its distinctive modulation in both single crystal and powder samples of $\text{Bi}_3\text{B}_5\text{O}_{12}$ (Fig. 9).¹³ The strength and orientation of H_{loc} had to be further evaluated from the SEE shape using the mathematical model. However, due to the low-symmetry structure of $\text{Bi}_3\text{B}_5\text{O}_{12}$, an increased multiplicity of the spectrum occurs in external magnetic field, thus revealing the magnetic non-equivalence of the bismuth sites. In order to avoid computational difficulties, a model¹³ was first elaborated for $\text{Bi}_2\text{Ge}_3\text{O}_9$ [benitoite-type structure, space group $P6_3/m$ (see Ref. 11)], the

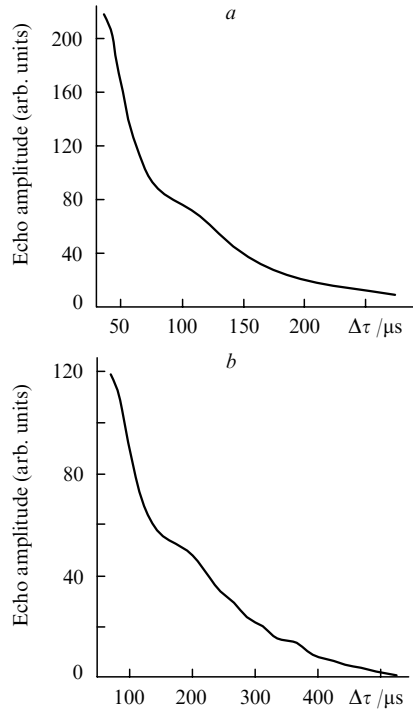


Figure 9. Zero-field spin echo envelopes assigned to the v_2 transition of Bi(1) (see Table 2) recorded for the $\text{Bi}_3\text{B}_5\text{O}_{12}$ single crystal at ambient temperature (a) and for a powder sample at 77 K (b).¹³

^{209}Bi NQR spectrum of which is given in Table 1. In agreement with the X-ray diffraction data, the spectrum reveals an axial symmetry of the crystallographically equivalent bismuth sites ($\eta = 0$, see Table 1). Earlier, the existence of local magnetic field in this compound has been suggested based on the analysis of the zero-field line shape (Fig. 10).⁴

As follows from the symmetry properties of the EFG tensor at the ^{209}Bi sites, the lattice charge contribution to the EFG tensor is the same for all the bismuth atoms in the unit cell of $\text{Bi}_2\text{Ge}_3\text{O}_9$, i.e., all the bismuth positions are crystallographically and magnetically equivalent. Hence, its ^{209}Bi NQR spectrum gives a single set of splittings in a magnetic field.¹³ In addition, the EFG principal axis q_{zz} is parallel to the sixfold axis of the hexagonal lattice, which is the z -axis of the crystal.

The zero-field SEE curves were recorded at room temperature for the lines assigned to the v_1 and v_2 transitions¹³ (see Table 1) using a powder sample of $\text{Bi}_2\text{Ge}_3\text{O}_9$ prepared as described in Ref. 3 (see Fig. 11). In zero external field, the SEE curve assigned

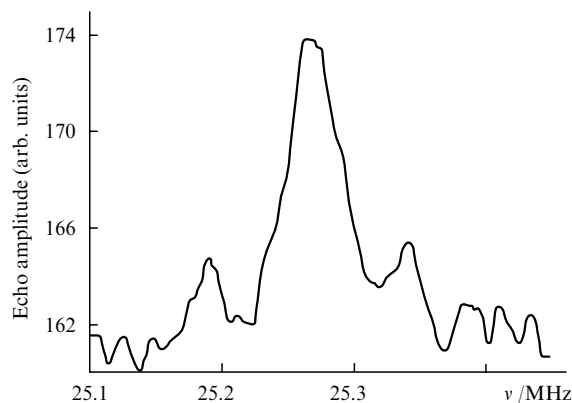


Figure 10. A zero-field line assigned to the transition v_1 ($\Delta m = 1/2 - 3/2$) in the ^{209}Bi NQR spectrum of a powder sample of $\text{Bi}_2\text{Ge}_3\text{O}_9$.

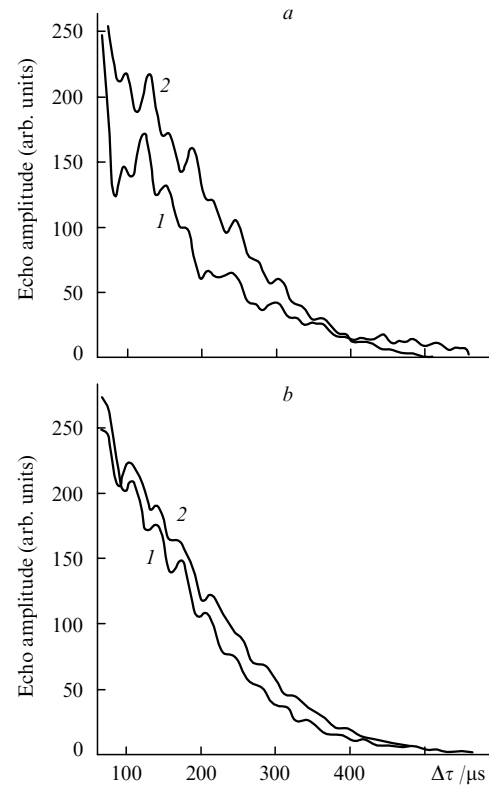


Figure 11. Observed (1) and calculated (2) zero-field spin echo envelopes assigned to the transitions v_1 ($\Delta m = 1/2 - 3/2$) (a) and v_2 ($\Delta m = 3/2 - 5/2$) (b) for a powder sample of $\text{Bi}_2\text{Ge}_3\text{O}_9$.¹³

to the v_2 transition exhibits apparently regular oscillations, whereas the modulation pattern of the SEE curve assigned to the v_1 line is more complicated, both indicating the presence of a local magnetic field in this compound. The evaluation of the local field characteristics was performed by modelling of the SEE that took into account the presence of local and external magnetic fields.¹³ Like the model described earlier²⁰ where the SEE was analysed for nuclei with the spin $3/2$, this approach was based on the density matrix formalism with the difference consisting in the consideration of the symmetry properties of the EFG and local magnetic field that substantially influence the SEE shape.¹³ The basic stages of the modelling¹³ as well as the algorithm for the SEE calculation in the presence of H_e and H_{loc} are given in the Appendix.

The simulated SEE curves are also shown in Fig. 11. It was found that the shape of the simulated curve assigned to the v_1 transition was in fairly good agreement with the experimental one assuming that the local magnetic field in $\text{Bi}_2\text{Ge}_3\text{O}_9$ amounts to 65 ± 5 G and directed at an angle $83 \pm 1^\circ$ to the EFG q_{zz} -axis. As to the transitions higher than v_1 , their line shapes are expected to be featureless in the external magnetic field, if $\eta = 0$ (Refs 20 and 21). In agreement with the results of studies,²¹ the simulated lines uniformly broadened to the Larmor frequency value. However, the results of modelling¹³ showed that, assuming even negligibly small deviation of the EFG symmetry from the axial ($\eta \sim 0.005$), the modulations of the SEE curve assigned to the v_2 transition are closely reproduced at the same characteristics of H_{loc} that have been found from the modelling of the SEE assigned to the v_1 transition (see Fig. 11). Naturally, such a small value of η is beyond the accuracy of NQR measurements. The question on whether the appropriate deviation of the electron density distribution from axial symmetry might be detected in an X-ray experiment seems to be interesting. The anomalies found in the magnetic properties of $\text{Bi}_2\text{Ge}_3\text{O}_9$ make the experiments on a single crystal very attractive. Unfortunately, all efforts to grow a single crystal of suitable size failed.¹³

The modelling of the SEE for $\text{Bi}_3\text{B}_5\text{O}_{12}$ having more complicated structure was carried out in a similar way (Fig. 12). As was mentioned above, the unit cell of $\text{Bi}_3\text{B}_5\text{O}_{12}$ is orthorhombic [space group $Pnma$ (D_{2h}^{16}), $Z = 2$] with four Bi(1) atoms occupying the c -sites in the symmetry plane and eight Bi(2) atoms, the d -positions of the general type.^{16,17} The analysis of the EFG symmetry at the c -sites showed that two types of the EFG tensors are available for the Bi(1), Bi(2) and Bi(3), Bi(4) atoms, respectively:

$$\begin{pmatrix} a & 0 & d \\ 0 & b & 0 \\ d & 0 & c \end{pmatrix} \text{ (I) and } \begin{pmatrix} a & 0 & -d \\ 0 & b & 0 \\ -d & 0 & c \end{pmatrix} \text{ (II),}$$

where a, b, c, d are the lattice sums of products of the atomic coordinates by derivatives of the crystal-field potentials at the atomic sites.⁷ The roots of the characteristic equations associated with the tensors (I) and (II) are equal to each other

$$\lambda_1 = b, \quad (24)$$

$$\lambda_{2,3} = \frac{a+c}{2} \pm \frac{1}{2} \sqrt{(a-c)^2 + 4d^2}.$$

The fact that one of the roots is equal to the diagonal element of the EFG tensor ($\lambda_1 = b$) complicates the procedure of finding the direction cosines for the principal axes of the tensors (I) and (II). However, one can show that the following symmetry relationships hold true:

$$\sigma_{21}^{(I)} = \sigma_{31}^{(II)}, \quad \sigma_{31}^{(I)} = \sigma_{21}^{(II)}, \quad \sigma_{23}^{(I)} = -\sigma_{33}^{(II)}, \quad \sigma_{33}^{(I)} = -\sigma_{23}^{(II)},$$

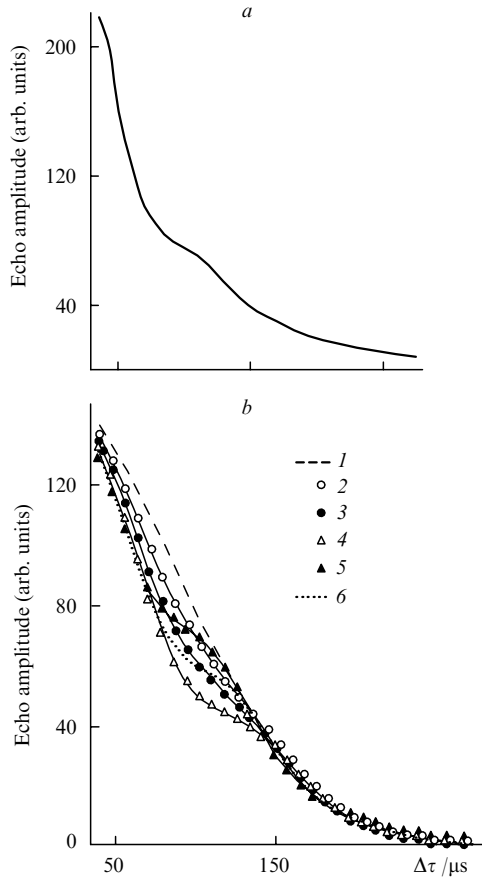


Figure 12. Observed (a) and simulated (b) SEE curves of the transition v_2 of the Bi(1) site in the ^{209}Bi NQR spectrum of the $\text{Bi}_3\text{B}_5\text{O}_{12}$ single crystal for the various parameters of local magnetic field ($H_{\text{loc}i} = H_{\text{loc}} \cos \theta_i$). $H_{\text{loc}i}/\text{G}$: 0 (1), 2 (2–4), 2.5 (5), 2.25 (6); θ_i/deg : 0 (1), 15 (2), 20 (3, 5), 25 (4), 22.5 (6).

$$\sigma_{12}^{(I)} = \sigma_{12}^{(II)} = 1 \quad (25)$$

$$\sigma_{11}^{(I)} = \sigma_{11}^{(II)} = \sigma_{22}^{(I)} = \sigma_{22}^{(II)} = \sigma_{33}^{(I)} = \sigma_{33}^{(II)} = \sigma_{23}^{(I)} = \sigma_{23}^{(II)} = 0.$$

These relationships enable one to determine the two of three Euler angles connecting the crystallographic coordinate system with those of the EFG principal axes (see Fig. 3b).

$$\theta_1, \varphi_1 = \frac{3\pi}{2}, \quad \psi_1 = \frac{\pi}{2}, \quad (26)$$

$$\theta_2 = \theta_1 + \frac{\pi}{2}, \quad \varphi_2 = \frac{\pi}{2}, \quad \psi_2 = \frac{3\pi}{2}.$$

The θ_1 -value for the Bi(1) positions in the $\text{Bi}_3\text{B}_5\text{O}_{12}$ lattice can be found from a comparison of the simulated and observed NQR Zeeman spectra.¹³ The modelling of the Zeeman spectra was performed as described above (see Part III). For the $\text{Bi}_3\text{B}_5\text{O}_{12}$ single crystal used in the experiments, the components of the rotation matrix D in the Hamiltonian $\hat{H}_e$ [see Eqn (8)] are

$$\begin{aligned} D_{13} &= -\cos \psi \cos \varphi \sin \alpha + \\ &+ \sin \psi (\cos \theta \sin \varphi \sin \alpha + \sin \theta \cos \alpha), \\ D_{23} &= \sin \psi \cos \varphi \sin \alpha + \\ &+ \cos \psi (\cos \theta \sin \varphi \sin \alpha + \sin \theta \cos \alpha), \\ D_{33} &= -\sin \theta \sin \varphi \sin \alpha + \cos \theta \cos \alpha, \end{aligned} \quad (27)$$

where θ, φ and ψ are the Euler angles [see Eqn (26)]. It is to be reminded that the field $\mathbf{H}_{\text{rf}}$ was parallel to the axis b of the single crystal, and the crystal was turned through the angle α about the coil axis coinciding with the $\mathbf{H}_{\text{rf}}$ direction. At $\alpha = 0^\circ$, the external field $\mathbf{H}_e$ was directed along the c -axis, and at $\alpha = -90^\circ$, along the a -axis of the crystal. In $\mathbf{H}_e \parallel c$ ($\alpha = 0^\circ$), the components of the rotation matrices in Eqn (27) referring to the two sets of the Euler angles (26) are described as

$$\begin{aligned} D_{13}^{(1)} &= \sin \theta_1, \quad D_{23}^{(1)} = 0, \quad D_{33}^{(1)} = \cos \theta_1, \\ D_{13}^{(2)} &= -\cos \theta_1, \quad D_{23}^{(2)} = 0, \quad D_{33}^{(2)} = -\sin \theta_1. \end{aligned} \quad (28)$$

In these expressions, the upper index corresponds to the set of the angular parameters in Eqn (26). In $\mathbf{H}_e \parallel a$ ($\alpha = -90^\circ$), the components of the rotation matrices become

$$\begin{aligned} D_{23}^{(1)} &= 0, \quad D_{33}^{(1)} = -\sin \theta_1, \\ D_{13}^{(2)} &= -\sin \theta_1, \quad D_{23}^{(2)} = 0, \quad D_{33}^{(2)} = \cos \theta_1. \end{aligned} \quad (29)$$

The angle $\theta_1 = 0 \pm 5^\circ$ was found from the comparison of the observed (Fig. 8) and simulated spectra of the $\text{Bi}_3\text{B}_5\text{O}_{12}$ single crystal in $H_e = 300$ G.

The calculation of the SEE shape by the program based on the density matrix formalism¹³ (see Appendix) enabled one to derive the value of local magnetic field in this compound (~ 2.5 G, see Fig. 12).

Thus, the above results showed that a weak local magnetic field exists in $\text{Bi}_3\text{B}_5\text{O}_{12}$. Assuming that the presence of these fields is related to the anomalies observed for the resonance intensity ratio [for instance, the local field unequally influences the intensities assigned to the v_2 resonances assigned to the Bi(1) and Bi(2) sites characterised by the EFG of presumably different symmetry¹³], one has to admit the existence of a strong coupling between the electronic and magnetic subsystems in $\text{Bi}_3\text{B}_5\text{O}_{12}$.

The zero-field modulations of the ^{209}Bi SEE curves were naturally observed in the compounds where $\mathbf{H}_{\text{loc}}$ has earlier been revealed from either Zeeman-perturbed or zero-field spectroscopic splittings.¹³ Distinctive modulations were also observed for BaBiO_2Cl (Fig. 13) the crystallochemical properties of which have much in common with those of the above described $\text{Bi}_3\text{O}_4\text{Br}$. In the structures of both compounds, the layers of bismuth oxide polyhedra alternate with those of halide anions.^{22,23} The

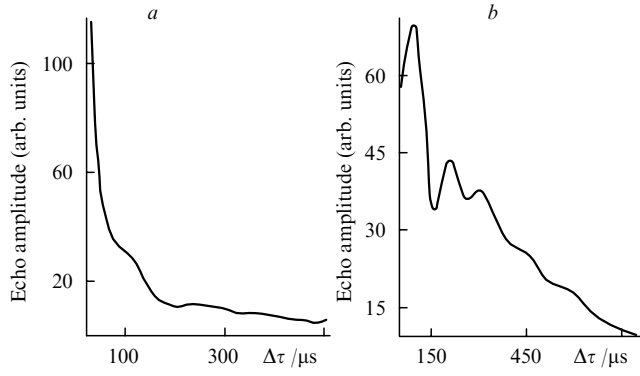


Figure 13. Zero-field spin echo envelopes of the ν_1 (a) and ν_2 (b) transitions in the ^{209}Bi NQR spectrum of powdered BaBiO_2Cl .

^{209}Bi NQR zero-field spectrum of a powder sample of BaBiO_2Cl measured at 300 K is given below.

Transition frequency /MHz				eQq/h /MHz	η (%)
ν_1	ν_2	ν_3	ν_4		
33.43	36.44	57.50	77.67	470.25	33.3

Nearly all the compounds discussed here featured extraordinary sensitivity of the NQR spectroscopic parameters to weak magnetic fields. For most of them, a considerable increase in the

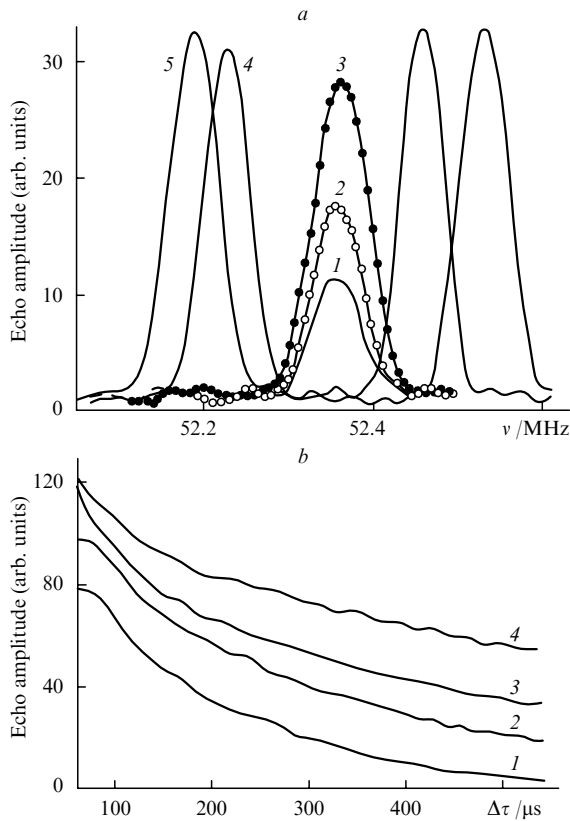


Figure 14. Line of the ν_2 transition of Bi(2) (see Table 2) in the ^{209}Bi NQR Zeeman spectra of $\text{Bi}_3\text{B}_5\text{O}_{12}$ (a) and spin-echo envelopes recorded for the same line in various magnetic fields (b).

H_c /kG: (a) 0 (1), 13 (2), 30 (3), 225 (4), 300 (5); (b) 0 (1), 7.5 (2), 18 (3), 45 (4).

resonance intensity depending on the ^{209}Bi EFG symmetry properties and mutual orientation of the fields disturbing the spin system was observed upon applying magnetic field (see, for instance, Figs 4 and 8). This phenomenon could explain the deviation of the $\nu_2\text{Bi}(1)$ -to- $\nu_2\text{Bi}(2)$ intensity ratio in $\text{Bi}_3\text{B}_5\text{O}_{12}$ from that in a pure quadrupole spectrum.¹³

A strong increase in the line intensity observed in the Zeeman spectrum of $\text{Bi}_4\text{Ge}_3\text{O}_{12}$ was suggested to result from the effect of external magnetic field on the spatial orientation of the EFG axes.¹² Recent experiments showed that H_e also strongly affects the spin–spin relaxation time and hence the resonance intensity (Fig. 14).²⁴ This problem for the high-spin systems with non-equidistant energy levels is, however, virtually unstudied.

It is important to note that no intensity increase in the ^{115}In NQR lines in a magnetic field was observed for crystallographically related indium compounds In_xB_y ($B = \text{O}, \text{Se}, \text{Te}$) where the valence electron shell of the central atom (the ^{115}In nuclear spin is $9/2$) has, unlike bismuth, no unshared pair of electrons (Table 4, Fig. 15).²⁴

Table 4. The ^{115}In NQR spectrum of In_2Te at 77 K.

Atom	Transition frequencies /MHz				eQq/h /MHz	η (%)
	ν_1	ν_2	ν_3	ν_4		
In(1)	10.55	15.12	23.20	31.00	188.0	21.0
In(2)	8.06	10.46	16.37	22.00	133.0	25.0

V. The results of magnetisation measurements and magnetoelectric effect in the $\alpha\text{-Bi}_2\text{O}_3$ single crystal

Studies of magnetic properties of the compounds by complementary methods included an examination of a powdered $\alpha\text{-Bi}_2\text{O}_3$ sample using a muon spin relaxation (μSR) technique^{25–27} and SQUID measurements of the $\alpha\text{-Bi}_2\text{O}_3$ single crystal.^{28,29} The results of the experiments were understood as indicative of previously unknown magnetic properties in the compound. The μSR experiments within 10–300 K revealed no pronounced precession of the muon spin, hence ruling out the existence of a long-range order in $\alpha\text{-Bi}_2\text{O}_3$. However, fast depolarisation of the muon spin was distinctly observed for short time intervals, which was interpreted as manifestation of local magnetic fields in interstices of the α -bismuth oxide crystal lattice.^{25–27}

In the experiments using a SQUID magnetometer with the sensitivity of about 10^{-7} G cm^3 , the magnetisation of the $\alpha\text{-Bi}_2\text{O}_3$ single crystal was measured as a function of the magnetic field and temperature to find the paramagnetic character of magnetisation at low temperatures ($\sim 4.2 \text{ K}$) in magnetic fields up to 3–5 kG (Figs 16 and 17).²⁸ The magnetisation of the single crystal was highly anisotropic, which makes groundless a suggestion of paramagnetic impurities as the cause of magnetisation: because of disordered distribution in a diamagnetic crystal, they can produce the isotropic magnetisation only.³⁰

As the temperature and external magnetic field increased, the magnetisation of $\alpha\text{-Bi}_2\text{O}_3$ passed from the para- to the diamagnetic region where it conformed to the conventional classification of this substance as diamagnetic. It is to be noted that this classification is based on the results of measurements of the magnetisation by the Faraday method using a magnetic balance at room temperature in magnetic fields of the order of 10 kG.

A strong dependence of the $\alpha\text{-Bi}_2\text{O}_3$ single crystal magnetisation (M) on the magnetic prehistory of the sample was observed.²⁹ Figure 18 demonstrates the $M(H)$ curves measured along the crystallographic c -axis of the sample at 4.2 K. The sample was cooled either in the zero external field (Zero-Field

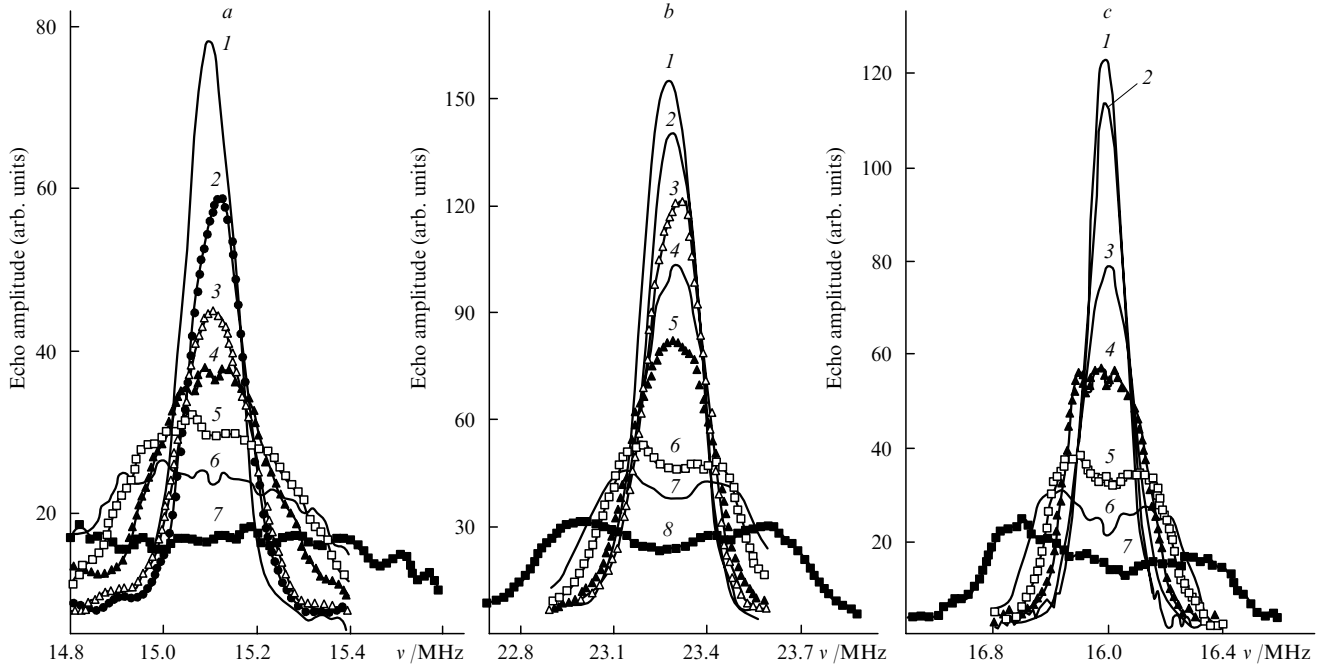


Figure 15. Selected lines assigned to the transitions ν_2 for In(1) (a), ν_3 for In(1) (b) and ν_3 for In(2) (c) in the ^{115}In NQR Zeeman spectra of powdered In_2Te (see Table 4).

H_c/G : (a) 0 (1), 21 (2), 60 (3), 150 (4), 225 (5), 300 (6), 480 (7); (b) 0 (1), 30 (2), 60 (3), 90 (4), 120 (5), 225 (6), 300 (7), 480 (8); (c) 0 (1), 30 (2), 90 (3), 150 (4), 225 (5), 300 (6), 480 (7).

Cooling, ZFC; the strength of H_c inside a magnetic screen containing the sample was several mG, or in the fields of the order of several hundred Oersted (Field Cooling, FC). The dependence $M(H)$ under the ZFC conditions was linear in weak fields and rapidly came to a saturation in the fields above 2.5 kG. However, the magnetisation dramatically increased upon cooling the crystal in the external magnetic field. Thus, it increased by an order of magnitude in the fields $H_c \sim 3\text{--}4$ kG for the sample

precooled in the field of 580 G, the tendency for saturation weakening as the field in which the sample was cooled increased.²⁹

The temperature dependence of the magnetisation also strongly depended on the magnetic prehistory of the sample.²⁹ Both curves in Fig. 19 were measured in the external field of 4850 G applied along the axis a of the crystal. The curve 1 was measured after ZFC, whereas the other one, after the crystal was stored for ~ 10 hours in a residual field of a solenoid ($H_c \sim 10$ G) at liquid nitrogen temperature.

The mechanism of this phenomenon is not yet clear, the suggestion being made of its magnetoelectric nature, because the magnetoelectric effect (electric polarisation in an applied magnetic field) linear with respect to the field was observed in $\alpha\text{-Bi}_2\text{O}_3$ at 4.2 K.^{28,29} In addition, α -bismuth oxide is similar to ferro- and antiferroelectrics in electric properties. This is supported by

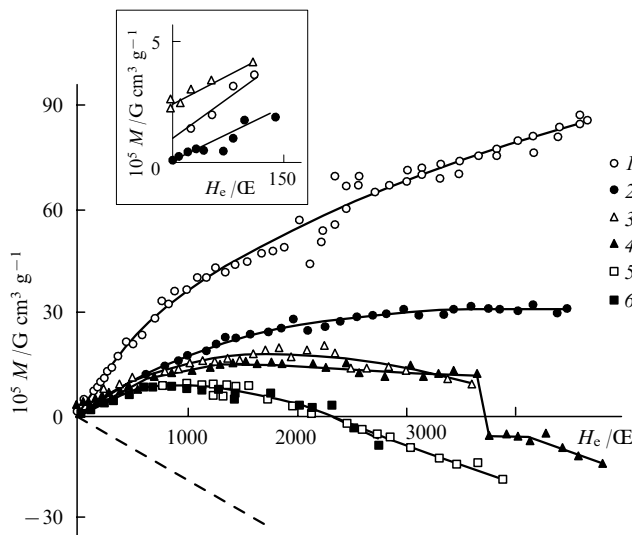


Figure 16. Magnetisation of the $\alpha\text{-Bi}_2\text{O}_3$ single crystal in external magnetic fields.²⁸

Measuring conditions: (1) $T = 4.2$ K, $H_c \parallel a$; (2) $T = 4.2$ K, $H_c \parallel b$; (3) $T = 4.2$ K, $H_c \parallel c$; (4) $T = 77$ K, $H_c \parallel a$; (5) $T = 77$ K, $H_c \parallel c$; (6) $T = 200$ K, $H_c \parallel c$. Dashed line is M_{dia} (see text). In the inset, the initial parts of some curves are shown.

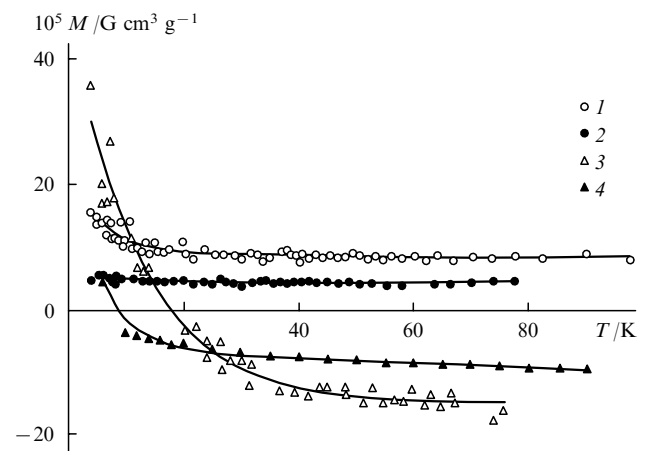


Figure 17. Temperature dependence of $\alpha\text{-Bi}_2\text{O}_3$ magnetisation.²⁸

Measuring conditions: (1) $H_c \parallel c$, $H = 1000$ G; (2) $H_c \parallel c$, $H = 124$ G; (3) $H_c \parallel a$, $H = 4850$ G; (4) powder sample, $H = 500$ G.

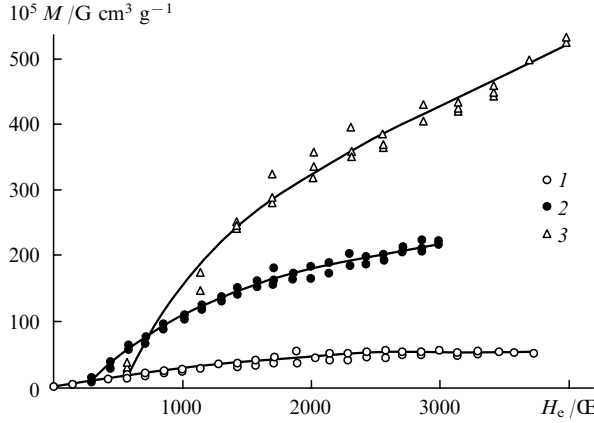


Figure 18. Field dependence of the α -Bi₂O₃ single crystal magnetisation measured at 4.2 K in $H_e \parallel c$.²⁹ (1) ZFC, (2) FC in the field 284 Oe, (3) FC in the field 566 Oe.

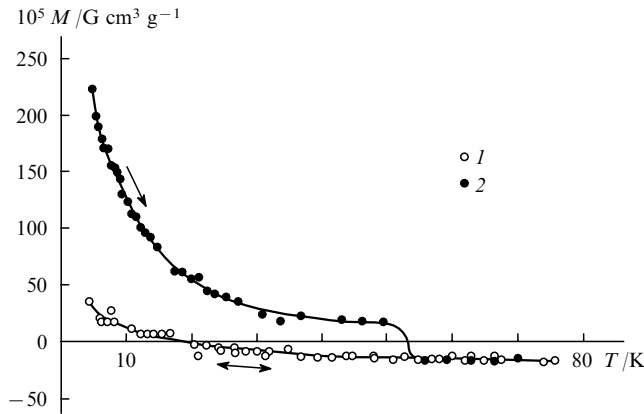


Figure 19. Temperature dependence of the α -Bi₂O₃ single crystal magnetisation measured in the field 4850 Oe, $H_e \parallel a$.²⁹ (1) ZFC, (2) a sample was stored in the field of 10 Oe at $T = 77$ K for 10 h. Arrows show the direction of temperature change.

several anomalies in its physical properties found between 450–570 K, for instance, a maximum displayed by the real part of the dielectric permeability.^{31, 32} These anomalies were however accompanied by neither distortions of monoclinic symmetry of the α -Bi₂O₃ lattice, nor sharp changes in the lattice parameters over 300–570 K. The monoclinic lattice of α -bismuth oxide remained stable also at low temperatures: the IR³³ and Raman³⁴ spectra of the single crystal were qualitatively very similar to those measured at room temperature.

Based on the results of measurements of the field and temperature dependences of the α -Bi₂O₃ magnetisation, the authors²⁹ evaluated the effective magnetic moment per unit cell of the crystal, assuming several contributions to the magnetisation:

$$M = M_{\text{dia}} + M_{\text{VV}} + M_{\text{para}}, \quad (30)$$

where $M_{\text{dia}} = \chi_{\text{dia}} H$ is the temperature-independent diamagnetic contribution of the ionic cores (the magnitude of $\chi_{\text{dia}} = -1.85 \times 10^{-7} \text{ cm}^3 \text{ g}^{-1}$ was estimated assuming additive contributions of the ion diamagnetic susceptibilities to the total diamagnetic susceptibility of α -Bi₂O₃³⁵); M_{VV} is the temperature-independent positive Van Vleck-type contribution; M_{para} is the paramagnetic Curie-type contribution. Both latter contributions depend on the magnetic prehistory of a sample (see Figs 18 and 19). The known formulae were used to evaluate M_{VV} and M_{para} :

$$M_{\text{VV}} = \chi_{\text{VV}} H, \\ \chi_{\text{VV}} \approx \frac{N_A \mu_B^2}{A} \frac{\alpha^2}{\Delta},$$

$$M_{\text{para}} = \chi_{\text{para}} H,$$

$$\chi_{\text{para}} = \frac{N_A \mu_B^2}{A} \frac{\mu_{\text{ef}}^2}{3kT},$$

(31)

where N_A is the Avogadro number, $A = 466 \text{ g mol}^{-1}$ is the molecular weight of α -Bi₂O₃, α^2 is the squared matrix element of the magnetic moment operator, Δ is the energy difference between the ground and excited states of the electronic subsystem, μ_{ef} is the effective magnetic moment of the unit cell of the crystal.

The parameters α^2/Δ and μ_{ef} were estimated at 4.2 and 77 K based on the results of ZFC magnetisation measurements²⁸ (Figs 16 and 17) in weak fields ($H_e < 500$ Oe) where M linearly depends on H_e directed along the axis a of the crystal. They were found to amount to $\alpha^2/\Delta \approx 4 \times 10^{-4} \text{ K}^{-1}$ and $\mu_{\text{ef}} \approx 0.06 \mu_B$ (per formula unit). Although the estimated value of the α -Bi₂O₃ magnetic moment appeared to be small compared to those in conventional ferro- and antiferromagnets, it unambiguously points to the electronic origin of the paramagnetism in this compound. Moreover, the magnetisation of the sample precooled in a constant magnetic field (the FC experiment) increased by factors 5–10 compared to that of the sample measured after ZFC (see Fig. 18). It is clear that if Eqns (31) hold true under the FC conditions, a similar analysis of the magnetisation will give the values of α^2/Δ and μ_{ef} increased accordingly.

As was mentioned above, the magnetoelectric effect was observed in the α -Bi₂O₃ single crystal.^{28, 29} This effect was studied for a plate $\sim 0.03 \text{ cm}^2$ in area and 0.13 cm thick that was cut in the bc plane of the crystal. A highly sensitive electrometer Kythley 642 was used for the measurements. The experiment was carried out at 4.2 K in a superconducting solenoid capable of producing magnetic field up to 150 kOe. The magnetic field $H \parallel E$ was applied perpendicularly to the plate surface, i.e., close to the axis a of the crystal. The results are shown in Fig. 20. As one can see, the polarisation linearly increased (the slope is 1.6×10^{-7}) in the fields up to 50 kOe showing a tendency for saturation in higher fields.

The crystal structure of α -Bi₂O₃ is known to be monoclinic.³⁶ There are four magnetic classes in the point group C_{2h} ,³⁷ from which C_{2h} and $C_{2h}(C_i)$ allow ferromagnetism, whereas $C_{2h}(C_2)$ and $C_{2h}(C_s)$, antiferromagnetism. An inversion (I) is present among the symmetry elements of the two former classes. This means that the linear magnetoelectric effect described by the magnetoelectric component of the thermodynamic potential³⁷

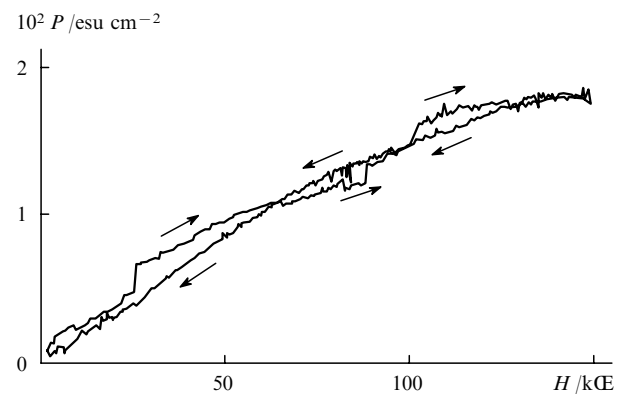


Figure 20. The magnetoelectric effect in the α -Bi₂O₃ single crystal measured at 4.2 K.²⁹ P is polarisation. Arrows show the direction of field change.

$$\Phi_{me} = -\alpha_{ij}E_iH_j \quad (32)$$

is forbidden for the C_{2h} and $C_{2h}(C_i)$ classes (α_{ij} is the magnetoelectric tensor) and allowed for $C_{2h}(C_2)$ and $C_{2h}(C_s)$. Based on the symmetry properties, it was shown²⁹ that the magnetoelectric tensor for the class $C_{2h}(C_2)$ is

$$\alpha_{ij} = \begin{pmatrix} \alpha_{xx} & 0 & \alpha_{xz} \\ 0 & \alpha_{yy} & 0 \\ \alpha_{zx} & 0 & \alpha_{zz} \end{pmatrix}. \quad (33)$$

For the class $C_{2h}(C_s)$, the components complementary to those of matrix (33) differ from zero:

$$\alpha_{ij} = \begin{pmatrix} 0 & \alpha_{xy} & 0 \\ \alpha_{yx} & 0 & \alpha_{yz} \\ 0 & \alpha_{zy} & 0 \end{pmatrix}. \quad (34)$$

Attempts to explain the origin of the linear magnetoelectric effect in α -bismuth oxide faced however several difficulties.

According to Landau and Lifshitz, who predicted the existence of the effect in magnetically ordered substances,³⁷ the tensor α_{ij} is an odd function with respect to time inversion. After theoretical prediction by Dzyaloshinskii³⁸ followed by observation of the magnetoelectric effect in antiferromagnetic Cr_2O_3 ,^{39,40} the systematic classification of magnetoelectric materials was performed.⁴¹ It was noted that the linear magnetoelectric effect described by Eqn (32) can exist only in substances characterised by the long-range ferro- or antiferro-magnetic ordering. However, the analysis of the α - Bi_2O_3 magnetisation carried out using Eqn (30) showed that the existence of the long-range magnetic ordering in α -bismuth oxide is unlikely.²⁹

The suggestion that the paramagnetoelectric effect, similar to that found in piezoelectric paramagnetic crystals,⁴² may exist also in α - Bi_2O_3 comes into conflict with several facts. This effect is described by a contribution into the thermodynamic potential of the type

$$\Phi_{\text{PME}} = -\zeta_{ijk}E_iH_jH_k,$$

where ζ_{ijk} is the magnetoelectric tensor of the third rank.

Hence, this is forbidden for the point group C_{2h} , because the inversion I is available among its symmetry elements. In addition, the electric polarisation is a function of H but not H^2 over a wide range of fields, as demonstrated in Fig. 20.

As to the existence of the magnetoelectric effect in diamagnetic dielectric crystals, the observation of this effect in crystals with paramagnetic defects was documented. Using EPR, a notable increase in magnetisation of α -quartz comprising the $\text{Al}-\text{O}^-$ centres was found in an alternating electric field.⁴³ The magnetic and electric characteristics are coupled in such systems by spin-orbit interaction. A tunnelling of the charged electron holes between the equilibrium positions, if available, enhances the effect considerably. The hole is known to carry the magnetic moment because it possesses both spin and orbital magnetic moments. Such a paramagnetic centre carries also the electric dipole moment. If a coupling exists between the electric and magnetic moment, one can observe the magnetoelectric effect.

The existence of a system of paramagnetic centres in α - Bi_2O_3 is quite probable. The holes in the p-electron shell of the oxygen atoms may presumably serve as such centres, whereas the $\text{Al}-\text{O}^-$ centres in α -quartz result from the Al^{3+} substitution for Si^{4+} . Considering the low symmetry of the electric field of the crystal at the oxygen sites and weak spin-orbit interaction (the spin-orbit coupling constant for the oxygen atom is ~ 10 meV) one can admit the presence of several low-lying crystal field levels, which are responsible for the observed field and temperature dependences of the paramagnetic contribution into the α - Bi_2O_3 magnetisation. Thus for the p^4 atomic configuration, the multiplets $^3P_2$ (ground) and excited $^3P_1$ and $^3P_0$ (lying, accordingly, 20 and 30 meV above the ground level in a free oxygen atom⁴⁴) must split into nine

crystal-field levels. To verify the hypothesis for the presence of the paramagnetic centres in α -bismuth oxide, a detailed examination of its electron structure is necessary.

VI. On the probable origin of anomalies in magnetic properties of bismuth oxy compounds

No information on the electron structure of α - Bi_2O_3 is available in the literature, so that the calculation of its electron band structure was found to be expedient. The program package used for the calculations was a version of the FP-LMTO (Full-Potential Linear-Muffin-Tin-Orbital) approach⁴⁵ based on the electron density functional theory.⁴⁶ This approach belongs to the so-called 'first principle' methods of calculating the electron structure, which require only the nuclear charges, lattice parameters and atomic coordinates to be given as the initials. Based on the electron density functional theory, the electron density is further computed by a self-consistence procedure, after which the full energy and electron band structure of the compound are evaluated. The calculated electron band structure of α - Bi_2O_3 appeared however too cumbersome, therefore the density of states only is shown in Fig. 21, which nevertheless carries a sufficient amount of information on the electronic properties of this compound.

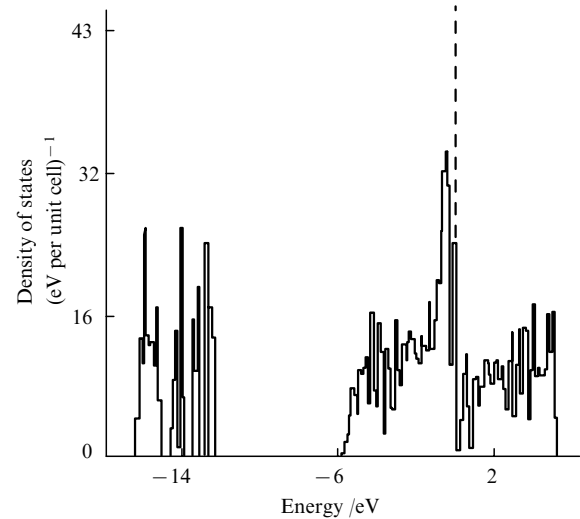


Figure 21. Density of states for α - Bi_2O_3 . Dashed line shows the Fermi level.

According to the results of the calculation, a peak of the density of states exists near the Fermi level, the ground state of the electron structure of α - Bi_2O_3 being metallic, whereas it is actually dielectric. A similar inconsistency results from the electron structure calculations of copper oxy compounds that served as the initial reagents for the preparation of high-temperature superconductors. This inconsistency can be removed, for instance, by the introduction of the Hubbard Hamiltonian, which takes into account the electron correlations. Examples are provided by transition or rare earth element compounds that exhibit sharp peaks of the density of states near the Fermi surface (Kondo-insulators).⁴⁷ Unlike the known systems with strong electron correlations, α - Bi_2O_3 comprises no atoms with unfilled d- or f-electron shells. Hence, the revealed features of the α - Bi_2O_3 electron structure allow one to raise the question about the existence of strong electron correlations in systems with valence s- and p-electrons also.

The analysis of the partial densities of states suggested that the $\text{Bi}6s$ - and $\text{O}2s$ -electrons make the predominant contribution to the peaks located in the energy range from -16 to -12 eV, the high density of states at -5.0 and -3.0 eV resulting largely from

the Bi6p- and O2p-electrons. The unoccupied states above the Fermi level are due mostly to the Bi6p-electronic states. Based on the results of the calculations, the conduction band width ($\sim 4-5$ eV) involving the hybridised O2p- and Bi6p-electronic states was evaluated as well as the band width for the O2p-states in the Fermi level ($2-3$ eV). As follows from the results obtained, the correlations between the O2p-electrons may be responsible for the semiconducting (close to dielectric) type of the α -Bi₂O₃ electron band structure as well as for the unusual magnetic properties: the existence of local magnetic fields, paramagnetism depending on the thermomagnetic prehistory of a sample and magnetoelectric effect. The Bi6s- and O2s-electronic states in α -bismuth oxide can hardly be the strongly correlated subsystem, if the high bonding energy and the Pauli principle are taken into account. The dominant role played by the Bi6p-electrons seems to be the participation in the superexchange O2p – Bi6p – O2p interactions accompanied with the electron spin-flip hoppings, which may result in the antiferromagnetic correlations and magnetoelectric effect.⁴⁸ This suggestion is supported by low (monoclinic) crystal symmetry of α -bismuth oxide removing the spin – orbit degeneracy of the 6p-electron levels, a gain in energy caused by the half-filled bismuth 6p-electron shell (the $6s^2 6p^3$ configuration), and high, as the calculation showed, density of the vacant 6p-states above the Fermi level. It is to be noted that the ferromagnetic correlations in systems comprising only p-electrons are forbidden by the Pauli principle.

VII. Conclusion

This review summarises the results of investigation of some unusual magnetic and electronic properties of bismuth oxy compounds comprising the Main Group elements only. The results were obtained using mainly the ²⁰⁹Bi NQR spectroscopy and SQUID-magnetometry. The quantitative analysis of both the complicated Zeeman NQR spectra of high multiplicity and quadrupole spin echo envelopes, measured on mono- and polycrystalline samples, became possible due to development of new approaches in the NQR theory, *viz.*, elaboration of the computer model of the quadrupole spin echo based on the density matrix formalism and account of the EFG symmetry properties. As a result, the high sensitivity of the NQR spectroscopy to the presence in substances of weak magnetic fields compared to the terrestrial field was demonstrated. Because of this superior sensitivity, the NQR method (along with NMR) may become a promising tool for the solution of topical problems concerned with the reading of an information stored by nuclear spin systems.

A variety of unusual magnetic properties revealed in the bismuth oxy compounds, which have been traditionally considered as diamagnets, namely,

- the existence of local magnetic fields,
- the paramagnetism depending on the magnetic prehistory of a sample,
- magnetoelectric effect linear in magnetic field

give, along with the calculated peaks of the density states near the Fermi surface, grounds to believe that the electron correlations may exist also in substances with valence s- and p-electrons.

The electronic and magnetic properties of the discussed bismuth oxy compounds, as well as those of extensively studied transition and rare earth element oxides, result from an interplay of a number of contributions, such as specific features of crystal structure, electron correlations, exchange and superexchange interactions and orbital degrees of freedom.

An extension and analysis of the experimental basis aimed at clarifying the origin and mechanism of the coupling between the electronic and magnetic subsystems in non-magnetic compounds make a valuable contribution to our knowledge of magnetism. Thus the material surveyed in this review suggests the important role of the matrix (of gallium arsenide-type) for the explanation of unconventional properties displayed by highly dilute magnetic

semiconductors recognised as promising materials for spintronics technology.

The authors are grateful to the Russian Foundation for Basic Research (Project No. 02-03-33280) for the support. The authors also appreciate the support of The Department of Chemistry and Materials Sciences of the RAS (the program ‘Elaboration of new efficient methods of chemical analysis and structural studies of substances and materials’, Project OKh-2.14) (E A Kravchenko); Federal Program for the Support of Leading Scientific Schools of the Russian Federation (Grant NSh-15722.2003.2) and The Foundation for the support of basic research in RSC ‘Kurchatov Institute’ (Project No. 17) (V G Orlov and M P Shlykov).

VIII. Appendix. The calculation of the nuclear quadrupole spin echo

The numerical modelling of the quadrupole spin echo was carried out for a two pulse spin echo sequence. The radiofrequency field H_{rf} was supposed to act during the time intervals $0 \leq t \leq t_1$ (the first pulse) and $\tau \leq t \leq \tau + t_2$ (the second pulse) and be switched off between the pulses ($t_1 \leq t \leq \tau$) and after the second pulse ($t \geq \tau + t_2$). The spin echo signal was expected to appear at the moment $t \cong 2\tau$. The duration of both pulses was assumed to be short compared to the interval between the pulses ($t_1, t_2 \ll \tau$). The interval τ is usually restricted to $\tau < T_2$ where T_2 is the spin – spin (transverse) relaxation time. In the modelling of the spin echo envelope, the magnitude of τ was varied in consistence with the time of measuring the SEE.

A distinctive feature of this model of the quadrupole spin echo consists of the presence of local and external magnetic fields. Both fields were assumed to be small: $\gamma H_{loc}, \gamma H_e \ll \omega_Q$, where $\gamma/2\pi = g_{Bi}\mu_B/h = 6.9 \times 10^{-4}$ MHz (G⁻¹) is the gyromagnetic ratio for the bismuth nucleus, ω_Q is the quadrupole transition frequency. The radiofrequency field H_{rf} was also assumed to be small: $\omega_1 = \gamma H_{rf} \ll \omega_Q$.

In the NQR experiments on the bismuth oxy compounds, the magnetic fields do fulfil the above requirements. Thus in the ²⁰⁹Bi NQR spectrum of Bi₂Ge₃O₉, the frequency ω_Q of transition between the nuclear spin levels $1/2 \rightarrow 3/2$ is ~ 160 MHz, the quadrupole coupling constant eQq_{zz}/h amounting to 605.9 MHz. One can easily find that the magnetic field strength H , derived from the relationship $\gamma H \sim \omega_Q$, is of the order of $(3-4) \times 10^4$ G, which is much larger than the local magnetic fields detected using NQR in the bismuth oxy compounds (30–250 G). In the NQR Zeeman experiments discussed here, the external magnetic fields up to 500 G were applied. The strength of H_{rf} in the coils of pulse NQR spectrometers also did not exceed several hundred Oersted, because the spin echo signal is observed if $\omega_1 t_{1,2} \sim 1$, the radiofrequency pulse widths $t_{1,2}$ being of the order of 1–10 μ s. Under the optimum observation conditions, the spin echo frequency ω_1 must be of the order of 1×10^6 s⁻¹, which gives $H_{rf} \sim 200$ G. In addition, the condition $\omega_Q t_{1,2} \gg 1$ is also satisfied.

In order to observe the nuclear quadrupole resonance signal, one has not to place a sample in a constant external magnetic field, because the nuclear spin levels are split due to the interaction of the nuclear electric quadrupole moment with a non-uniform electric field inherent in the sample. The level spacing can be found by the calculation of the energy levels of the quadrupole Hamiltonian. In the system of the EFG principal axes (x', y', z'), the quadrupole Hamiltonian is

$$\hat{H}_Q = \frac{eQq_{zz}}{4I(2I-1)} \left[3I_z'^2 - I(I+1) + \frac{\eta}{2}(I_+^2 + I_-^2) \right], \quad (A.1)$$

where $I_{\pm} = I_{x'} \pm iI_{y'}$.

In the presence of external and local magnetic fields, the term describing the interaction of the nuclear magnetic moment with these fields should be added to Eqn (A.1) to give the time-independent Hamiltonian

$$\hat{H}_0 = \hat{H}_Q - \gamma \hbar \mathbf{H}_{\text{loc}} \hat{\mathbf{I}} - \gamma \hbar \mathbf{H}_e \hat{\mathbf{I}}. \quad (\text{A.2})$$

The interaction of the nuclear magnetic moment with radio-frequency field $\mathbf{H}_{\text{rf}}$ is described as follows:

$$\hat{H}_1 = -\gamma \hbar 2 \mathbf{H}_{\text{rf}} \hat{\mathbf{I}} \cos \omega t. \quad (\text{A.3})$$

The total Hamiltonian is the sum of the Hamiltonians (A.2) and (A.3):

$$\hat{H} = \hat{H}_0 + \hat{H}_1. \quad (\text{A.4})$$

Under the action of pulsed radiofrequency field, the nuclear spin operators will evolve in time, so it is convenient to model the quadrupole spin echo using the time dependent density matrix^{20,49} with the elements

$$\rho_{mm'} = \langle m | \rho | m' \rangle, \quad (\text{A.5})$$

where m, m' are the state numbers. The time dependence of ρ can be found from the Liouville quantum equation (the Neumann equation)⁴⁹

$$i\hbar \frac{\partial \rho}{\partial t} = [\hat{H}, \rho] = \hat{H}\rho - \rho\hat{H}, \quad (\text{A.6})$$

where $\hat{H}$ is the total Hamiltonian (A.4).

Thus, the calculation of the quadrupole spin echo deals with the response of the nuclear spin system described by the Hamiltonian (A.2), the Hamiltonian (A.3) being taken into account.

At the initial moment, the density matrix $\rho(0)$ is given by the normalised Boltzmann distribution

$$\rho(0) = \frac{N}{2I+1} \exp\left(-\frac{H_0}{kT}\right), \quad (\text{A.7})$$

where N is the number of nuclei in a sample. In the high-temperature approximation ($eQq_{zz} \ll kT$) this formula becomes

$$\rho(0) \approx \frac{N}{2I+1} \left(1 - \frac{H_0}{kT}\right). \quad (\text{A.8})$$

The solution of Eqn (A.6) using an evolution operator S ⁴⁹ is described as follows:

$$\rho(t) = S\rho(0)S^{-1}. \quad (\text{A.9})$$

The evolution operator S obeys the Schrödinger equation, the unit matrix E satisfying the initial condition

$$i\hbar \frac{\partial S}{\partial t} = \hat{H}S, \text{ at } S(0) = E. \quad (\text{A.10})$$

In the earlier publications on the quadrupole spin echo theory that made use of the density matrix formalism (see, for instance, Ref. 20), the evolution operator S was used as the product of transformation matrices R and D , referring, respectively, to the duration of the radiofrequency field action and intervals between the pulses:

$$S = D_n R_n \dots D_2 R_2 D_1 R_1. \quad (\text{A.11})$$

Here

$$D_n(t, t_{n0} + t_n) = \exp\left[-\left(\frac{i}{\hbar}\right) H_0(t - t_{n0} - t_n)\right]$$

is the solution of the Schrödinger equation in the interval between the n th and $(n+1)$ th pulses ($H_1 = 0$); $R_n(t, t_{n0})$ is the solution of the Schrödinger equation at the moment t of the n th pulse duration ($t_{n0} \leq t \leq t_{n0} + t_n$)

$$i\hbar \frac{\partial R_n(t, t_{n0})}{\partial t} = (H_0 + H_1) R_n(t, t_{n0}), \quad (\text{A.12})$$

where t_{n0} is the time of switching the n th pulse on and t_n is its duration (the first pulse is assumed to be switched on at the moment $t_{10} = 0$).

The Schrödinger equation was solved with the unit matrix E satisfying the initial condition for all the matrices R and D in (A.11) (see Ref. 20). Using the interaction representation,⁴⁹ Eqn (A.12) can be rewritten as follows:

$$R_n(t, t_{n0}) = \exp\left[-\frac{i}{\hbar} H_0(t - t_{n0})\right] \tilde{R}_n(t, t_{n0}), \quad (\text{A.13})$$

$$i\hbar \frac{\partial \tilde{R}_n}{\partial t} = \tilde{H}_1 \tilde{R}_n,$$

where

$$\tilde{H}_1(t) = \exp\left[\frac{i}{\hbar} H_0(t - t_{n0})\right] H_1(t) \exp\left[-\frac{i}{\hbar} H_0(t - t_{n0})\right].$$

The solution of (A.13) was given in Ref. 20 as

$$\tilde{R}_n(t, t_{n0}) = \exp\left[-\frac{i}{\hbar} \int_{t_{n0}}^t \tilde{H}_1(t') dt'\right]. \quad (\text{A.14})$$

Formula (A.14) as well as the presentation of the evolution matrix as a chain of products of matrices $S = D_n R_n \dots D_2 R_2 D_1 R_1$, each being a solution of the Schrödinger equation with the unit matrix E satisfying the initial condition, are valid, provided the Hamiltonian $\tilde{H}_1(t)$ in (A.13) is independent of time. Since in the latter case $\tilde{H}_1(t)$ is a function of time, the procedure of finding S should be modified, the changes concerning the calculation of matrices $R_n(t, t_{n0})$. Generally, when the condition $\omega_Q t_{1,2} \gg 1$ is ignored and magnetic fields are not small, these matrices can be found by Eqn (A.13). Upon solving this equation, it is not E that should be taken to satisfy the initial condition but rather the evolution matrix value at the preceding stage $D_{n-1} R_{n-1}$.

As before, the matrix D_n in the interval between the n th and $(n+1)$ th pulses may be presented in the form

$$D_n(t, t_{n0} + t_n) = \exp\left[-\frac{i}{\hbar} H_0(t - t_{n0} - t_n)\right],$$

which follows from the solution of the Schrödinger equation, the unit matrix E satisfying the initial condition. In this case, the evolution matrix at the moment of switching the $(n+1)$ th pulse on is calculated by multiplying the matrices $S = D_n R_n$. For instance, the procedure of calculating the evolution matrix for the two-pulse method of spin echo registration may be presented as follows:

$$S(t, 0) = D_2(t, \tau + t_2) R_2(\tau + t_2, \tau) \Big|_{D_1(\tau, t_1) R_1(t_1, 0)} \Big|_E \quad (\text{A.15})$$

A shorthand notation was introduced in order to avoid a cumbersome description of the initial conditions:

$$S = D_2 R_2 \times D_1 R_1, \quad (\text{A.16})$$

where $\times$ denotes a procedure of calculating matrix R_2 , the initial condition being $D_1 R_1$. A multipulse chain can be presented similarly:

$$S = D_n R_n \times D_{n-1} R_{n-1} \times \dots \times D_2 R_2 \times D_1 R_1, \quad (\text{A.17})$$

where $\times$ denotes the operation specified by Eqns (A.15) and (A.16).

One can show that equation (A.17) is transformed to (A.11), which was used in the earlier publications on the quadrupole spin echo theory,²⁰ if, along with the above mentioned conditions ($\gamma H_e \ll \omega_Q$, $\gamma H_{\text{loc}} \ll \omega_Q$, $\omega_Q t_{1,2} \gg 1$), the following condition is also satisfied:

$$\gamma H_{e, \text{loc}} t_{1,2} \ll 1. \quad (\text{A.18})$$

The condition (A.18) imposes the restriction $H_{e, \text{loc}} \ll 200$ $\text{\AA}$ on the external (or local) magnetic field strength in the bismuth

compounds. If Eqn (A.18) holds true, Eqn (A.13) for the matrix $\tilde{R}_n$ is reduced to

$$\frac{\partial \tilde{R}_n}{\partial t} = A \tilde{R}_n, \quad (\text{A.19})$$

where A is a time-independent matrix. An explicit expression for the matrix $\tilde{R}_n$ can further be found by a cumbersome computation. If the condition (A.18) is not satisfied, the matrix $\tilde{R}_n$ can be found by a numerical solution of Eqn (A.13).

Assuming the condition (A.18) is satisfied and Eqn (A.11) holds true, one can derive the formula for the average value of nuclear spin projection onto the rf-coil axis $\langle I \rangle$, and use it as the basic formula for further elaborating a scheme of modelling of the SEE in $H_{e,loc} \ll 200$ G (the latter restriction was undoubtedly satisfied in the experiments discussed). If the time dependence of $\langle I \rangle$ is known, one can find a derivative $d\langle M \rangle/dt$ of the nuclear magnetic moment projection ($\langle M \rangle = g_{\text{Bi}} \mu_B \langle I \rangle$), to which the intensity of the spin echo signal is proportional.

According to the density matrix formalism, the average spin of a nuclear subsystem is evaluated by the formula

$$\langle I \rangle = \text{Sp}(\rho \hat{I}). \quad (\text{A.20})$$

In the high-temperature approximation, the density matrix at the initial moment is determined by formula (A.8). At any subsequent moment, the value of the matrix can be found by Eqn (A.9). Since $\text{Sp}(\hat{I}) = 0$, the expression for the average moment is

$$\langle I \rangle = C \text{Sp}(S H_0 S^{-1} I), \quad (\text{A.21})$$

where

$$C = -\frac{N}{(2I+1)kT}.$$

Using Eqn (A.11) for the evolution operator S , one can derive an expression for calculating the average nuclear spin after the action of the first

$$\langle I \rangle = C \text{Sp}(D_1 R_1 H_0 R_1^{-1} D_1^{-1} I) \quad (\text{A.22})$$

and second

$$\langle I \rangle = C \text{Sp}(D_2 R_2 D_1 R_1 H_0 R_1^{-1} D_1^{-1} R_2^{-1} D_2^{-1} I) \quad (\text{A.23})$$

radiofrequency pulses.

Substituting D_1 and D_2 into Eqns (A.22) and (A.23) and using the interaction representation, one obtains

$$\langle I \rangle = C \text{Sp} \left[\left(-\frac{i}{\hbar} H_0 t \right) \tilde{R}_1 H_0 \tilde{R}_1^{-1} \exp \left(\frac{i}{\hbar} H_0 t \right) I \right], \quad (\text{A.24})$$

$$\langle I \rangle = C \text{Sp} \left[\exp \left(-\frac{i}{\hbar} H_0 (t - \tau) \right) \times \quad (\text{A.25}) \right.$$

$$\times \tilde{R}_2 \exp \left(-\frac{i}{\hbar} H_0 \tau \right) \tilde{R}_1 H_0 \tilde{R}_1^{-1} \exp \left(\frac{i}{\hbar} H_0 \tau \right) \tilde{R}_2^{-1} \times$$

$$\times \exp \left(\frac{i}{\hbar} H_0 (t - \tau) \right) I \left. \right].$$

Using further the representation of operators in the basis of eigenfunctions for the operator H_0 (A.2) and denoting $\omega_{ij} = \lambda_i - \lambda_j$ (where $\lambda_i = E_i/\hbar$ and E_i are the eigenvalues of the Hamiltonian H_0), one can derive the expressions for calculating the average nuclear spin at instants after the first [formula (A.26)] and second [formula (A.28)] radiofrequency pulses

$$\langle I \rangle = C \sum_{m,s} A_{ms}(t) I_{sm}, \quad (\text{A.26})$$

where

$$A_{ms}(t) = e^{i\omega_{sm}t} \sum_n \lambda_n (\tilde{R}_1)_{mn} (\tilde{R}_1^*)_{sn}, \quad (\text{A.27})$$

$$\langle I \rangle = C \sum_{m,s} B_{ms}(t, \tau) I_{sm}, \quad (\text{A.28})$$

$$B_{ms}(t, \tau) = \sum_{n,k,p} \left\{ \exp i\omega_{sm} \left[t - \left(1 + \frac{\omega_{np}}{\omega_{sm}} \right) \tau \right] \right\} \times \quad (\text{A.29})$$

$$\times \lambda_k (\tilde{R}_2)_{mn} (\tilde{R}_1)_{nk} (\tilde{R}_1^*)_{pk} (\tilde{R}_2^*)_{sp}.$$

Since the operator $\hat{I}$ is Hermitian and the eigenfunctions of the Hamiltonian H_0 are real, the following relationships hold true: $A_{sm}^* = A_{ms}$, $B_{sm}^* = B_{ms}$. As a result, the average spin values calculated by formulae (A.26) and (A.28) are real.

The formula (A.29) clearly indicates when the spin echo signal appears. It is important that the Hamiltonian (A.2), which determines the scale of energy levels spacing [in this case, the quadrupole Hamiltonian (A.1)], be independent of time in the absence of radiofrequency field. The spin echo signal appears at the instants

$$t = \left(1 + \frac{\omega_{np}}{\omega_{sm}} \right) \tau,$$

defined by the ratio of various frequencies in the Hamiltonian (A.2). Among them, the spin echo appearing at the moment $t = 2\tau$ is always present. The signal intensity is determined by coefficients B_{ms} (A.29), which reach their maxima when the frequency of H_{rf} is close to the frequencies ω_{sm} and ω_{np} .

The free induction decay signals appearing after the first and second pulses ($t = t_1$ and $t = \tau + t_2$) can also be modelled using expression (A.28). As formulae (A.28) and (A.29) show, one can observe the spin echo signals for nuclei with spin $I > 3/2$ not only at the moment 2τ , but, for instance, also at $t = 3\tau$. For nuclei with spin $I = 3/2$, the spin echo is observed at $t = 2\tau$ solely, because only one quadrupole transition frequency is available. Whether the spin echo at $t = 3\tau$ is observable, depends on the signal intensity, which is defined by Eqn (A.29).

Formulae (A.26) and (A.28) can be conveniently used for calculating the average nuclear spin in an external magnetic field. Upon varying a pulse separation τ [see Eqns (A.28) and (A.29)] in the presence of static external or local magnetic fields, one can observe modulations (beats) on the SEE curve.²⁰ Their frequencies are proportional to the Zeeman-perturbed splittings of the nuclear spin levels described by the Hamiltonian (A.2). For the calculation of SEE, the absolute maximum of expression (A.29) at $t \sim 2\tau$ should be found for each τ .

Since the relaxation effects (a decay of the spin echo signal) were ignored in the Hamiltonian (A.4), on simulation they can be incorporated by simple multiplying the spin echo amplitude by a factor $\exp[-(1/2T_2^2)\tau^2]$, the value of T_2 being taken from the experiment.

The procedure of modelling the quadrupole spin echo signals should also take account of a mutual orientation of the laboratory $(\tilde{x}, \tilde{y}, \tilde{z})$ and crystallographic (x, y, z) coordinate systems. The appropriate relationships involve the Euler angles α, β and γ . The system of the EFG principal axes (x', y', z') is related to the crystallographic system by another set of the Euler angles θ, φ and ψ . The orientation of the local magnetic field vector H_{loc} with respect to the EFG principal axes is determined by angles θ_{loc} and φ_{loc} . Thus, the direction of the fields H_e , H_{loc} and H_{rf} with respect to the principal axes system (x', y', z') of the quadrupole Hamiltonian (A.2) is completely determined by the angles $\alpha, \beta, \gamma, \theta, \varphi, \psi, \theta_{\text{loc}}$ and φ_{loc} . All the scalar products $H_e J$, $H_{\text{loc}} J$ and $H_{\text{rf}} J$ in the Hamiltonians (A.2) and (A.3) have to be determined in the same coordinate system. For this purpose, the matrix D determined by angles $\theta, \varphi, \psi, \alpha, \beta$ and γ , which projects the vectors H_e and H_{rf}

onto the EFG principal axes, is involved into the calculation scheme. The crystallographically equivalent bismuth sites may appear to be magnetically non-equivalent. In such a case, each type of the EFG tensors is specified in external magnetic field by its own principal axes system (see Section III), so that the average nuclear spin is calculated for each orientation of the EFG tensors. The net average spin of the nuclear subsystem will evidently be the sum of the contributions from all the magnetically nonequivalent EFG tensors.

For a polycrystalline (powdered) specimen, the calculation procedure is similar. It differs in that the calculated spin is averaged over all the orientations of the crystallites with respect to the laboratory system, *i.e.*, over the Euler angles α , β and γ .

Thus, the procedure of calculation of the spin-echo amplitude as a function of radiofrequency pulse separation τ in weak ($\ll 200$ G) magnetic field involves the following stages:

1) the analysis of the EFG tensor symmetry; the evaluation of the matrix D : the calculation is performed for each magnetically non-equivalent EFG tensor;

2) the calculation of the eigenvalues and eigenfunctions of the Hamiltonian $\hat{H}_0$ (see A.2);

3) the calculation of matrix elements for operators using the representation in the eigenfunctions basis of the operator $\hat{H}_0$;

4) the evaluation of the matrix $\hat{R}$ with the unit initial condition by solving the Schrödinger equation (A.13);

5) the computation of coefficients A_{ms} and B_{ms} in equations (A.27) and (A.29);

6) the evaluation of the absolute maximum of expression (A.29);

7) the incorporation of the spin echo relaxation effect by multiplying by a factor $\exp[-(1/2T_2^2)\tau^2]$.

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^d — *Phys. At. Nucl.* (Engl. Transl.)

^e — *J. Exp. Theor. Phys.* (Engl. Transl.)

^f — *Phys. Solid. State* (Engl. Transl.)

Silylium ions[†]

T A Kochina, D V Vrazhnov, E N Sinotova, M G Voronkov

Contents

I. Introduction	95
II. History of investigations into silylium ions	95
III. State of the art of research on silylium ions	97
IV. Ion-molecular reactions of silylium ions	103

Abstract. The history and state of the art of research on silylium ions are summarised. Achievements of the last two decades in the preparation of silylium ions as individual species in solutions and crystals and as intermediates in reactions of organosilicon compounds are considered. Attention is focused on ion-molecular reactions of silylium ions with nucleophilic reagents in the gas and condensed phases. The bibliography includes 164 references.

I. Introduction

For more than five decades, scientists have debated whether silicon compounds can exhibit chemical properties characteristic of their carbon analogues. Since silicon and carbon are both Group 14 elements, attempts were made to find features of organosilicon chemistry characteristic of organic chemistry, *e.g.*, the ability of Si atoms to be involved in formation of Si=E double bonds (E = Si, C, O, N, *etc.*), long-chain silicon polymers and intermediates analogous to carbon compounds (for example, to carbenes and carbocations). Available experimental data show that the chemical properties of carbon are very different from those of silicon. First and foremost, silicon compounds containing multiple bonds are very unstable (unlike carbon analogues). Up to the mid-twentieth century, the existence of such compounds has been doubted.¹ First publications on the synthesis of unstable silicon compounds containing Si=Si, Si=C, *etc.* bonds date back to 1967.^{2–7} Nowadays, the opinion that silicon cannot form multiple bonds is completely disproved.^{8,9} The formation of polysilanes, whose properties have long been poorly known, was also proved.^{10,11} However, the existence of silicon intermediates analogous to carbon intermediates is still an open question. In recent years, silylenes,^{12–14} which are silicon analogues of well-known carbenes,¹⁵ have been synthesised and their properties

have been studied. However, it appeared to be very difficult to obtain (particularly, in the condensed phase) the tricoordinate organosilicon cations R_3Si^+ analogous to the carbocations R_3C^+ and prove their existence. Earlier, silylium ions in the gas phase have been studied primarily by ion cyclotron resonance and conventional mass spectrometry.¹⁶ However, the applicability of these methods is limited to observations of charged particles in a rarefied-gas atmosphere.

The present review deals with silylium ions and summarises both the history and state of the art of research in this field. The review covers the achievements of the last two decades in the synthesis of silylium ions as individual species both in solutions and crystals and as intermediates in reactions of organosilicon compounds. Emphasis is given to the reactivity of silylium ions and their ion-molecular reactions with nucleophilic reagents in the gas and condensed phases, which have remained virtually unknown until recently. It should be noted that in Russia the latest review of research into silylium ions was published by Nefedov *et al.*¹⁷ in 1986. Data on the synthesis and results of studies of silylium ions in the gas and condensed phases have been partially systematised.^{18–20} In addition, certain aspects of this problem have been summarised in short publications.^{21,22} The aim of the present review is to provide a deep insight into the development of chemistry of silylium ions.

II. History of investigations into silylium ions

The discovery of carbenium ions R_3C^+ isoelectronic with the silylium ions R_3Si^+ has played a great role in the development of organic chemistry because most organic reactions proceed *via* these reactive intermediates.²³ Their existence was established in the early twentieth century (see, for example, Ref. 24). For almost a century, these intermediates have attracted the most attention in studies of mechanisms of various chemical processes. In the 1990s, researchers have shifted their interest to the related species, *viz.*, silylium ions.

The ways of development of the chemistry of organosilicon cations R_3Si^+ and their carbon analogues R_3C^+ are substantially different. Even the name of the R_3Si^+ cation has long been debated. At different times, this cation was referred to as the siliconium,²⁵ silycenium²⁶ or silylenium²⁷ cation. Nowadays, it is called the silylium ion.²⁸ Taking into account that the carbenium ions are of tremendous importance in organic chemistry, the formation of silylium ions as intermediates in many organosilicon

T A Kochina, D V Vrazhnov I V Grebenshchikov Institute of Silicate Chemistry, Russian Academy of Sciences, ul. Odoevskogo 24/2, 199155 St Petersburg, Russian Federation. Fax (7-812) 328 54 01, tel. (7-812) 328 48 02, e-mail: kom@isc.nw.ru

E N Sinotova St Petersburg State University, Scientific Research Institute of Chemistry, Universitetskyy pr. 26, Petrodvorets, 198504 St Petersburg, Russian Federation. Fax (7-812) 428 69 39, tel. (7-812) 328 94 46

M G Voronkov A E Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, ul. Favorskogo 1, 664033 Irkutsk, Russian Federation. Fax (7-395) 239 60 46, tel. (7-395) 246 24 00, e-mail: voronkov@iioch.irk.ru

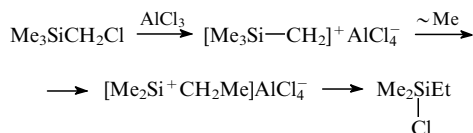
Received 6 July 2005

Uspekhi Khimii 75 (2) 107–124 (2006); translated by T N Safonova

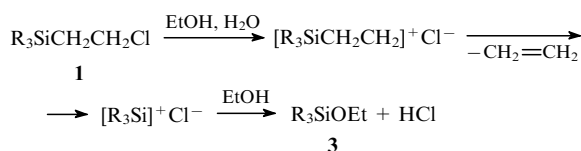
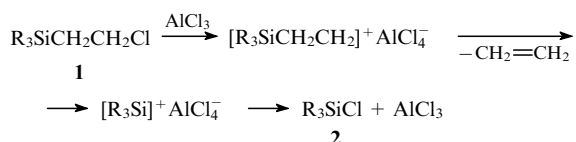
[†] According to the latest IUPAC recommendations, the tricoordinate R_3Si^+ cation is called the silylium ion.

reactions was often postulated without proof. However, alternative mechanisms can, as a rule, be suggested for such reactions.

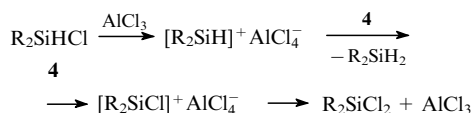
The possible involvement of silylium ions as intermediates in reactions has been reported for the first time by Whitmore and Sommer,²⁵ who studied the rearrangement of chloromethyltrimethylsilane under the action of AlCl_3 .



The formation of silylium ions as reactive intermediates was also postulated in the rearrangement of (1-haloalkyl)trimethylsilanes in the presence of SbF_5 (see Ref. 29) and in the rearrangement of (1-hydroxyalkyl)trimethylsilanes in the presence of BF_3 .³⁰ The ionic mechanism was proposed without proof to account for the so-called β -cleavage of trialkyl(2-haloethyl)silanes **1** in the presence of AlCl_3 ³¹ or in an aqueous ethanolic medium.³² These reactions afford trialkylchlorosilanes **2** or trialkylethoxysilanes **3**.

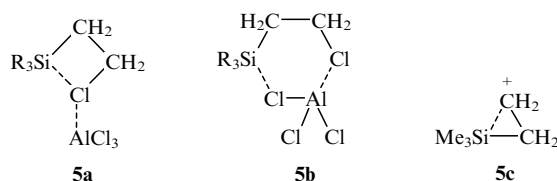

$$R = \text{Alk.}$$

Dolgov *et al.*^{33,34} studied disproportionation of dialkylchlorosilanes **4** and also suggested that this reaction proceeds by the ionic mechanism.



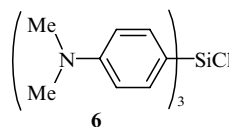
In this case, no experimental evidence for the proposed reaction mechanism was reported as well.

Alternative mechanisms of the above-considered reactions involve the intermediate formation of a four- (structure **5a**) or six-centred (**5b**) activated complex³⁵ and a non-classical carbenium ion **5c**.³⁶



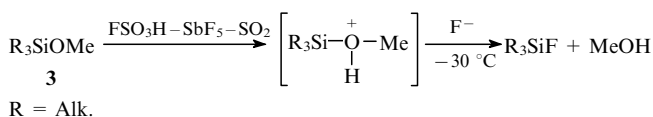
It is noteworthy that the rearrangement of fluorodiethylsilane occurs spontaneously in the absence of catalysts,³⁷ which suggests that this reaction proceeds through a cyclic transition state of type **5c**.

Many researchers attempted to prepare and characterise stable silylium ions isostructural with carbenium ions in the condensed phase. A silicon analogue of ionic tris(*p*-dimethylaminophenyl)chloromethane, *viz.*, silyl chloride **6**, was synthesised.^{38, 39}

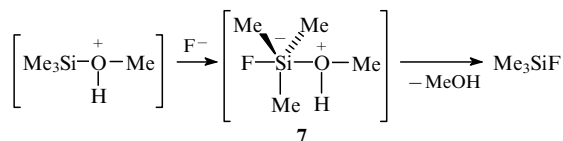


However, studies by physicochemical methods (conductometry, IR and UV spectroscopy, X-ray diffraction analysis, *etc.*) demonstrated that compound **6** is covalent. Silicon perchlorates R_3SiClO_4 ($R = \text{Alk}$) were demonstrated⁴⁰ to be covalent, unlike ionic crystalline triarylmethyl perchlorates.

Olah *et al.*^{20,41} attempted to synthesise classical silylium ions in a superacidic medium ($\text{FSO}_3\text{H}-\text{SbF}_5-\text{SO}_2$ system) of extremely low nucleophilicity. Under these conditions, non-primary carbenium cations are stable and are generated from various organic compounds.⁴² In this medium, the behaviour of trialkylalkoxysilanes **3** was studied by low-temperature NMR spectroscopy. It was found that these compounds initially undergo protonation followed by the replacement giving rise to trialkylfluorosilane.

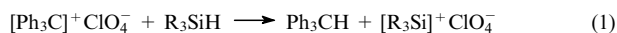


In this process, no R_3Si^+ ions were detected. The formation of trialkylfluorosilanes was accounted for by the formation of a pentacovalent intermediate **7** (for $\text{R} = \text{Me}$).⁴¹



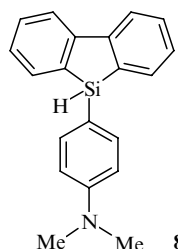
Analogous results were obtained upon storage of hexaalkyldisiloxanes in a superacidic medium.⁴¹

One of the main problems in preparing silylium ions in the condensed phase is associated with the nature of the leaving group. In organic chemistry, carbenium ions are traditionally generated by the S_N1 or $E1$ mechanisms, a halogen- (I^- , Cl^- , *etc.*) or oxygen-containing anion serving, as a rule, as the leaving group. Taking into account high strength of the silicon bonds with halogens and oxygen, the latter cannot be used as the leaving groups for generation of silylium ions. Corey⁴³ described the synthesis of silylium ions by reaction (1) with the use of the hydride ion as the leaving group.



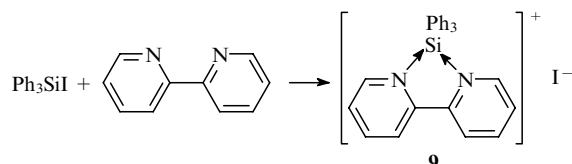
Actually, the Si—H bond is weaker than the C—H bond and, consequently, reaction (1) is thermodynamically favourable. This reaction is named after Corey and it has been used for years to prove the formation of silylium ions as stable species and short-lived intermediates in various transformations.

In 1975, the synthesis of stable silylium ions as a result of hydride ion abstraction from compound **8** was documented.^{44,45}



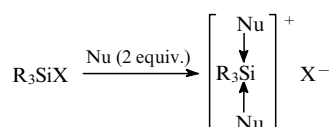
However, these results were later rejected.^{27, 46} These studies ended in failure apparently because the researchers assumed that the properties of silicon are completely analogous to those of carbon.

In the study,⁴⁷ the authors succeeded in preparing positively charged organosilicon ions by coordination of silicon with compounds having a basic character. For example, the reaction of iodotriphenylsilane with 2,2'-bipyridine gave salt **9** with a penta-covalent silicon ion.



More recently, other analogous pentacoordinate cations were prepared.^{48, 49}

In the review,¹⁸ which summarises the results of research on silylium ions obtained by that time, a conclusion was drawn that positively charged organosilicon ions can be generated only as a result of the nucleophilic attack on the Si atom.



R = Alk, Ar; X is a halogen; Nu is a nucleophile.

However, it should be emphasised that the pentacoordinate ion thus produced differs in principle from the trivalent silylium ion R_3Si^+ . The latter, like the carbenium ion, could be formed upon the heterolytic cleavage of the Si–X bond.

Although the attempts to detect the silylium ions R_3Si^+ in condensed phases failed, these species were reliably identified in rarefied gases. Taking into account that the physical properties of silicon (thermodynamic, electronic, *etc.*) should make the generation of silylium ions easier compared to the structurally similar carbenium ions, the reasonable question arises as to why this process is hindered in the condensed phase?

The answer to this question can be found by analysing the results of quantum-chemical studies,⁵⁰ which confirm a substantial difference in the chemical properties of carbon and silicon. First and foremost, this refers to the unique ability of the silicon atom to increase its coordination number. For example, compounds with the hypercoordinate silicon atom (for example, the SiF_6^{2-} anion) are well known, whereas analogous carbon compounds are absent. Due to the ability of silicon to have high coordination numbers, silylium ions, unlike carbocations, are more prone to complexation with various nucleophiles, including counterions and solvents used in the synthesis of organosilicon compounds. Apparently, this is responsible for the fact that all attempts to observe silylium ions in solution failed.

The above facts argue against the conclusion¹⁸ that it is impossible to prepare the trivalent silylium ions R_3Si^+ in the condensed state; that is, a different in principle strategy is required for their generation.

III. State of the art of research on silylium ions

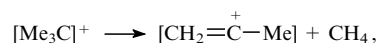
1. Silylium ions in the gas phase

The existence of silylium ions in the gas phase is beyond doubt. These ions are easily generated in rarefied gases by various methods, including electron impact, photoionisation and chemical ionisation. The appearance potentials of silylium ions are substantially lower than those of carbenium ions.⁵¹ Taking into account that, until recently, virtually all attempts to generate and characterise silylium ions in the condensed phase failed, any information on these ions obtained in gas-phase studies is of

considerable importance and is very useful. Not only thermodynamic but also certain physical characteristics of silylium ions were determined. In particular, studies of the H_3Si^+ ion by gas-phase infrared laser spectroscopy demonstrated⁵² that this cation (like the H_3C^+ ion) is planar, the Si–H bond length is 1.462 Å, and the fundamental stretching band is at 838.0674 cm^{-1} .

The gas-phase chemistry of silylium ions is versatile and includes unusual rearrangements, which differ substantially from the rearrangements of carbenium ions. The rearrangements of silylium ions require activation,^{53, 54} whereas the rearrangements of carbenium ions can occur at very low temperatures and even in the solid phase.^{55, 56}

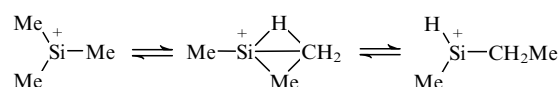
The mechanism of rearrangements of silylium ions differs from that of rearrangements of carbenium ions proceeding under the same conditions.^{57–59} For example, dissociation of the *tert*-butyl cation in a mass-spectrometer chamber occurs primarily with elimination of methane⁵⁹



whereas dissociation of the trimethylsilyl cation results in elimination of an ethylene molecule^{57–59}



The mechanism of the latter rearrangement has been extensively studied over many years. Bakhtiar *et al.*,⁵⁷ who were the first to observe this rearrangement, described a mechanism involving isomerisation of the activated trimethylsilylium ion to give $EtMeHSi^+$ followed by elimination of ethylene. However, more recently it has been demonstrated⁵⁸ that these ions can undergo interconversions before elimination of ethylene.



Consequently, a less stable isomeric form of the silylium ion can be transformed into a more stable form if the activation energy is sufficiently high and the isomerisation barrier is lower than the dissociation threshold. Analogous isomerisation of the $C_2H_7Si^+$ ion was also studied:^{53, 57–60}



Since the Me_2HSi^+ ion is more stable than the EtH_2Si^+ ion by $22.5\text{ kcal mol}^{-1}$,⁵³ the amount of the Me_2HSi^+ ions increases with increasing kinetic energy of the EtH_2Si^+ ions⁶⁰ (Fig. 1). At

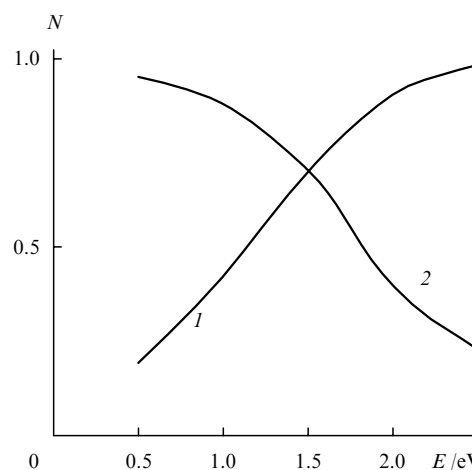


Figure 1. Yields of the Me_2HSi^+ (1) and EtH_2Si^+ (2) ions vs. the activation energy.⁵⁸

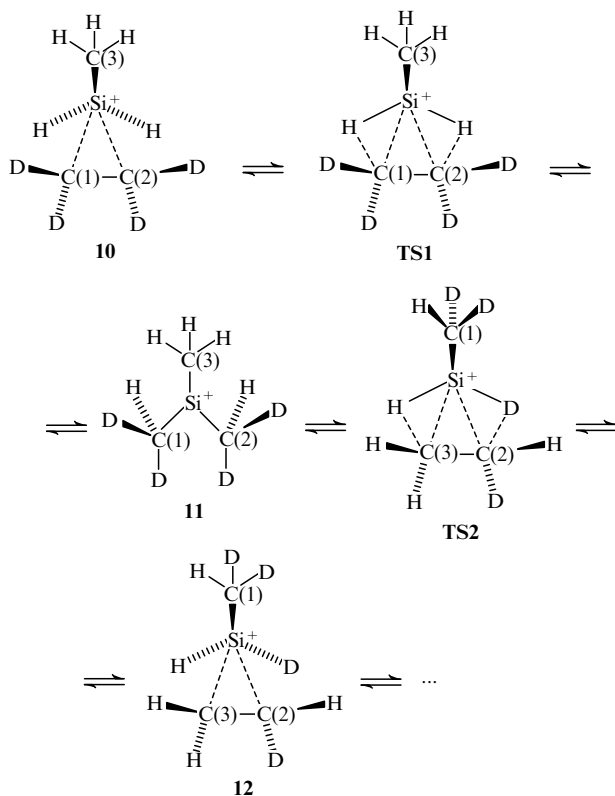
higher energies, dissociation of the EtH_2Si^+ ion with elimination of ethylene occurs.

According to the results of mass-spectrometric studies,^{57, 58} 90% of the EtH_2Si^+ ions are isomerised into the thermodynamically more stable Me_2HSi^+ ions. Evidently, in this case the isomerisation barrier is lower than the energy required for elimination of ethylene. A totally different situation is observed for the EtMeHSi^+ ion. The isomerisation and dissociation barriers of this ion have similar heights,⁵⁴ due to which its isomerisation to the trimethylsilylium ion proceeds by only 5%.⁶¹

Only 28% of the $\text{C}_2\text{H}_7\text{Si}^+$ ions decompose to form ethylene.⁶² Dissociation of $\text{C}_2\text{H}_7\text{Si}^+$ affords hydrogen molecules as the major product (72%). It appeared that the composition and the kinetic energy of the reaction products are independent of the isomer type of this ion, *viz.*, Me_2HSi^+ or EtH_2Si^+ . This suggests that the equilibrium between the isomers is established prior to dissociation. By contrast, the isomers of the $\text{C}_3\text{H}_9\text{Si}^+$ ion, *viz.*, Me_3Si^+ and EtMeHSi^+ , decompose to give primarily ethylene (89% and 97%, respectively) and differ substantially in the kinetic energy.

Structural isomers of silylium ions, unlike those of carbenium ions, can be distinguished by qualitative reactions.^{60, 61} Isomerisation of the ethylsilylium ion to the dimethylsilylium ion was confirmed by the isotope exchange between this ion and perdeuterated ethylene. In the disubstituted R_2HSi^+ ion ($\text{R} = \text{Me}$ or Et), only the silicon-bound ^1H atom can be exchanged for deuterium, whereas all hydrogen atoms in the monoalkyl-substituted RH_2Si^+ ion can be involved in the isotope exchange.⁶⁰

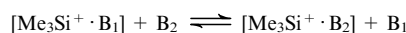
The theoretical explanation of this phenomenon was given in the study.⁵³ The proposed mechanism of the reaction of MeH_2Si^+ with C_2D_4 involves the formation of the $[\text{MeH}_2\text{Si}^+ \cdot \text{C}_2\text{D}_4]$ complex (**10**) as an intermediate followed by the migration of the hydrogen atoms from the silicon atom to the ethylene moiety to give the asymmetrical $\text{Me}(\text{CD}_2\text{H})_2\text{Si}^+$ cation (**11**) *via* a transition state **TS1** with a minimum energy.



The reverse transformation of ion **11** into the starting complex can involve the unlabelled methyl group. In this case, complex **12** is, for example, formed *via* a transition state **TS2**. Its subsequent dissociation affords the $(\text{CD}_2\text{H})\text{HDSi}^+$ ion and the $\text{H}_2\text{C}=\text{CDH}$ molecule. The perdeuterated methylsilylium ion can be obtained

by repeating these processes many times. The reaction of Me_2HSi^+ with $\text{CD}_2=\text{CD}_2$ produces the $\text{Me}_2(\text{CD}_2\text{CD}_2\text{H})\text{Si}^+$ ion as the most stable isomer. Its transformation can afford only Me_2DSi^+ and $\text{HDC}=\text{CD}_2$, *i.e.*, only the hydrogen atom bound to silicon can be replaced by the deuterium atom. The hydrogen exchange between the methyl and silyl groups does not occur due to a high energy barrier.

Wojtyniak and Stone⁶³ made a substantial contribution to investigations of the reactivity of silylium ions with respect to nucleophilic reagents. They studied the gas-phase reactions of the Me_3Si^+ ion with alcohols, ethers, esters and aromatic hydrocarbons at a pressure of 3–5 mm Hg and a temperature from 298 to 600 K by mass spectrometry. The reactions gave the $[\text{Me}_3\text{Si}^+ \cdot \text{B}]$ adducts ($\text{B} = \text{AlkOH}$, $\text{AlkOAlk}'$, $\text{AlkCO}_2\text{Alk}'$ or ArH). The equilibrium constants of the reactions of the Me_3Si^+ cation with the oxygen-containing bases B_1 and B_2



were measured and the relative basicities of these compounds towards Me_3Si^+ were determined from these constants. The change in the free energy of this reaction served as a measure of the basicity.

The basicity of various alcohols and water was demonstrated to increase in the same order as the proton affinity: butanol > propanol > ethanol > methanol > water.

It should be noted that the energy of association of alcohols with the Me_3Si^+ ion is higher than that with the Me_3C^+ and Me_3Sn^+ ions by ~20 and 7 kcal mol⁻¹, respectively (Table 1). For all cations, the energy of association increases with increasing basicity of alcohol ROH, *i.e.*, with increasing length of the alkyl substituent.

Table 1. Changes in the enthalpy ΔH_0 (kcal mol⁻¹) of the reaction $[\text{Me}_3\text{E}^+ \cdot \text{B}] \rightarrow [\text{Me}_3\text{E}]^+ + \text{B}$.⁶³

B	E			
	C	Si	Sn	
H ₂ O	11.7	30.1	25.7	
MeOH	22.8	39.2	32.6	
EtOH	26.9	42.0	34.8	
Pr ⁱ OH	24.9	43.9	—	

The difference in the energies of association of the Me_3Si^+ and Me_3C^+ ions with alcohols can be attributed to a higher positive charge density on the silicon atom compared to that on the carbon atom due primarily to the different degree of interaction between the unoccupied orbital of these cations and the orbitals of the methyl substituents.⁶⁴ For example, analysis of the populations of the unoccupied p_z orbitals demonstrated⁶⁵ that the population in the H_3Si^+ and H_3C^+ ions is virtually equal to zero (the orbital is actually unoccupied), whereas the population in the Me_2HC^+ and Me_2HSi^+ ions increases to 0.37 and 0.1, respectively. The electron density transfer to the carbon atom is much more substantial than that to the silicon atom. The inductive effect of the methyl substituents in the Me_3C^+ ion also leads to certain delocalisation of the positive charge on the cationic centre. In the Me_3Si^+ cation, the positive charge delocalisation due to the presence of the alkyl substituents is virtually absent because the electronegativity of silicon is lower than that of carbon.

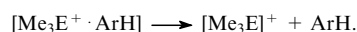
The higher energy of association of the Me_3Si^+ ion with alcohols compared to that of the Me_3Sn^+ ions is apparently attributed to the larger volume of the tin atom and, consequently, the larger Sn—O bond length in the adduct.

The energy of association of the above-considered Me_3E^+ ions ($\text{E} = \text{C}$, Si and Sn) changes in the same order as that observed for other oxygen-containing compounds (for example, for ethers and esters).⁶³ Consequently, due to the larger positive charge

density on the silicon atom compared to that on the carbon atom and the smaller volume of silicon compared to tin, the trimethylsilylium ion is the most reactive species in this series with respect to oxygen-containing compounds in spite of the fact that the position of silicon in the Periodic table is between a typical non-metal (C) and a metal (Sn).

The basicity of different classes of oxygen-containing compounds towards the Me_3Si^+ cation changes in the following series: water < alcohols < ethers < esters.⁶³

The energies of association of the Me_3Si^+ and Me_3Sn^+ ions with aromatic hydrocarbons (ArH), such as mesitylene and *o*-xylene, have similar values, which are slightly smaller than the energies of association with oxygen-containing compounds. Below are given the changes in the enthalpy (kcal mol^{-1}) of the reactions



E	ArH		Ref.
	mesitylene	<i>o</i> -xylene	
Si	31.1	29.2	63
Sn	32.0	29.9	66

A decrease in the difference between the energies of association of the Me_3Si^+ and Me_3Sn^+ ions with aromatic hydrocarbons can be explained in terms of hard and soft acids and bases.⁶⁷ For example, less polarisable silicon in the Me_3Si^+ ion more readily reacts with hard oxygen-containing bases, whereas the reaction of the Me_3Sn^+ ion becomes more preferable in the case of soft aromatic bases.

Amines are stronger bases than oxygen-containing compounds towards the trimethylsilylium ion. This is evident from the fact that the energies of association of the Me_3Si^+ ion with amines are substantially higher than those with alcohols. Table 2 gives the affinities (*i.e.*, the energies of association) of various amines to the Me_3Si^+ ion and the proton. As can be seen from Table 2, the affinity of amines to the Me_3Si^+ ion increases in the same order as the proton affinity: $\text{NH}_3 < \text{MeNH}_2 < \text{EtNH}_2 < \text{Bu}^n\text{NH}_2$, and it is determined by the increase in polarisability of the alkyl substituent in the amine.

Table 2. Affinities of amines to the Me_3Si^+ ion and the proton (kcal mol^{-1}).

Amine	Me_3Si^+ (see ⁶⁸)	H^+ (see ⁶⁹)
NH_3	46.5	204
MeNH_2	55.4	214.1
EtNH_2	57.4	217.0
Bu^nNH_2	59.5	218.4
Bu^sNH_2	57.9	220.5
Bu^tNH_2	58.0	220.8
Me_2NH	60.0	220.6

The basicities towards the Me_3Si^+ ion and the proton affinities of selected aromatic oxygen- and nitrogen-containing compounds were determined (Table 3).⁷⁰ As can be seen from

Table 3. Relative basicities of aromatic compounds towards the Me_3Si^+ ion and the proton affinities (kcal mol^{-1}).

Compound	Me_3Si^+	H^+
PhC(O)H	36.2	191.7
PhC(O)Me	37.8	198.2
PhNH_2	35.5	203.3
PhNMe_2	39.5	217.3
Py	47.1	214.7

Table 3, the characteristics of these compounds can be arranged in different series of increasing values because they are determined by different factors. For example, the basicities of compounds towards Me_3Si^+ can be influenced by steric factors, which have no effect on the proton affinity.⁶³ Nevertheless, these two characteristics equally depend on the nature of the substituents in the aromatic ring. In addition, as in the case of protonated organic compounds, the bonds between the Me_3Si^+ ions and the O (or N) atoms in adducts are essentially covalent in character.

Therefore, the above-described studies showed that silylium ions not only are readily generated in the gas phase but also exhibit substantially higher affinity to π - and n -electron-donating compounds than carbenium ions.

2. Silylium ions in the condensed phase

The proof of the existence of silylium ions in the condensed phase is still a challenging problem of organosilicon chemistry. As we demonstrated above, conventional methods, which are generally used in organic chemistry for the generation of carbenium ions, are unsuitable for the synthesis of silicon analogues. Evidently, non-conventional approaches are required for the generation of silylium ions and investigation of their chemical behaviour in the condensed phase.

Studies by Lambert and co-workers (see, for example, Ref. 71) have opened a new stage in solving the problem of the synthesis of silylium ions in the condensed phase. Lambert proposed that silylium ions should be generated with the use of

- substituents at the silicon atom that enhance thermodynamic stability of silylium ions;
- counterions and solvents of low nucleophilicity;
- substituents creating steric hindrance to the approach of nucleophiles to the silicon centre.

All subsequent studies on the generation of silylium ions in the condensed phase were carried out taking into account these ideas.

In the chemistry of carbenium ions, the positive charge on the cation is stabilised primarily through $\pi-\pi$ and $n-\pi$ resonance interactions (for example, in the benzyl PhCH_2^+ , allyl $\text{CH}_2=\text{CHCH}_2^+$ and methoxymethyl MeOCH_2^+ cations) and $\sigma-\pi$ resonance interactions (in the *tert*-butyl cation Me_3C^+). By contrast, the electron-withdrawing inductive effect of such substituents as Ph, $\text{CH}=\text{CH}_2$ or OMe destabilises the carbenium ion. Consequently, the positive charge can be stabilised only if the $\pi-\pi$ and $n-\pi$ interactions not only compensate but are stronger than the undesired inductive effect, which is observed in the chemistry of carbenium ions. In the case of the silicon atom, resonance interactions with electronegative elements (N, O or F) are very weak and cannot compete with the destabilising inductive effect of the latter, due to which these elements are inefficient for stabilisation of silylium ions.

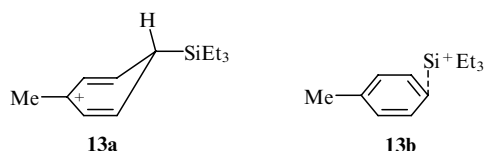
According to Lambert and Sun,⁷¹ the positive charge in silylium ions can be stabilised by organosilicon substituents directly bound to the cation centre [for example, in the $\text{Me}_3\text{SiMe}_2\text{Si}^+$ or $(\text{Me}_3\text{Si})_3\text{Si}^+$ ions]. Since the silicon atom is less electronegative and more polarisable than the carbon atom, the inductive effect of a silicon-containing substituent will stabilise the cation centre.

Quantum-chemical calculations demonstrated⁷² that silylium ions can be efficiently stabilised by resonance $3p-3p$ interactions in the $(\text{RX})_3\text{Si}^+$ or $(\text{R}_2\text{X})_3\text{Si}^+$ cations, where X are third-period elements (X = S or P). Actually, the bond between the sulfur and silicon atoms is rather highly polarisable. In addition, the sulfur atom has $3p$ lone pairs and its electronegativity is approximately equal to that of the carbon atom (~ 2.5). For this reason, its inductive effect is expected to be smaller than that in the case of phenyl or oxygen-containing substituents.

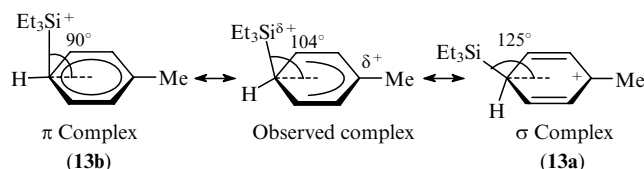
Taking into account the above facts, the silylium ion $(\text{Pr}^i\text{S})_3\text{Si}^+$ was prepared⁷³ by the Corey reaction. The hydride ion abstraction was performed with the use of triphenylmethyl perchlorate in dichloromethane or sulfolane. The conductivity of the resulting tris(isopropylthio)silyl perchlorate in both solvents

355 ppm (Ref. 79)] and Et_3Si^+ [371.2 ppm (Ref. 81)], whereas it is similar to the chemical shift calculated for the $[\text{Me}_3\text{SiC}_6\text{H}_6]^+$ complex [80.9 ppm (Ref. 75)]. In traditional organic chemistry, the structures of carbenium ions are, as a rule, beyond doubt due to a good agreement between ^{13}C NMR spectroscopic data and the results of quantum-chemical calculations.

Another important question was whether the compound synthesised by Lambert is σ complex **13a** or π complex **13b**.

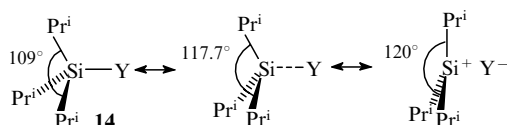


It was hypothesised⁹⁵ that the $[\text{Et}_3\text{Si} \cdot \text{PhMe}]^+$ cation is neither a pure σ complex nor a pure π complex but is a particular hybrid. The argument was that the $\text{Et}_3\text{Si}-\text{C}-\text{C}(\text{para})$ angle in the complex synthesised by Lambert (104°) is intermediate between the values of this angle in the ideal π complex (90°) and the ideal σ complex (125°).



In 1995, Reed and co-workers⁹⁶ synthesised crystalline trialkylsilyl(hexachloro)carboranes containing the silyl group structurally similar to the silyl cation. Halocarborane $(\text{CB}_{11}\text{H}_6\text{Cl}_6)^-$ was used as the anion of low nucleophilicity. In all the complexes under study, the cation and the anion were coordinated through the halogen atom involved in the anion. However, the distance between the silicon and chlorine atoms was rather large (2.23 Å).

The structure most similar to that of the silylium ion was observed in the $\text{Pr}^i_3\text{Si}(\text{CB}_{11}\text{H}_6\text{Cl}_6)$ (**14**), where the average angle $\text{C}(\text{Pr}^i)-\text{Si}-\text{C}(\text{Pr}^i)$ is 117.7° .



$\text{Si}-\text{Y}$ $\text{Y} = \text{CB}_{11}\text{H}_6\text{Cl}_6$.

bond type: covalent ionic-like ionic

The angle, the rather large $\text{Si}-\text{Cl}(\text{CB}_{11}\text{H}_6\text{Cl}_6)$ bond length (2.23 Å) and the fact that the $\text{Si}-\text{C}(\text{Pr}^i)$ bond length remains unchanged (1.85 Å) led the authors to conclude that the charges in this compound are sufficiently separated, which is an indication of the formation of silylium ions. Unlike the carbon chemistry, where the covalent compounds R_3CX are clearly distinguished from the carbenium ions $\text{R}_3\text{C}^+\text{X}^-$, trialkyl-substituted derivatives of silicon R_3SiX have a geometry characteristic of bonds intermediate between covalent (sp^3 -hybridisation) and ionic (sp^2 -hybridisation).

According to calculations⁹⁶ of the total energy for the model compound $\text{Me}_3\text{Si}^+\text{Cl}^{6-}$, the degree of ionicity of compound **14** with the $\text{C}(\text{Pr}^i)-\text{Si}-\text{C}(\text{Pr}^i)$ angle of 117.7° is 60%.

However, the chemical shift of the silicon atom in the ^{29}Si NMR spectrum of compound **14** ($\delta = 115$) differs substantially from that calculated for the Pr^i_3Si^+ cation [$\delta = 342.3$ (calculations by the GIAO method) and 371.0 (calculations by the SOS-DFPT method)⁷⁹].

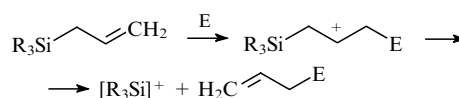
High-level calculations performed in 1996 (see Ref. 97) demonstrated that silylium ions can form complexes with weak Lewis bases, such as ethylene, benzene, bromomethane and fluoromethane, and even with methane and noble gases. This

fact suggests that in none of the solvents the silylium ion can be isolated in the 'free state'. Hence, the problem is not to generate silylium ions but to estimate the degree to which the silylium ion in a complex with a solvent is cationic.

However, the final conclusion drawn by theorists has stimulated the research teams headed by Lambert and Reed to examine the possibility of introducing other substituents at the silicon atom with the aim of solving the problem of silylium ions. These substituents should not only stabilise the positive charge on the silicon atom but also cause steric hindrance to the approach of the anion or solvent molecules to the cation centre, thus preventing complexation. Since the *tert*-butyl and hexyl groups^{21, 89} are unsuitable for this purpose, 1,3,5-trimethylphenyl (mesityl, Mes) was chosen as the substituent. In this case, the charge can be stabilised by a resonance interaction between the silicon and the aromatic ring with the simultaneous protection of the cationic centre by steric hindrance due to the presence of the *ortho*-methyl substituents.

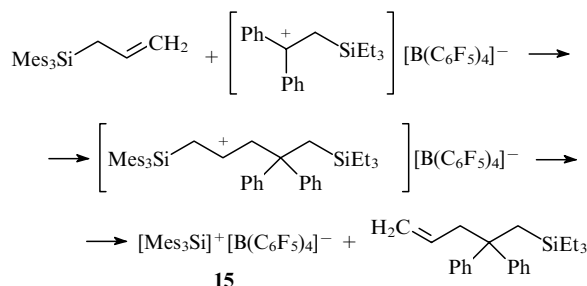
However, bulky substituents, in turn, make it impossible to generate silylium ions by the Corey reaction based on bimolecular[‡] hydride ion abstraction from R_3SiH because such substituents hinder the approach of the carbocation to the hydrogen atom of the $\text{Si}-\text{H}$ bond. Because of this, the hydride ion was replaced with the bulkier allyl (All) group (the chemical behaviour of All with respect to nucleophiles is similar to that of H).

As a result, the following reaction scheme was proposed for the synthesis of silylium ions:⁹⁸



$\text{R} = \text{Mes}$, E is an electrophile.

In this case, the allyl group interacts with an electrophile, thus facilitating release of the silylium ion containing bulky substituents. Lambert *et al.*⁹⁸ applied this approach to the synthesis of the $[\text{Mes}_3\text{Si}^+][\text{B}(\text{C}_6\text{F}_5)_4^-]$ salt (**15**).



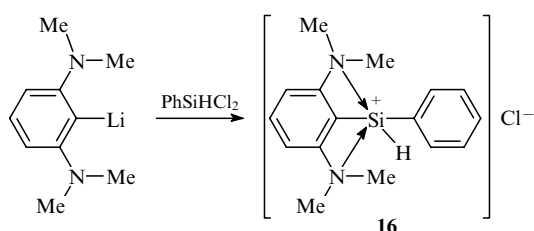
The chemical shift of the silicon atom ($\delta = 225.5$) in the ^{29}Si NMR spectrum of compound **15** is similar to the calculated chemical shift for the Ph_3Si^+ cation ($\delta = 208.9$). This suggests that at least the major portion of the positive charge is localised on the silicon atom. However, the question whether the silylium ion is 'free' can ultimately be answered only by demonstrating that the position of this signal is independent of the nature of both the solvent and anion. It was found that the silicon atom has similar chemical shifts in the ^{29}Si NMR spectra of trimesitylsilyl tetrakis(pentafluorophenyl)borate (**15**) in aromatic hydrocarbons: δ 225.5 in benzene, 225.7 in a 1 : 3 benzene-toluene mixture and 225.6 in a 1 : 1 benzene-*p*-xylene mixture. However, in acetonitrile this signal in the spectrum was observed at δ 37.0. Apparently, the acetonitrile molecule is so small that it can reach the cationic centre even in the presence of three bulky substituents at the silicon atom.

[‡] Unlike carbenium ions, which are readily generated by the $\text{S}_{\text{N}}1$ mechanism, silylium ions can be generated only in bimolecular reactions due to high affinity of silicon to the leaving group.

After the replacement of the $[\text{B}(\text{C}_6\text{F}_5)_4]^-$ anion with the carborane derivative $(\text{CB}_{11}\text{H}_6\text{Cl}_6)^-$, the chemical shift in the ^{29}Si NMR spectrum remains virtually unchanged (225.9 ppm), which confirms the absence of complexation of the Me_3Si^+ cation with these anions.⁹⁹ The calculated ^{29}Si chemical shift for the trimesitylsilylium ion in the equilibrium geometry is 230.1 ppm,^{100, 101} which is in good agreement with the experimental value (225 ppm).

Therefore, in spite of tremendous difficulties associated with the choice of the anion, the leaving group, substituents at the silicon atom and the solvent, the research teams headed by Lambert and Reed succeeded in demonstrating the possibility of the existence of the free silylium ion in the condensed phase.

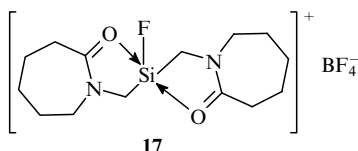
The use of substituents containing electronegative heteroatoms with lone pairs (N or O) is yet another interesting way of stabilising the positive charge on the silicon atom. In this case, the so-called intramolecular stabilisation of the cationic centre can occur. Corriu and co-workers¹⁰² was the first to synthesise this type of nitrogen-containing cations.



The ^{29}Si NMR spectrum of compound **16** confirms the structure of the pentacoordinate ion both in solution and in the solid state.

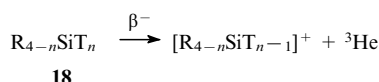
In the $[\text{R}_2\text{SiC}_6\text{H}_3(\text{CH}_2\text{NMe}_2)_2\cdot 2,6]^+$ cations ($\text{R} = \text{H}$ or Me), the intramolecular coordination of silicon by the nitrogen atom is so strong that it prevents solvation with solvent molecules.¹⁰³

Baukov and co-workers^{104–106} synthesised silylium ions **17**, in which the positive charge is stabilised by the coordination interaction $\text{O} \rightarrow \text{Si}$.



However, in spite of the fact that the positive charge on the silicon atom in these cations is stabilised, such structures can hardly be considered as classical free trivalent silylium ions.

A non-traditional radiochemical approach to solving the problem of the generation of silylium ions in the condensed phase was developed by a research group from St Petersburg.^{17, 107–111} This approach is based on the use of β -decay of tritium (incorporated in substituted silanes), which is independent of external conditions.



$\text{R} = \text{Me}, \text{Et}, \text{Ph}; n = 1-3.$

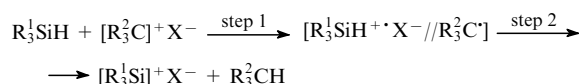
The uniqueness of this nuclear-chemical method is that it allows one to generate free (without a counterion and an equilibrium solvent shell) silylium ions with a desired charge localisation both in the gas phase in a wide pressure range and in the condensed phase. This method was used for the generation of the silylium ions Me_2TSi^+ , Et_2TSi^+ , Et_2TSi^+ and PhT_2Si^+ , and the properties of these ions were studied (for details see Section IV.2).

3. Silylium ions as short-lived reaction intermediates

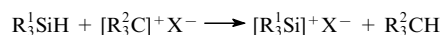
In spite of all difficulties associated with the generation of stable silylium ions in the condensed phase, their formation as short-

lived intermediates was not ruled out; moreover, their formation in many reactions was postulated by analogy with carbenium ions. Comprehensive kinetic studies of the reaction mechanisms of organosilicon compounds are presently underway. Charged silylium species are assumed to be involved in these reactions. The hydride ion abstraction from the R_3SiH molecule with the use of carbenium ion resulting in the generation of the silylium ion R_3Si^+ (the above-considered Corey reaction) is one of such reactions.

Chojnowski *et al.*^{112, 113} studied the kinetics of this reaction in detail for silanes R_3SiH ($\text{R} = \text{Et}, \text{Bu}, \text{Ph}, \text{etc.}$) and the salts $[\text{Ph}_3\text{C}]^+\text{BF}_4^-$ and $[\text{Ph}_3\text{C}]^+\text{SbF}_6^-$. Investigation of the influence of the steric and electronic effects of the substituents at the Si atom on the reaction rate and the use of isotopic indicators led the authors to conclude that the electron transfer is the rate-determining step of the reaction. The second (fast) step gives silylium ions.



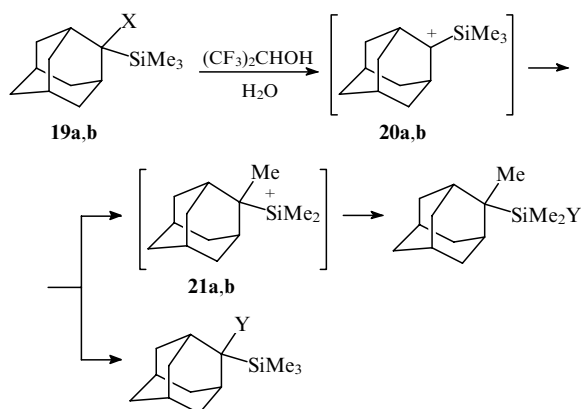
However, according to calculations,¹¹⁴ the reaction mechanism involving electron transfer is energetically unfavourable, and the synchronous barrierless hydride transfer is the rate-determining step.



Studies on the influence of the steric and electronic effects of the substituents at the silicon atom on the reaction pathway of R_3SiH with the diarylcarbenium ions Ar_2CH^+ ($\text{Ar} = \text{Ph}, p\text{-Tol}, p\text{-MeOC}_6\text{H}_4$ and $p\text{-PhOC}_6\text{H}_4$) and investigation of the reaction mechanism demonstrated¹¹⁵ that the formation of silylium ions is the rate-determining step of the process.

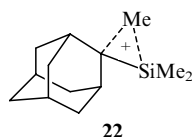
In the study of dimethyl(trimethylelementomethyl)silanes $(\text{Me}_3\text{ECH}_2)\text{Me}_2\text{SiH}$ ($\text{E} = \text{C}, \text{Si}, \text{Ge}$ or Sn),¹¹⁶ it was demonstrated that the steric and electronic effects, as well as the conjugation effects, which can stabilise the positive charge on the silicon atom, substantially influence the rate of reactions of these compounds with carbenium ions. This fact suggests that silylium ions are formed as reaction intermediates.

The formation of solvolysis products of 2-chloro- or 2-benzyloxy-2-(trimethylsilyl)adamantanes (**19a,b**) in aqueous hexafluoropropan-2-ol was accounted for by the rearrangement of the initially formed carbenium ions **20a,b** into silylium ions **21a,b** through the 1,2-methyl shift.¹¹⁷

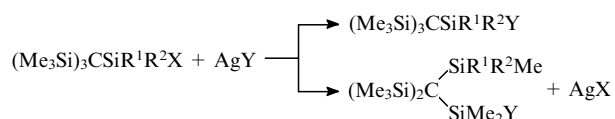


$\text{X} = \text{Cl}$ (**a**), $\text{O}_2\text{CC}_6\text{H}_4\text{NO}_2\text{-4}$ (**b**); $\text{Y} = \text{OH}, \text{OCH}(\text{CF}_3)_2$.

The possibility of this rearrangement was confirmed by gas-phase studies and calculations, which provided evidence that silylium ions are thermodynamically more stable than carbenium ions. Alternatively, this reaction can be explained by the involvement of a non-classical bridged cationic intermediate **22** in this process.

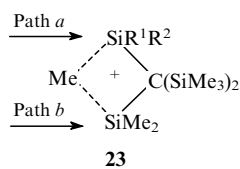


Eaborn¹¹⁸ reasoned that bridged silylium ions of type **22** are formed as intermediate species in some reactions of organosilicon compounds containing bulky substituents, for example, $(\text{Me}_3\text{Si})_3\text{C}$. In particular, Eaborn and co-workers demonstrated¹¹⁹ that the reactions of compounds of the type $(\text{Me}_3\text{Si})_3\text{CSiR}^1\text{R}^2\text{X}$ and $(\text{Me}_3\text{Si})_2\text{C}(\text{SiMe}_2\text{X})(\text{SiR}^1\text{R}^2\text{X})$ with some electrophiles, including silver salts AgY ($\text{Y} = \text{AcO}$, CF_3CO_2 , ClO_4 , etc.), $\text{CF}_3\text{CO}_2\text{H}$ and ICl_3 , afford mixtures of rearranged and non-rearranged $\text{Si}-\text{X}$ -bond cleavage products.



$\text{R}^1, \text{R}^2 = \text{Me}, \text{Et}, \text{Ph}, \text{etc.}; \text{X} = \text{Hal}, \text{H}, \text{etc.}$

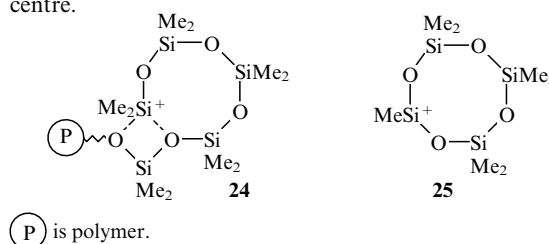
These results can most adequately be explained by the formation of a non-classical bridged ion **23**. In this process, the attack of the nucleophile on one end (path *a*) affords non-rearranged products, whereas the attack on another end (path *b*) gives rise to rearranged products.



Dihalosilylenes SiX_2 ($\text{X} = \text{F}, \text{Cl}, \text{Br}$ or I) generated in the gas phase and concentrated in a toluene solution in the presence of I_2 or ICl at -90°C give mixtures of *ortho*, *meta* and *para* isomers of $\text{MeC}_6\text{H}_4\text{SiX}_2\text{I}$.¹²⁰ The authors attributed the formation of these compounds to the electrophilic attack of the short-lived cations X_2ISi^+ on the aromatic ring. The isomer ratio for $\text{X} = \text{Cl}$ in the presence of I_2 was *ortho*:*para*:*meta* = 10:4:3, i.e., the *ortho*-substituted isomer was the major product. When ethylbenzene was used as the solvent, the yield of the *ortho* isomer sharply decreased and the isomer ratio was 4:2:3. These results are attributed to the influence of the steric effects of the alkyl group and are consistent with the data obtained by Lambert.⁹²

It was hypothesised^{121, 122} that silylium ions are intermediates of radiation-induced polymerisation of permethylcyclorosiloxanes $(\text{Me}_2\text{SiO})_n$, where $n = 3-5$. The initial ionisation of the molecule occurs as a result of elimination of the methyl anion from cyclorosiloxane. The authors postulated that the resulting silylium ions

contain either a coordinated (**24**) or non-coordinated (**25**) cationic centre.



The above-considered published data are conclusive proof of the formation of silylium ions postulated earlier as short-lived intermediates in organosilicon reactions.

IV. Ion-molecular reactions of silylium ions

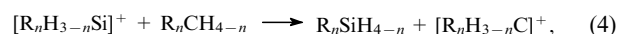
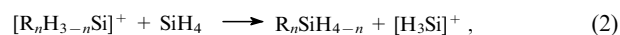
1. Reactivity

The concepts 'reactivity' and 'thermodynamic stability' are closely related to each other. To estimate the reactivity of silylium ions, it is necessary to consider the factors responsible for stability of these ions.

The physicochemical properties of silicon suggest that silylium ions are thermodynamically more stable than isostructural carbenium ions. This is associated with both lower electronegativity of the silicon atom and its larger radius compared to those of the carbon atom (1.8 and 2.5,¹²³ 1.17 and 0.77 Å,¹²⁴ respectively). The ionisation potentials of the alkyl and silyl radicals, the enthalpies of formation of the silylium and carbenium ions and their hydride ion affinities are also indicative of higher thermodynamic stability of silylium ions compared to carbenium ions (Table 4).

Quantum-chemical calculations showed that the silylium cation H_3Si^+ is at least 54 kcal mol⁻¹ more stable than the methyl cation H_3C^+ .¹³¹ However, this difference becomes substantially smaller in the presence of alkyl substituents, as well as π - and n -electron-donating substituents, in the cationic centre.^{50, 132}

The relative stabilities of silylium ions can be estimated from the enthalpies of isodesmic⁸ reactions (2)–(4).⁵⁰



$n = 0-3$.

The stabilisation energies of the $\text{R}_n\text{H}_{3-n}\text{Si}^+$ and $\text{R}_n\text{H}_{3-n}\text{C}^+$ ions calculated for these reactions are given in Table 5.

All the above-considered substituents, except for F, stabilise silylium ions. However, the stabilisation effect is substantially

§ Isodesmic reactions are reactions that involve only charge transfer, whereas the chemical bond configuration remains unchanged.¹³³

Table 4. Thermodynamic characteristics of carbenium and silylium ions.

Parameter	Species	E = C		E = Si	
		value	ref.	value	ref.
Ionisation potential of radicals/eV	$\text{H}_3\text{E}^\bullet$	9.84	125	8.01	126
	$\text{Me}_3\text{E}^\bullet$	6.34	125	5.93	126
Hydride ion affinity /kcal mol ⁻¹	MeH_2E^+	270.5	127	245.9	127
	Me_2HE^+	251.5	127	230.1	127
	Me_3E^+	233.6	127	220.5	127
Enthalpy of formation of the ion (ΔH_{298}°)/kcal mol ⁻¹	H_3E^+	261.3	128	235.2	129
	MeH_2E^+	216.0	130	204.1	129
	Me_2HE^+	192.0	130	173.2	129
	Me_3E^+	166.0	130	145.0	129

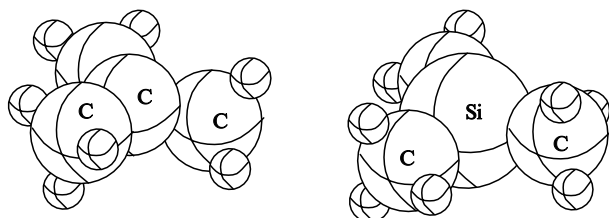
Table 5. Stabilisation energies of substituted silylium ($R_nH_{3-n}Si^+$) and carbenium ($R_nH_{3-n}C^+$) ions calculated⁵⁰ by the MP2(fc)/6-31G*//MP2(fc)/6-31G* method from the enthalpies of isodesmic reactions (2)–(4).

R_n	Stabilisation energy /kcal mol ⁻¹		
	reaction (2)	reaction (3)	reaction (4)
H	0.0	0.0	57.4
Me	15.1	40.6	31.8
Me ₂	27.9	58.7	26.6
Me ₃	38.4	74.8	21.0
Ph	31.5	76.2	—
H ₂ N ^a	37.5	100.5	−5.6
(H ₂ N) ₃	63.5	135.0	−22.8
HO	19.1	66.3	10.1
F	−1.1	25.3	31.0
H ₃ Si	12.3	16.5	53.2
(H ₃ Si) ₂	20.0	—	—
(H ₃ Si) ₃	24.9	—	—
H ₂ P	17.6	63.4	11.6
HS	18.5	63.6	12.2
Cl	2.2	29.2	30.3

^a The results of calculations for the planar structure are given.

smaller than that in the case of carbenium ions. Silylium ions in the gas phase are always more stable than the corresponding carbenium ions. An increase in the number of substituents at the cationic centre stabilises silylium ions to a lesser extent than carbenium ions (see Table 5).

Substituents that cause steric hindrance to the approach of a nucleophile to the cationic centre, thus increasing stability of the latter, stabilise silylium ions to a lesser degree than carbenium ions. This is explained by a substantially larger atomic radius of silicon compared to that of carbon. The stereo projections of the Me_3C^+ and Me_3Si^+ ions calculated by the MP2(fc)/6-31G* method⁵⁰ are given below.



Therefore, in spite of the fact that the introduction of substituents of different nature and an increase in their number diminish the difference between stabilities of carbenium and silylium ions, the latter remain thermodynamically more stable.

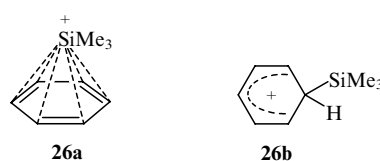
The high positive enthalpies of formation (ΔH°) (and, correspondingly, high free energies ΔG°) are indicative of the high reactivity of silylium ions, because the reactions can follow several pathways resulting in a decrease in the free energy of the system. Reactions of silylium ions are fast due to the presence of the unoccupied 3p orbital in these ions and the positive charge on the silicon atom. This leads to the appearance of a long-range polarisation interaction whose energy can be even higher than the activation energies of various transformations of a complex formed from the ion. The above-mentioned thermodynamic and kinetic requirements for ion-molecular interactions are equally characteristic of silylium and carbenium ions. However, as mentioned above, silylium ions are highly prone to expansion of the coordination sphere. As a result, these ions become even more electrophilic and can react with any nucleophile, including counterions and solvent molecules. That is why silylium ions, which are thermodynamically more stable in the gas phase than carbenium ions, remain virtually undetectable in the condensed phase.

Because of the difficulties in generating silylium ions in the condensed phase, their chemical behaviour in solution have remained unknown for many years. In the first studies dealing with this problem, ion-molecular reactions of the Et_2HSi^+ ions with benzene, dibutyl ether and (*tert*-butylamino)trimethylsilane were investigated by a radiochemical method.^{108–111}

2. Ion-molecular reactions of silylium ions with π - and n -electron-donor compounds

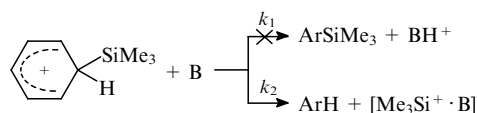
Among chemical transformations of silylium ions, ionic silylation of nucleophilic reagents in the condensed phase is of particular interest.

Benzene is a classical representative of π -electron-donor compounds. The importance of electrophilic ionic alkylation of benzene in organic chemistry is difficult to overestimate. A different situation arises with electrophilic ionic silylation of aromatic compounds. First attempts to perform electrophilic silylation of benzene^{63, 134} in the gas phase led only to the identification of an adduct to which the structure of π complex **26a** was assigned.



More recently, experimental^{135–138} and theoretical⁷⁵ studies demonstrated that the reactions of silylium ions with aromatic compounds yield σ complex **26b**. Actually, the energies of association of silylium ions with aromatic compounds are even higher than those with their carbenium analogues (Table 6), and the role of the σ complex in electrophilic alkylation is well known.

In spite of the fact that the formation of σ complexes in the reactions of the H_3Si^+ and Me_3Si^+ cations with benzene and toluene was proved, silylation products of these aromatic compounds were not detected.¹³⁶ This can be attributed to the fact that, under the experimental conditions used, desilylation of σ complexes occurs much faster than their deprotonation ($k_2 \gg k_1$).



B is a Lewis base.

More recently, it has been demonstrated^{136–138} that electrophilic silylation of benzene and toluene in the gas phase occurs only in the presence of strong proton acceptors (for example, of amines). Oxygen-containing bases induce predominantly desilylation.

A comprehensive insight into reactions of these species with nucleophilic compounds under different conditions was obtained for the first time with the use of the nuclear-chemical method of generation of silylium ions and a radiochemical approach to investigation of their reactions.^{17, 107–111, 139–146}

Ion-molecular reactions of the ethyl- (see Ref. 139) and diethylsilylium ions^{108, 109} with benzene in the gas and condensed phases in the absence of additives were studied by the radiochemical method. In the case of tritium-labelled ions, silylation products were identified for both cations. However, the ethylsilylium cation gives not the expected silane $PhSiH_2Et$ but its isomer $PhSiHMe_2$ in very low yield (4%); this reaction affords labelled benzene as the major product (96%). These data agree well with the mass spectrometric data and results of quantum-chemical calculations for the $C_2H_7Si^+$ ion.^{54, 57, 58}

In the case of diethylsilylium ion, the reactions afford predominantly silylation products (>95%), whereas the yield of labelled benzene is 2%–5% (Table. 7).

The reaction products contain both the starting (Et_2HSi) and rearranged (EtH_2Si and Me_2HSi) silyl groups. Ethyl(dimethyl)-

Table 6. Experimental^{135–138} and calculated⁷⁵ energies of association (kcal mol^{−1}) of silylium ions and *tert*-butyl cations with benzene.

σ Complex	Calculations	value	Experiment
	method		
$[\text{H}_3\text{SiC}_6\text{H}_6]^+$	HF/3-21G(*)//3-21G(*)	−51.1	—
	HF/6-31G*//6-31G*	−47.1	
	MP2(fc)/6-31G*//MP2(fc)/6-31G*	−54.8	
$[\text{Me}_3\text{SiC}_6\text{H}_6]^+$	HF/3-21G(*)//3-21G(*)	−25.2	−23.9
	HF/6-31G*//6-31G*	−20.5	
	MP2(fc)/6-31G*//MP2(fc)/6-31G*	−31.1	
$[ipso\text{-Me}_3\text{CC}_6\text{H}_6]^+$	MP2(fc)/6-31G*//MP2(fc)/6-31G*	−14.9	−22
$[p\text{-Me}_3\text{CC}_6\text{H}_6]^+$	MP2(fc)/6-31G*//MP2(fc)/6-31G*	−21.1	—
$[p\text{-MeC}_6\text{H}_5\text{SiMe}_3]^+$	HF/3-21G(*)//3-21G(*)	−29.7	−28.4
	HF/6-31G*//6-31G*	−25.1	
	MP2(fc)/6-31G*//MP2(fc)/6-31G*	−34.2	
$[p\text{-CD}_3\text{C}_6\text{D}_5\text{SiMe}_3]^+$	—	—	−31.3
$[p\text{-MeC}_6\text{H}_5\text{CMe}_3]^+$	—	—	−29.1
$[p\text{-CD}_3\text{C}_6\text{D}_5\text{CMe}_3]^+$	—	—	−28.6

Table 7. Relative yields of labeled reaction products of EtT_2Si^+ and Et_2TSi^+ with benzene.

Cation	Products ^a	Yields ^b (%)	
		gas phase	liquid phase
EtT_2Si^+	PhSiHMe_2	4	—
	PhH	96	—
Et_2TSi^+	PhSiHEt_2	13	32
	PhSiH_2Et	31	40
	PhSiHMe_2	54	23
	PhH	2	5

^a The products contains the tritium label; ^b in the calculations of the yields, volatile silanes and ethylene formed in insignificant amounts were ignored.

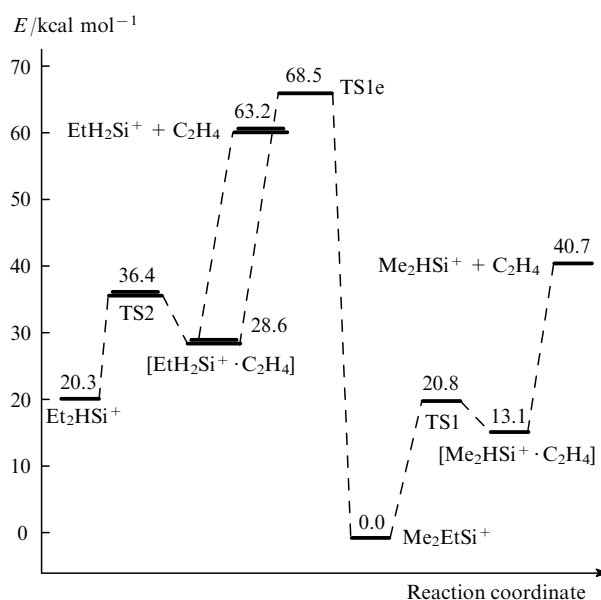
phenylsilane resulting from the reaction with the most stable tertiary silylium ion Me_2EtSi^+ , was not detected.

Quantum-chemical calculations of the potential energy surface of the $\text{C}_4\text{H}_{11}\text{Si}^+$ cation by the B3LYP/6-31G** method demonstrated¹⁰⁹ that isomerisation of the diethylsilylium cation giving rise to the most stable ethyl(dimethyl)silylium ion has to overcome two activation barriers. One of these processes gives the intermediate complex $[\text{EtH}_2\text{Si}^+ \cdot \text{C}_2\text{H}_4]$, whereas another process leads to the rearrangement into the most stable isomeric form Me_2EtSi^+ (Fig. 2). The dissociation threshold of the initially formed $[\text{EtH}_2\text{Si}^+ \cdot \text{C}_2\text{H}_4]$ complex (63.2 kcal mol^{−1}) is 5.3 kcal mol^{−1} lower than the isomerisation barrier (68.5 kcal mol^{−1}), which provides dissociation of the complex to form ethylene and the ethylsilylium ion. Consequently, even having the required energy, the Et_2HSi^+ ion does not undergo isomerisation to form the most stable tertiary cation Me_2EtSi^+ , which is confirmed by the absence of ethyl(dimethyl)phenylsilane among the reaction products.

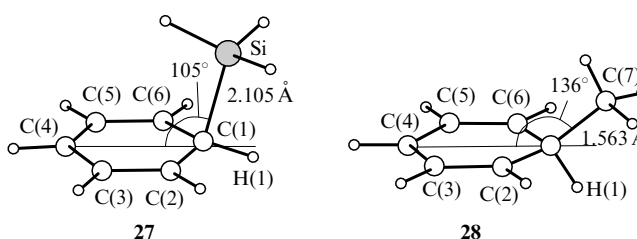
In spite of the fact that the ratios of the silylation products of benzene with ethyl- and diethylsilylium ions are substantially different, there is no reason to assume that these reactions proceed by different mechanisms. This is evidenced by the similar energies of complexation of the ethyl- and diethylsilylium ions with benzene (−39.7 and −31.2 kcal mol^{−1}, respectively, calculated by the B3LYP/6-31G** method) and the structure of a model intermediate **27**.¹⁴⁷

The Si—C(1)—C(4) angle in the complex **27** ($\sim 105^\circ$) is similar to the corresponding angle in classical π complexes (90°).

The charge distribution in the complex **27** was calculated by the NBO (Natural Bond Orbital analysis) method.¹⁴⁷ It appeared that the major positive charge (+0.99) is localised on the silicon atom. The positive charge on the hydrogen atom in the *ipso*

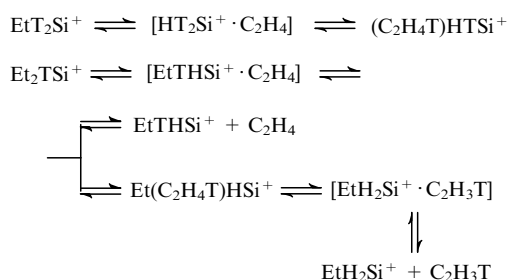
**Figure 2.** Potential energy surface for the transformations of the $\text{C}_4\text{H}_{11}\text{Si}^+$ cation.¹⁰⁹

position (+0.33) is virtually equal to that on the other hydrogen atoms of the benzene ring (+0.28). Alkylation of aromatic compounds is known¹⁴⁸ to give covalently bonded σ complex **28** as an intermediate. In this complex, the angle between the alkyl group and the plane of the ring is $\sim 136^\circ$. The positive charge is transferred from the carbenoid carbon atom to the hydrogen atoms of the benzene ring, the charge being most substantially transferred to the *ipso* position (+0.36). The charge of the C(7) atom in the complex **28** is −0.65.



Evidently, the structure and the charge distribution in the σ complex formed by the reaction of silylium ions with benzene favour desilylation rather than deprotonation. The difference in

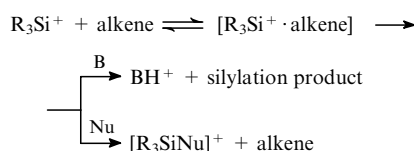
the experimental yields of the silylation products of benzene with ethyl- and diethylsilylium ions is associated with the difference in the ability of these species to be involved in the isotope exchange with the hydrogen atom in the *ipso* position. As a result, monomolecular decomposition of the σ complex with diethylsilylium ion affords tritium-free benzene as the major product.¹⁰⁸ The interconversions of the $\text{C}_2\text{H}_7\text{Si}^+$ and $\text{C}_4\text{H}_{11}\text{Si}^+$ ions proceed *via* ethylene complexes and can be accompanied by migration of silicon-bound tritium to the ethyl group.¹⁰⁹ Since only the silicon-bound tritium can be exchanged with the aromatic hydrogen atom, it is evident that the probability of this process in the case of diethylsilylium ions is substantially lower. Larger lability of the hydrogen atom in the monosubstituted ethylsilylium ion also leads to an increase in the rate of isotope exchange.



Therefore, desilylation occurs as the major process in the case of both the Et_2HSi^+ and EtH_2Si^+ cations, as in the case of Me_3Si^+ .^{135–138}

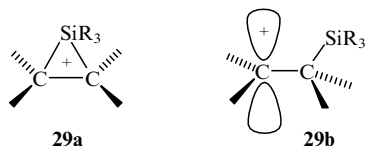
High isomerisation barriers compared to the energy acquired by the silylium ion, which is generated by the nuclear-chemical method, upon the rearrangement of the tetrahedral structure into the planar structure [$\sim 22\text{--}24\text{ kcal mol}^{-1}$ (see Ref. 149)] suggest that isomerisation of silylium ions in the reaction with the benzene molecule occurs in an intermediate complex. The difference in the lifetime of the intermediate complex in the gas and condensed phases is responsible for the difference in the degree of isomerisation of the diethylsilylium ion. As a result, the percentage of products containing the rearranged silyl fragment is lower in the condensed phase.^{108, 109}

The $[\text{R}_3\text{Si}^+ \cdot \text{alkene}]$ adduct [reaction product of alkenes with the R_3Si^+ ions ($\text{R} = \text{Me}, \text{Et}$)] and its subsequent transformations were studied¹⁵⁰ in the gas phase by the radiolytic method. A high concentration of the adduct is provided by a high pressure of a dilutant gas. It was found that this rather stable ionic adduct can decompose only in the presence of strong bases, *viz.*, by deprotonation in the presence of amines (for example, Et_3N) or desilylation in the presence of oxygen-containing nucleophiles (for example, H_2O , MeOH , *etc.*).



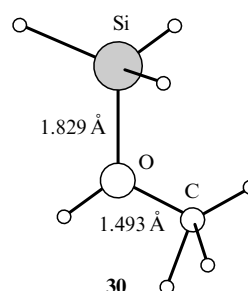
The direct reaction of the ethylsilylium ion generated by the nuclear-chemical method with ethylene affords dimethylvinylsilane in low yield ($\sim 10\%$).¹³⁹

The structures of the adducts of silylium ions with alkenes have been debated for many years. Both the bridged (**29a**)¹⁵¹ and open (**29b**)¹⁵² structures were considered.



Quantum-chemical calculations demonstrated¹⁰⁹ that the resulting adduct is the bridged ethene complex, for example, $[\text{EtH}_2\text{Si}^+ \cdot \text{C}_2\text{H}_4]$, located in a local minimum on the potential energy surface (see Fig. 2), which is $28.6\text{ kcal mol}^{-1}$ higher than the global minimum. Another local minimum, which is only 13 kcal mol^{-1} higher than the global minimum, corresponds to the ethene complex of the isomeric dimethylsilylium ion $[\text{Me}_2\text{HSi}^+ \cdot \text{C}_2\text{H}_4]$. A minimum corresponding to the open structure was not found.

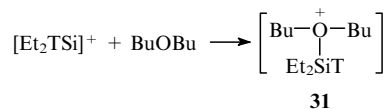
Unlike π -electron-donor compounds, n-electron-donor compounds readily undergo silylation under the action of silylium ions. The reactions of the silylium ions $\text{R}_{3-n}\text{T}_n\text{Si}^+$ ($\text{R} = \text{Me}$ or Et ; $n = 1$ or 2) with alcohols^{141–144} in the gas phase afford primarily silylation products, *viz.*, the corresponding alkoxy-silanes. These reactions give rather strong covalently bonded oxonium ions of type **30** (calculations by the B3LYP/6-31G** method for the adduct of H_3Si^+ and methanol) as intermediates. In the latter, the positive charge ($+0.58$, estimated by NBO) is localised to a large extent on the proton of the hydroxy group.



This proton is readily abstracted (for example, is transferred to substrate molecules), resulting in the formation of alkylalkoxy-silanes from complexes of type **30**.

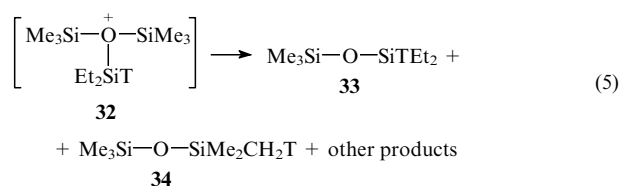
The oxonium complex can also undergo monomolecular decomposition with elimination of the carbenium or silylium ion to give the corresponding disiloxane or tritium-labelled alcohol.^{141–144} The formation of the latter is attributed to isotope exchange between the hydrogen atom of the alcoholic hydroxy group and the tritium atom in the silylium ion. As with benzene, this exchange occurs much more easily in the case of the EtT_2Si^+ ion.^{141–144}

The reaction of the diethylsilylium ions Et_2TSi^+ with yet another representative of n-electron-donor oxygen-containing compounds, *viz.*, dibutyl ether, also proceeds *via* an oxonium complex **31**.¹¹⁰ The exothermicity of the reaction is $72.7\text{ kcal mol}^{-1}$.



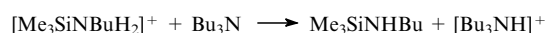
Taking into account the relaxation energy of the silylium ion,¹⁴⁹ the total excitation energy of the oxonium complex appears to be rather high, which facilitates its monomolecular decomposition with elimination of the diethylsilylium or the butyl cation.¹¹⁰ Since there are no labile hydrogen atoms in this complex, its reactions with substrate molecules can lead only to energy transfer. Because of the absence of labile hydrogen atoms in the ether molecule, the isotope exchange, *i.e.*, the formation of tritium-labelled dibutyl ether, becomes impossible. Consequently, the formation of silylation products (Et_2TSiOBu , EtT_2SiOBu and Me_2TSiOBu ; the yield was 80%) in the gas and condensed phases is attributed to monomolecular dissociation of complex **31** with elimination of the butyl cation.¹¹⁰

The reaction of the Et_2TSi^+ ions with hexamethyldisiloxane gives an intermediate adduct **32** which decomposes according to the following scheme:



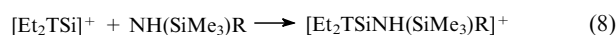
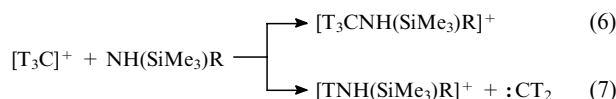
Along with the main reaction product, *viz.*, unsymmetrical disiloxane **33**, a series of disiloxanes containing rearranged terminal silyl substituents were identified.¹⁴⁵ Unlike the reaction with dibutyl ether, the reaction of the diethylsilylium ion with hexamethyldisiloxane affords, among other products, labelled substrate **34**. Hexamethyldisiloxane is an organosilicon ether. It contains no labile hydrogen atoms and, at first glance, would not form a labelled substrate. According to quantum-chemical calculations [the HF/4-21(O*)G method]¹⁵³ for the model $\text{H}_3\text{C}^+-\text{Me}_2\text{O}$ and $\text{H}_3\text{C}^+-(\text{H}_3\text{Si})_2\text{O}$ systems, the ether methyl group in the oxonium complex retains the tetrahedral structure, whereas the silyl group in the $[\text{H}_3\text{C}(\text{H}_3\text{Si})_2\text{O}]^+$ complex is virtually planar. Apparently, the trimethylsilyl substituent in oxonium complex **32** is substantially ionic in character and can undergo isomerisation to give the EtMeHSi substituent containing the labile hydrogen atom. As a result, the isotope exchange between the hydrogen atom of the silyl fragment of the substrate and the tritium label in the diethylsilylium ion in the reaction (5) becomes possible.¹⁴⁵

According to the results of mass spectrometry,⁶⁸ the reaction of the trimethylsilylium ion with *n*-butylamine gives the $[\text{Me}_3\text{SiNH}_2\text{Bu}]^+$ adduct as the major product, whereas the reaction of this cation with tributylamine involves two competitive processes. One process affords the $[\text{Me}_3\text{SiNBu}_3]^+$ adduct, whereas another process is accompanied by the hydride ion abstraction from the butyl substituent of the amine molecule under the action of the Me_3Si^+ ion to form the carbenium ion $[\text{C}_{12}\text{H}_{26}\text{N}]^+$. It should be noted that, in spite of the fact that the proton affinity of the Bu_3N molecule is higher than that of $\text{Me}_2\text{Si}=\text{CH}_2$, the reaction of the Me_3Si^+ ion with a mixture of Bu_3N and BuNH_2 gives the protonated tributylamine in insignificant amount. The authors hypothesised that this compound, unlike alkyl cations,^{154–163} is formed in the reaction of the $[\text{Me}_3\text{SiNBuH}_2]^+$ adduct with tributylamine rather than due to the proton transfer from the trimethylsilylium ion to the tributylamine molecule.



The reactions of ethyl- and diethylsilylium ions with trimethyl(*tert*-butylamino)silane in the gas and condensed phases were studied by the radiochemical method.^{111, 146}

It is known^{154–163} that reactions of carbenium ions with organic and organosilicon amines follow two competitive pathways, *e.g.*, occur as condensation (6) and proton transfer (7). In the former reaction, amine reacts as a nucleophile, whereas it acts as a base in the latter reaction. Silylium ions and amines are involved only in condensation (8), in spite of the fact that the proton transfer is not energetically forbidden.^{111, 164}



$\text{R} = \text{Me}_3\text{C}, \text{Me}_3\text{Si}.$

This difference is associated with the difference in the electron density distribution in carbenium and silylium ions. According to quantum-chemical calculations,¹⁴⁷ the positive charge in the H_3Si^+ cations is virtually completely localised on the silicon

atom, and the hydrogen atoms are hydride in character, whereas the positive charge in carbenium ions is uniformly distributed between the carbon atom and the hydrogen atoms.



In the condensed phase, the qualitative composition of the reaction mixture remains unchanged, and only the component ratio becomes different: the mixture contains a higher percentage of the products formed by bimolecular reactions whose efficiency increases in the condensed phase.¹¹¹

Therefore, products containing the starting Et_2HSi group and the EtH_2Si and Me_2HSi groups as the silyl fragment were obtained in radiochemical studies of ion-molecular reactions of diethylsilylium ions with π - and n -electron-donor compounds (Table 8). Consequently, the rearrangement into ethyl- and dimethylsilylium ions takes place; this rearrangement is characteristic of diethylsilylium ions.^{110, 111, 143–145}

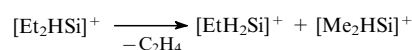


Table 8. The ratio of silylation products of oxygen-containing organic compounds and benzene with diethylsilylium ions.

Silyl substituent in the product	Ratio of silylation products (%) ^a			
	Bu_2O	BuOH	$(\text{Me}_3\text{Si})_2\text{O}$	PhH
Et_2HSi	90	62	29	13
$\text{EtH}_2\text{Si} + \text{Me}_2\text{HSi}$	10	38	71	87

^a The ratio was calculated from the relative yields of the corresponding silylation products.

The degree of this conversion is determined to a large extent by the nature of the electron-donor substrate. For example, for all studied oxygen-containing compounds and benzene, the percentage of products containing non-rearranged silyl substituents sharply decreases in benzene compared to that in dibutyl ether (see Table 8).¹⁶⁴ The activity series of the compounds inducing this rearrangement $\text{Bu}_2\text{O} < \text{BuOH} < (\text{Me}_3\text{Si})_2\text{O} < \text{PhH}$ correlates with their nucleophilicities and is determined by the excitation energy of the intermediate complex and the possibilities of its transfer to the substrate molecules. The association energies calculated by a quantum-chemical method¹⁶⁴ for the H_3Si^+ ion and related model compounds increase in the following series (kcal mol^{-1}): $\text{PhH} (47.6) < (\text{H}_3\text{Si})_2\text{O} (65.0) < \text{MeOH} (69.7) < \text{Me}_2\text{O} (72.7)$.

The minimum energy of association of the silylium ion with benzene ensures a longer lifetime of the complex and, as a consequence, the maximum degree of conversion. The opposite situation is observed for dibutyl ether. In this case, the degree of conversion is 10%, whereas the association energy of the similar model $\text{H}_3\text{Si}^+-\text{Me}_2\text{O}$ system is the highest in this series of compounds ($72.7 \text{ kcal mol}^{-1}$).

Although the calculated energies of association of the silylium ion with MeOH and Me_2O have similar values, the experimentally determined degree of conversion of the diethylsilylium ion in the reaction with butanol differs from that in the reaction with dibutyl ether. This is attributed to the different mechanisms of excitation energy transfer. In the case of alcohols, the complex undergoes both mono- and bimolecular decomposition, whereas only monomolecular decomposition can occur in the case of ethers.

From the above, it is clear that studies of ion-molecular reactions of silylium ions with nucleophilic reagents are in their infancy. The mechanisms of these transformations cannot be reliably established based on the results of mass-spectrometric

studies performed so far in the gas phase. The nuclear-chemical method of generation of silylium ions provides exhaustive information on their reactions with nucleophiles both in the gas and condensed phases. This method allows one to observe not only usual reaction products but also their isomeric forms, due to which more reliable conclusions about the mechanisms of reactions of silylium ions with nucleophilic compounds can be drawn.

* * *

Based on the above-considered data, the following conclusions can be drawn.

First, in spite of the fact that silylium ions have long been considered as analogues of carbenium ions, studies of the reactivity of the former ions have rejected this statement. The differences in the chemical behaviour are associated primarily with the difference in the electron density distribution in these cations. Second, the unique ability of the silicon atom to expand its coordination sphere results in higher electrophilicity of silylium ions compared to carbon analogues. Silylium ions can react with all types of nucleophiles, including counterions and solvent molecules, which make them undetectable in the condensed phase. Third, the existence of silylium ions as both reactive intermediates and individual species was unambiguously established with the use of non-traditional approaches to the generation of these ions in various media described in the present review. Nevertheless, it should be noted that further investigations of the properties of silylium ions will allow these species to play an important role in silicon chemistry.

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^a — *Russ. J. Gen. Chem. (Engl. Transl.)*

^b — *Russ. J Org. Chem. (Engl. Transl.)*

Metal-mediated reactions of oximes

D A Garnovskii, V Yu Kukushkin

Contents

I. Introduction	111
II. Reactions with loss of integrity of the C=NOH fragment	111
III. Reaction with retention of the C=NOH fragment	117
IV. Miscellaneous oxime reactions involving metal complexes	120
V. Conclusion	121

Abstract. The published data on metal-mediated reactions of oximes are described systematically. The attention is focused on the reactions that serve as convenient methods for the synthesis of various organic compounds or models for the interpretation of the mechanisms of catalytic processes and the reactions resulting in new ligand systems. The bibliography includes 182 references.

I. Introduction

The permanent interest in ligand reactivity is caused, first of all, by the necessity of interpretation of the mechanisms of homogeneous metal-catalysed processes (including industrially important ones) in which a substrate is activated upon its coordination to a metal site. Usually it results in drastic changes in the substrate properties, particularly its electrophilicity (or nucleophilicity), acidity or redox properties. This alters the reactivity of the ligands to such an extent that the chemical reactions, impossible for a free ligand, become achievable. Books and reviews^{1–25} concerning ligands' reactions are mainly focused on complexes with 'simple' (containing only one reaction site) ligands: hydrides,¹¹ carbonyls,¹² alkenes,¹³ dinitrogen,¹⁴ azides,¹⁵ cyanides,¹⁶ nitrosyls,¹⁷ nitriles,^{18,19} isonitriles,²⁰ amines,²¹ sulfoxides,²² sulfides and thiols,²³ pseudohalides²⁴ and phosphines.²⁵ Their chemical transformations mimic some catalytic processes and organic reactions taking place in the presence of metal complexes.

In contrast to the above-mentioned ligands, a coordinated oxime contains three active sites (C, N and O atoms) and an OH group the acidity of which increases drastically upon coordination.²⁶ Virtually all types of metal-mediated transformations are possible for the coordinated oximes, *viz.*, nucleophilic and electrophilic reactions, intramolecular redox reactions, template synthesis,^{27,28} metal-induced Beckmann rearrangement, *etc.*

Abundant experimental material on these transformations and on the metal-catalysed reactions of oximes and their complexes was considered in several reviews.^{29–37} However, the

problem is still topical, which is circumstantially proved by quite a number of recent papers on the subject. New reports together with previously non-reviewed results lead to a new insight into reactions of metal-activated oximes.

Retention or loss of integrity of the oxime fragment C=NOH during the coordination was the main characteristic used for our systematisation of metal-mediated reactions of oximes. According to this feature, all reactions are divided into two large groups.

The first group comprises transformations occurring with the cleavage of the O–N, O–H and C=N bonds. Two sub-groups within this first group involve non-redox reactions (first of all, addition or elimination of water molecules) and redox reactions.

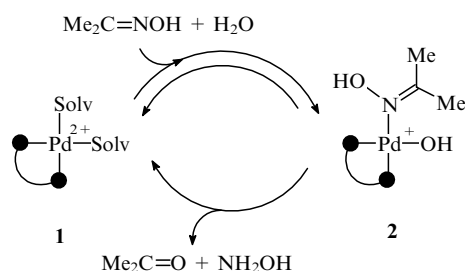
Metal-mediated reactions of oximes with retention of the C=NOH fragment involve mostly the oxygen atom (less common, N and C atoms) of the oximes, they are represented by the nucleophilic addition reactions to substrates containing multiple bonds. Reactions involving peripheral groups in oxime and oximate complexes also belong to this category.

II. Reactions with loss of integrity of the C=NOH fragment

1. Metal-mediated hydrolysis of oximes

Examples of metal-mediated hydrolytic cleavage of oximes occurring without change in the oxidation state of the nitrogen atom are discussed below.

A study of a catalytic process of acetone oxime hydrolysis in the presence of *cis*-[Pd(en)(Solv)₂]²⁺ or *cis*-[Pd(dtod)(Solv)₂]²⁺ (**1**) [en is ethylenediamine, dtod is 3,6-dithiaoctane-1,8-diol, Solv is H₂O or (CD₃)₂CO], including its kinetics, was reported.³⁸ A mechanism of the Pd-catalysed hydrolysis of acetone oxime has been proposed.



Palladium centre coordinates both the oxime and the hydroxide ion in the first step of the process yielding complex **2**. In the second step the C=N bond activated due to metal coordination is subject to intramolecular nucleophilic attack by the hydroxyl

D A Garnovskii Southern Scientific Centre of the Russian Academy of Sciences, ul. Chekhova 41, 344006 Rostov-on-Don, Russian Federation. Fax (7-863) 243 46 67, e-mail: garn@ipoc.rsu.ru

V Yu Kukushkin Department of Chemistry, St Petersburg State University, Universitetsky pr. 26, Petrodvorets, 198504 St Petersburg, Russian Federation, Fax (7-812) 428 69 39, tel. (7-812) 428 45 82, e-mail: kukushkin@VK2100.spb.edu

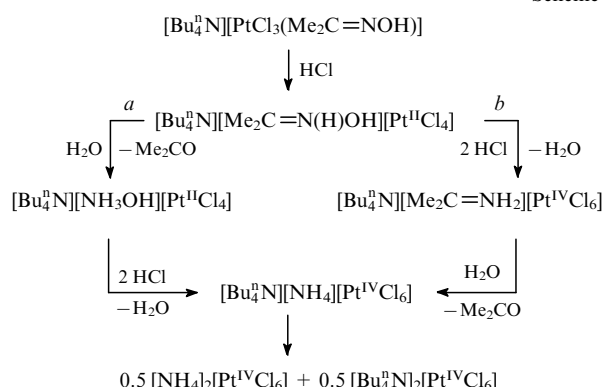
Received 1 February 2005

Uspekhi Khimii 75 (2) 125–140 (2006); translated by D S Yufit

ligand. As a result, the bond is hydrolytically cleaved to form acetone. The last and the rate determining step of the process is release of hydroxylamine upon dissociation of its Pd(II) complex. This step significantly reduces the efficiency of the catalytic process (the turnover number of the catalyst does not exceed 4). The presence of acetone and hydroxylamine (both free and coordinated) was confirmed by NMR spectroscopy.

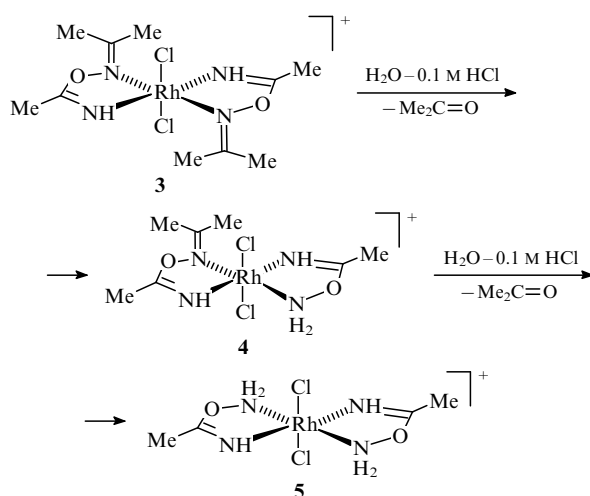
Treatment of the complex $[\text{Bu}_4\text{N}][\text{PtCl}_3(\text{Me}_2\text{C}=\text{NOH})]$ with concentrated hydrochloric acid for 30 days at room temperature leads to two products, *viz.*, $[\text{NH}_4]_2[\text{PtCl}_6]$ and $[\text{Bu}_4\text{N}]_2[\text{PtCl}_6]$,³⁹ which presumably result from consecutive redox and hydrolytic processes. Two alternative pathways of the process are presented in Scheme 1: acid hydrolysis of the oxime in the starting complex followed by intramolecular oxidation of Pt(II) to Pt(IV) by the eliminated $[\text{NH}_3\text{OH}]^+$ cation (path *a*), or oxidative deoxygenation of the oxime followed by hydrolysis of the produced iminium fragment (path *b*).

Scheme 1



However, no solid evidence in favour of one or another mechanism has been obtained. Nevertheless, it has to be stressed that both hydrolysis and oxidative deoxygenation of acetone oxime in this case are mediated by platinum(II).

Study on the reactivity of rhodium imino complexes formed in the nucleophilic addition of acetone oxime to rhodium(III) nitrile complexes reveals⁴⁰ that it is the oxime fragment of the imino-ligand that undergoes hydrolysis at pH 1 and 80 °C, while the imine fragment[†] manifests enormous stability under the same conditions. This implies that Rh(III) selectively activates the C=N bond of the oxime fragment.



¹H NMR study of this reaction has shown that the starting complex **3** completely transforms into a mixed-ligand product **4** in

[†] It is known that non-coordinated imines are readily hydrolysed at low pH values.

36 h; the formation of acetone was also observed. When complex **4** was treated under the same conditions for 4 weeks, hydrolysis of the second imino-ligand occurred to give new bis-chelate complex **5**, which was isolated and structurally characterised. It is of note that the reaction proceeds faster in the absence of HCl, however the selectivity decreases substantially. In this case, considerable amount of by-products prevents isolation of compounds **4** and **5** in individual state.

Technetium imine-oxime complexes behave similarly.⁴¹

2. Dehydration of oximes

Synthesis of nitriles by dehydration of the corresponding aldoximes is long known and successfully employed in organic chemistry.^{42,43} However, there are few examples of metal-mediated conversions of $\text{R(H)C}=\text{NOH}$ into RCN .

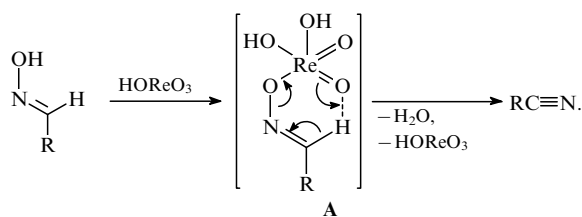
Thus synthesis of two osmium nitrile complexes $[(\eta^6\text{-C}_6\text{H}_6)\text{OsH}(\text{NCR})(\text{PMeBu}_2)]^+$ ($\text{R} = \text{Me}, \text{Ph}$) by reactions of $[(\eta^6\text{-C}_6\text{H}_6)\text{OsHI}(\text{PMeBu}_2)]$ with aldoximes $\text{RCH}=\text{NOH}$ in the presence of AgPF_6 used for abstraction of the iodide ligand was described.⁴⁴ Tungsten nitrile complexes $[\text{W}(\text{NCR})(\text{CO})_5]$ ($\text{R} = \text{Me}, \text{Ph}, \text{C}_6\text{H}_4\text{OMe-}p$) were obtained from the corresponding aldoximes and $[\text{W}(\text{THF})(\text{CO})_5]$.⁴⁵

The reaction of RuBr_3 with benzaldoxime in 6 M aqueous HBr furnishes the mixed-valence ruthenium complex $[\text{RuBr}(\text{NCPH})_5][\text{RuBr}_4(\text{NCPH})_2]$.⁴⁶ Refluxing of the osmium acetonitrile trinuclear cluster $[\text{Os}_3(\text{CO})_{11}(\text{NCMe})]$ with anthracene-9-carbaldoxime in chloroform for 5 h resulted in the anthracene-carbonitrile complex $[\text{Os}_3(\text{CO})_{11}(\text{NCC}_{14}\text{H}_9)]$ in 46% yield.⁴⁷ The formation of N-coordinated oxime intermediates in the initial stages of the above-mentioned reactions was suggested.^{44–47} The electron density on the aldoxime nitrogen atom increases as a result of coordination to the metal (due to dative interaction of the occupied d-orbitals of a metal with the unoccupied π^* -orbitals of a ligand), which facilitates cleavage of the N–O bond followed by dehydration and formation of a nitrile.

A number of studies on the dehydration of oximes assisted by Ru and Os complexes were reported. It is known that these metal sites possess strong affinities for nitriles. Obviously, the formation of highly stable nitrile complexes is one of the main driving forces of the reaction. This suggestion was indirectly supported by the results of a study⁴⁸ where it was shown that the reaction of the ruthenium complex $[\text{Ru}(\text{NH}_3)_5(\text{H}_2\text{O})]^{2+}$ with the ketoximes $\text{Me(R)C}=\text{NOH}$ [$\text{R} = \text{C}(\text{O})\text{Me}, \text{C}(\text{O})\text{Ph}$ and $\text{CH}(\text{OH})\text{Ph}$] leads to the acetonitrile complex $[\text{Ru}(\text{NH}_3)_5(\text{NCMe})]^{2+}$ and elimination of ROH. The affinity of Ru(II) to nitrile is so high that even the cleavage of the ketoxime C–C bond becomes favourable.

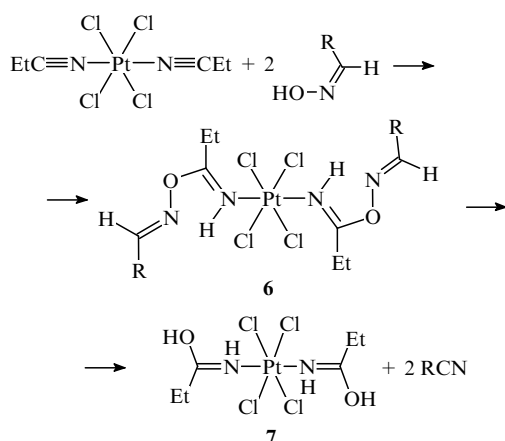
Attanasi *et al.*⁴⁹ have shown that refluxing of aldoximes in acetonitrile in the presence of catalytic amounts of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ produces the corresponding nitriles in good yield (85%–98%). Refluxing of benzaldoxime with AlI_3 (molar ratio 1:2) in acetonitrile for 2 h resulted in benzonitrile (92%).⁵⁰ Aldoximes undergo dehydration under mild conditions in the presence of titanium and indium trifluoromethanesulfonates $[\text{TiCl}_3(\text{OTf})]$ ⁵¹ and $[\text{In}(\text{OTf})_3]$ ⁵² affording the corresponding nitriles. Heterogeneous ruthenium catalysts obtained by adsorption of $[\text{RuCl}_2\text{L}_2]$ (L is *p*-cymene) on activated charcoal⁵³ or molecular sieves⁵⁴ are also used for conversion of aldoximes into nitriles.

Various aldoximes are converted into the corresponding nitriles in less than 1 h in more than 95% yields by azeotropic distillation with toluene or mesitylene in the presence of catalytic amounts of perhenic acid HOREO_3 (1 mol.%, an aqueous solution).⁵⁵ A plausible reaction mechanism consists of nucleophilic addition of aldoximes to rhenium with formation of six-membered M,H-cyclic intermediates **A** which are split to give the corresponding nitriles:



Solid-phase dehydration of oxime ligands is also known.^{56–58} The formation of PhCN as a result of thermal decomposition of the copper complex $[\text{Cu}\{2\text{-OC}_6\text{H}_4\text{C(Ph)=NOH}\}_2]$ was proved by combination of TGA and mass spectrometry.⁵⁶ Pyrolysis of Co(II) dimethylglyoximate and cyclohexanedione-1,2-dioximate complexes afforded acetonitrile and hexanedinitrile, respectively.⁵⁷ Lead(II) bis(salicylaldoximate) decomposes in the temperature range from 160 to 200 °C yielding the nitrile complex $[\text{NCC}_6\text{H}_4\text{OPb}]_2\text{O}$ with elimination of water.⁵⁸ Unfortunately, the formation of this product was confirmed only by elemental analysis.

An example of promotion of aldoxime dehydration by a coordinated ligand is known.⁵⁹ Thus the nucleophilic addition of aldoximes R(H)C=NOH to the platinum(IV) nitrile complex *trans*- $[\text{PtCl}_4(\text{NCEt})_2]$ results in iminoacyl (imide) derivatives *trans*- $[\text{PtCl}_4\{\text{HN}=\text{C(Et)ON}=\text{CHR}\}_2]$ (**6**).



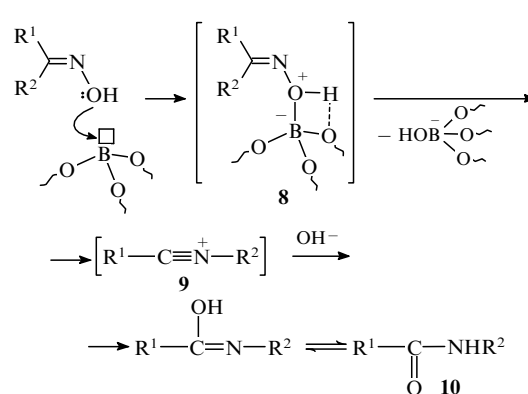
R = Me, Ph, C(O)Ph.

Complexes **6**, when stored in a solution, decompose yielding a Pt(IV) propionamide complex **7** (where the amide is stabilised in the imidic form) and the corresponding nitriles. This was confirmed by ¹H and ¹³C NMR spectroscopy, thin layer chromatography and mass spectrometry. Comparison of the results presented in two papers (Refs 47 and 59) suggests that the reaction of the Os cluster (Ref. 47) also proceeds *via* an osmium iminoacyl intermediate, its decomposition results in anthracene-9-carbonitrile, which further reacts with Os.

3. Metal-mediated Beckmann rearrangement

The Beckmann rearrangement is still the simplest and the most convenient method of oxime conversion^{60,61} into the corresponding amides both in laboratory and industry.[‡] Strong Brønsted or Lewis acids are normally used as catalysts of this conversion.

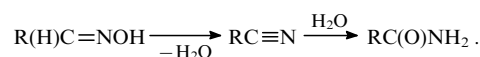
The mechanism of the reaction was studied for borophosphates as Lewis acids.⁶² In the first step, oximes react with borophosphates to form intermediate **8** (Scheme 2) stabilised by a hydrogen bond. Decomposition of the latter yields nitrilium cation **9**, which is converted into an amide **10** upon the reaction with the hydroxide ion.



Scheme 2

The rearrangement of oximes into amides is also catalysed by metal ions. For instance, benzamide was obtained from benzaldoxime in the presence of CuCl_2 .⁶³ Later, it was shown⁶⁴ that monosaccharide oximes are converted into the corresponding aldonamides upon refluxing in 1,4-dioxane in the presence of $\text{Cu(OAc)}_2 \cdot \text{H}_2\text{O}$. Presumably,⁶⁴ copper(II) oximate complexes isolated from the reaction mixture are intermediates of this conversion. Unfortunately, no other experimental data on the reaction mechanism have been obtained.

Studies on the Beckmann rearrangement of various aldoximes into the corresponding amides catalysed by nickel(II) salts were carried out.^{65–67} In particular, in the presence of catalytic amounts of $\text{Ni(OAc)}_2 \cdot 4\text{H}_2\text{O}$, aldoximes isomerise into amides in xylene or water in high yields. The role of the metal in this process was studied in detail^{68,69} using rearrangement of a number of aldoximes into the corresponding amides in the presence of catalytic amounts of the complexes $[\text{M}(\text{acac})_2]$ (M = Pd, Ni) or $[\text{Pd}(\text{CH}_2\text{NO}_2)(\text{acac})(\text{PPh}_3)]$ as a model reaction. The reaction mixtures contained aldoxime and $[\text{Pd}(\text{acac})_2]$, the presence of small amounts of acetonitrile was revealed by GLC and ¹H NMR spectroscopy. Heating of a three-component mixture $\text{Me(H)C=NOH} - \text{PhCH}_2\text{CN} - [\text{Pd}(\text{acac})_2]$ results in the conversion of acetaldoxime into acetonitrile and of phenylacetonitrile into phenylacetamide. Thus, a stepwise mechanism was suggested,^{68,69} which includes dehydration of the aldoxime into the corresponding nitrile and hydrolysis of the latter into the amide.



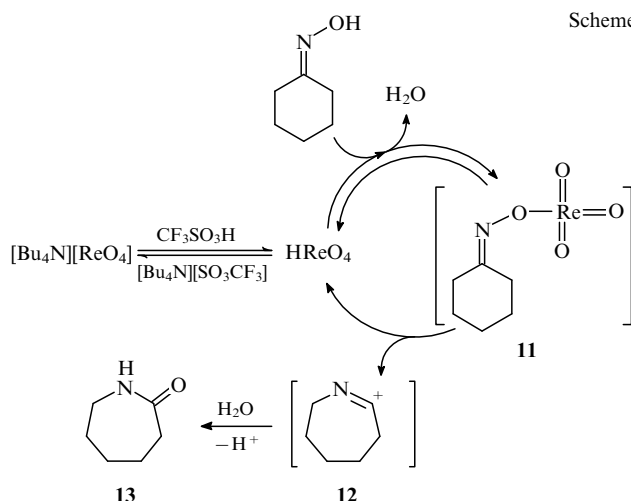
Similar mechanism was suggested for the conversion of aldoximes into amides in the presence of catalytic amounts of the Wilkinson complex $[\text{RhCl}(\text{PPh}_3)_3]$ (DMF, 150 °C).⁷⁰ In this case, the formation of small (~8%) amounts of nitriles was also observed. Unsuccessful attempts of rearrangements of ketoximes and *O*-alkylaldoximes into amides were yet another evidence in favour of the suggested stepwise mechanism of this reaction.

It was shown^{71,72} that various ketoximes were converted in high yields into amides upon refluxing in nitromethane as the result of the Beckmann rearrangement catalysed by a mixture of $[\text{Bu}_4\text{N}][\text{ReO}_4]$ and $\text{CF}_3\text{SO}_3\text{H}$. No reaction occurs in the absence of $[\text{Bu}_4\text{N}][\text{ReO}_4]$. It was suggested that oxime perchrenate **11** (Scheme 3) is an intermediate of this process in the case of cyclohexanone oxime. This intermediate **11** decomposes yielding a seven-membered cation **12** and HReO_4 . Hydrolysis of the cation **12** yields ω -caprolactam (**13**).

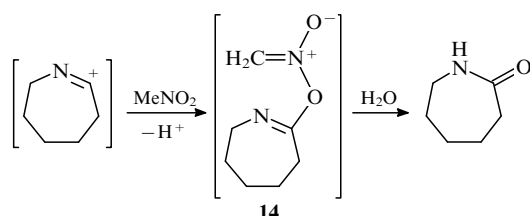
To increase the yield of ω -caprolactam, $\text{NH}_2\text{OH} \cdot \text{HCl}$ was added to the reaction mixture in order to bind the ketone formed as a by-product. The use of MeNO_2 as a solvent also increases the yields of amides, which is explained by possible formation of

‡ This is an industrial method for the manufacture of ω -caprolactam.

Scheme 3



intermediate **14**, *i.e.*, an adduct of nitromethane (in aci-nitro form) to the cation **12**, which is easily hydrolysed to give ω -caprolactam.



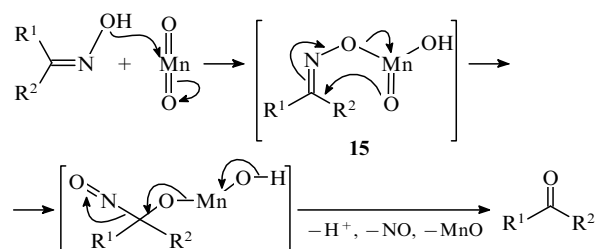
$[\text{Yb}(\text{OTf})_3]^{73}$ and $[\text{La}(\text{OTf})_3]^{74}$ appeared to be very efficient catalysts of the Beckmann rearrangement of some ketoximes. Unfortunately, the role of metal in this process was not discussed.

Analysis of the published data shows that the role of the metal in the metal-mediated Beckmann rearrangement is reduced to the dehydration of aldoximes, on one hand, and, on the other hand, to activation of the nitriles formed with respect to hydrolysis, which affords amides (for metal-mediated hydrolysis of nitriles, see a review ⁷⁵).

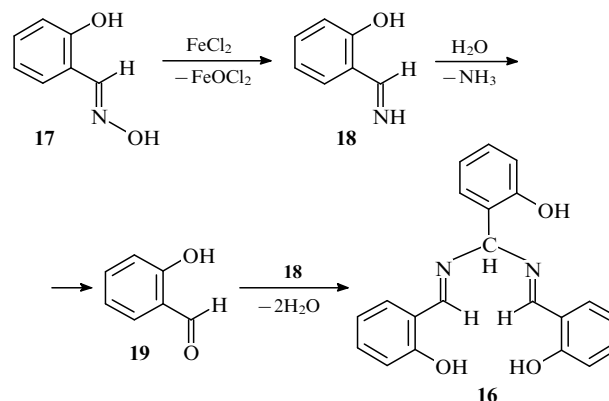
4. Reductive and oxidative deoxygenation

Among the methods for conversion of oximes into carbonyl compounds, reductive and oxidative deoxygenation are of the greatest interest, particularly, the reactions occurring in the presence of various metal compounds. These reactions are accompanied by changes in the oxidation state of the oxime nitrogen atom followed by hydrolytic cleavage of the C–N bond resulting in carbonyl compounds.

For instance, oxidation of various aldoximes and ketoximes in the presence of activated MnO_2 in aprotic solvents (dichloromethane, chloroform) proceeds under mild conditions (room temperature) and produces the corresponding carbonyl compounds in very high yields.⁷⁶ A plausible reaction mechanism involving the metal site was suggested. In the first step of the process, addition of an oxime to MnO_2 occurs to yield intermediate **15**, which then undergoes a [2,3]-sigmatropic shift followed by decomposition of the complex and formation of the carbonyl compound:



Reaction of ferrous chloride FeCl_2 with salicylaldoxime in the presence of triethylamine leading to the formation of the trinuclear complex $[\text{Fe}_3^{\text{III}}(\mu_3\text{-O})(\mu_2\text{-OPh})]^{6+}$ is an example of oxidative deoxygenation (see Ref. 77). The reaction proceeds in methanol in an atmosphere of argon. The formation of 2-[bis(salicylideneimino)methyl]phenol (**16**) is explained by reductive deoxygenation of the starting oxime **17** into the corresponding imine **18**, hydrolysis of the imine **18** to salicylaldehyde **19** and condensation of the latter with the imine **18** (the ratio **18**:**19** = 2:1).



Numerous experimental papers on the subject in question published before 2001 were thoroughly analysed in a review.⁷⁸ Therefore, only the data published after 2000 are discussed in the present review with indication of the oxidising agents used.

Quaternary heterocyclic halochromates $[\text{HetH}](\text{CrO}_3\text{X})$ (Het is pyridine, methylpiperidine, quinoline; X = Cl, F),^{79–85} $\text{Mg}(\text{HSO}_4)_2$ in the presence of wet SiO_2 ,⁸⁶ MnO_2 ,⁸⁷ $[\text{Cu}(\text{NH}_3)_4](\text{MnO}_4)_2$,⁸⁸ LnCl_3 ⁸⁹ and KMnO_4 ⁹⁰ were used as oxidants in the oxidative deoxygenation.

Reductive deoxygenation of oximes to the corresponding carbonyl compounds proceeds in high yield using a suspension of zinc powder in non-dried MeCN in the presence of tungsten(VI) and molybdenum(VI) chlorides.⁹¹

Microwave irradiation was shown to effect oxidative deoxygenation. For example, oximes are cleaved in the presence of BiCl_3 in refluxing THF in 10 h (the yield of ketones is 40%). The same reactions under microwave irradiation are completed in a few minutes and in high yields, which allows smooth conversion of even such a sterically hindered substrate as camphor oxime into the corresponding ketone.⁹²

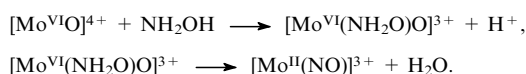
Thus, reductive and oxidative deoxygenation of oximes can be effected with various oxidants or reductive agents and can be used as a method of synthesis of carbonyl compounds.

5. Oxime-mediated nitrosylation of metals

In the previous Section, we discussed the method of synthesis of carbonyl compounds from oximes by reductive and oxidative cleavage of the oxime C=N bond with involvement of metal complexes. Nitroso complexes of metals formed upon oxidation of the oxime nitrogen atom are intermediates in these processes. In this Section, we present examples of obtaining stable metal nitroso complexes by splitting of oximes. We assume that these examples are complementary and, therefore, their discussion in one paper will provide more detailed understanding of the mechanism of the oxidative deoxygenation.

The possibility of application of oximes as nitrosylating agents was demonstrated by the synthesis of the molybdenum nitroso complex $[\text{Mo}(\text{acac})_2(\text{NO})\{\text{MeC}(\text{NH}_2)\text{NO}\}]$ by reaction of acetamideoxime $\text{MeC}(\text{NH}_2)=\text{NOH}$ with $[\text{MoO}_2(\text{acac})_2]$ in methanol at room temperature.⁹³ The structure of the complex was confirmed by X-ray diffraction analysis. Nitroso complexes were also obtained from acetone oxime and various Mo(VI) oxo complexes.⁹⁴ For instance, the complex $[\text{Mo}(\text{acac})_2(\text{NO})\{\text{Me}_2\text{C}=\text{NO}\}]$ was obtained by refluxing $[\text{MoO}_2(\text{acac})_2]$ with acetone oxime in methanol for 5.5 h. The formation of nitroso

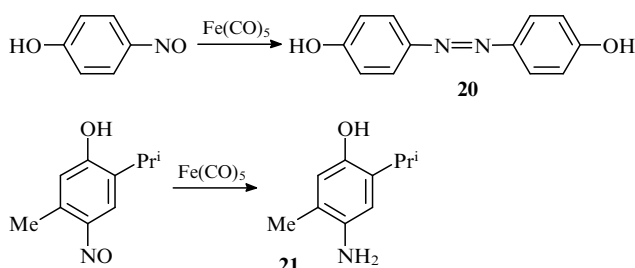
complexes in these reactions is explained⁹⁴ by hydrolytic splitting of acetone oxime to hydroxylamine followed by reductive nitrosylation of Mo(VI). The mechanism of reductive nitrosylation of molybdenum oxo complexes with hydroxylamine in water was studied in detail⁹⁵ and may be illustrated as follows:



The ruthenium(III) nitroso complex $[\text{NH}_4]_2[\text{RuCl}_5(\text{NO})]$ was prepared by reaction of various oximes (acetaldoxime, acetone oxime, cyclohexanone and cyclopentanone oximes) with $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$.^{96,97} The formation of the same product in all cases is explained by metal-mediated hydrolysis of oximes resulting in hydroxylamine and further disproportionation of the latter into nitrosyl and ammonium ion. High affinity of ruthenium to the nitrosyl ligand is yet another factor favouring the formation of the nitroso complexes.

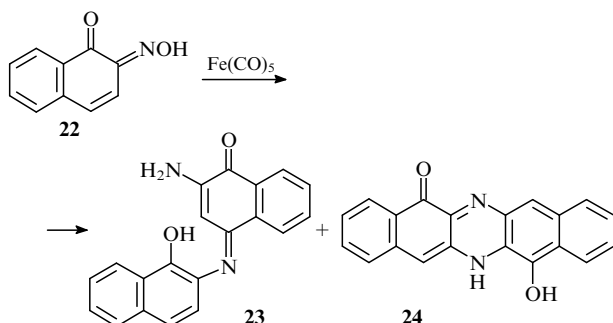
6. Reductive deoxygenation

Alper and Edward⁹⁸ have shown that the reaction of *p*-nitrosophenol (a tautomeric form of *p*-quinone monooxime) with $\text{Fe}(\text{CO})_5$ results in 4,4'-dihydroxyazobenzene (**20**). However, 2-isopropyl-5-methyl-4-nitrosophenol is converted into 4-amino-2-isopropyl-5-methylphenol (**21**) under the same conditions.



Later, the process of metal-mediated reductive deoxygenation of quinone and benzoquinone oximes in the presence of $\text{Fe}(\text{CO})_5$ (Ref. 99) or the trinuclear ruthenium carbonyl cluster $\text{Ru}_3(\text{CO})_{12}$ (Ref. 100) was studied in detail. In both cases, the reactions of quinone oximes with metal carbonyls were carried out in refluxing THF under argon.

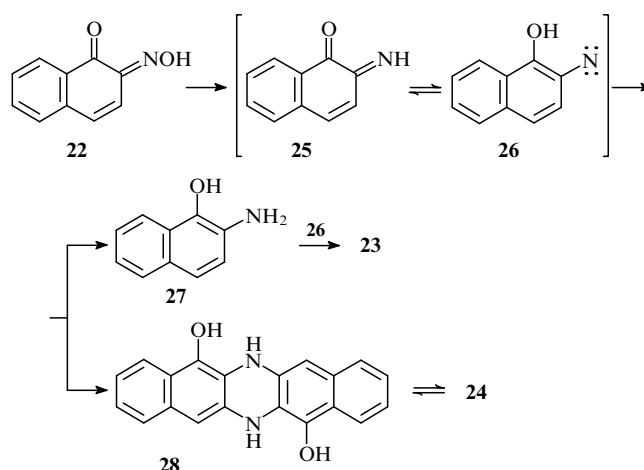
In the reaction of 1,2-naphthoquinone 2-oxime (**22**) with $\text{Fe}(\text{CO})_5$, 2-amino-*N*-(1-hydroxy-2-naphthyl)-1,4-naphthoquinone 4-imine (**23**) and 5-hydroxydibenzo[*b,i*]phenazin-12(6*H*)-one (**24**) were identified.



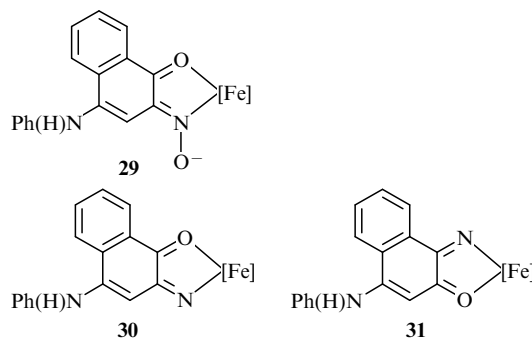
The formation of these products is explained⁹⁹ by conversion of the quinone oxime into a quinone imine **25** (as a result of deoxygenation) (Scheme 4) followed by possible formation of nitrene intermediate **26**, which is readily converted into aminonaphthol **26** (due to proton abstraction) or into dihydroxyphenazine derivative **28** (due to recombination).

Iron(II) quinone oximate complex **29** (the main product) and trace amounts of isomeric quinone imine complexes **31** and **31** are

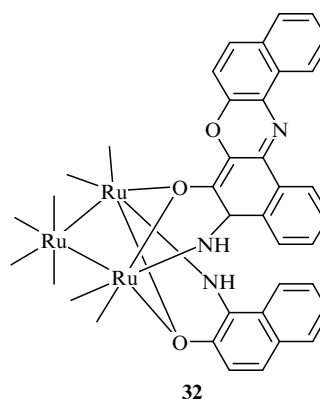
Scheme 4



formed alongside with compounds **23** and **24** in the presence of aniline.

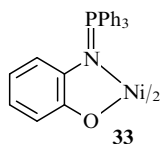


Mononuclear ruthenium naphthoquinone oximate complexes are the main products in similar reactions with $\text{Ru}_3(\text{CO})_{12}$.¹⁰⁰ In addition to these complexes, mixed-ligand cluster **32** was isolated in the case of 1,2-naphthoquinone 1-oxime.



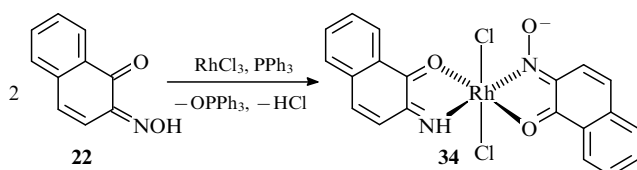
Presumably,¹⁰⁰ two types of ligands in the cluster **32** are formed as a result of deoxygenation of 1,2-naphthoquinone 1-oxime in the presence of $\text{Ru}_3(\text{CO})_{12}$, which yields a nitrene intermediate of the type **26**, and its further conversions, similar to those shown in Scheme 4.

Reactions of quinone oximate complexes of 3d metals [Cu(II), Ni(II), Zn(II) and Fe(III)] with PPh_3 and RNH_2 afford compounds similar to those described previously (see Scheme 4).^{101–105} It has to be noted, that in reactions with Cu(II) and Fe(III) complexes,¹⁰¹ only mixtures of unidentified products with low oxidation states of the metal sites have been obtained. Reaction of a Ni(II) quinone oximate complex with PPh_3 ¹⁰⁵ yields a triphenyl(*o*-hydroxyphenylimino)phosphorane complex **33**.



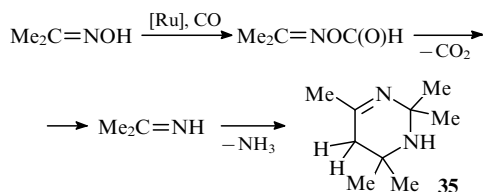
Ketoximes unable to tautomerise into nitroso-derivatives yield either the corresponding imines in reactions with $\text{Fe}(\text{CO})_5$,¹⁰⁶ or ketones.¹⁰⁷

The reaction of $\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$ with 1,2-naphthoquinone 2-oxime (**22**) in the presence of P- or N-donors (triphenylphosphine, pyridine or its 4-phenyl derivatives)¹⁰⁸ results in a mixture of Rh(III) complexes. Mixed-ligand complex **34** was isolated from this mixture and its structure was determined by X-ray crystallography.

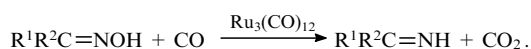


Steinborn *et al.*⁴¹ have found that the rhodium glyoximate $[\text{Rh}(\text{dmgH})_2(\text{PPh}_3)_2]^-$ (hereinafter referred to as $[\text{Rh}]^-$) (dmgH_2 is dimethylglyoxime) reacts with dihalomethanes CH_2X_2 ($\text{X} = \text{Br}, \text{Cl}$) producing both previously known compounds of the $[\text{Rh}]-\text{CH}_2\text{X}$ type and the new imino-oximate complexes $[\text{Rh}(\text{CH}_2\text{X})\{\text{ON}=\text{C}(\text{Me})-\text{C}(\text{Me})=\text{NH}\}(\text{dmgH})(\text{PPh}_3)]$. The complex $[\text{RhCl}_2(\text{dmgH})(\text{dmgH}_2)]$ reacts with trialkylphosphines in the presence of NaBH_4 to afford an imino-oximate complex $[\text{Rh}(\text{dmgH})(\text{bdioH})(\text{PR}_3)_2]\text{Cl}$ (bdioH is butane-2,3-dione 2-imine-3-oximate).¹⁰⁹ Unusually high resistance of the newly formed imine bond against hydrolysis has been noted.³⁹ The boron–technetium imino-oximate binuclear complex obtained in the reaction of $[\text{ReCl}_3(\text{NCMe})(\text{PPh}_3)_2]$ with dmgH_2 and $\text{EtB}(\text{OH})_2$ appeared to be stable as well. This binuclear complex was isolated using 1 M HCl.¹¹⁰ Reactions of salicylaldoximes with $[\text{RuCl}_2(\text{PPh}_3)_3]$ ¹¹¹ and $[\text{ReOCl}_3(\text{PPh}_3)_3]$ ¹¹² demonstrated a possibility of synthesising imino-oximate complexes.

Deoxygenation of ketoximes in the presence of catalytic amounts of the complex $[\text{Ru}_2(\text{CO})_4(\mu_2-\eta^2-\text{Me}_2\text{C}=\text{NO})_2] \cdot (\text{Me}_2\text{C}=\text{NOH})_2$ resulting in imines has been studied.¹¹³ 2,3,4,5-Tetrahydro-2,2,4,4,6-pentamethylpyrimidine (**35**), CO_2 and NH_3 are formed upon deoxygenation of acetone oxime with CO . A plausible mechanism of this process includes carbonylation of acetone oxime followed by decarboxylation of an unstable intermediate $\text{Me}_2\text{C}=\text{NOC}(\text{O})\text{H}$ to yield the imine $\text{Me}_2\text{C}=\text{NH}$. This undergoes trimerisation with elimination of NH_3 .



It was shown¹¹⁴ that, in the presence of $\text{Ru}_3(\text{CO})_{12}$, various ketoximes are converted (CO , 20 atm) into the corresponding ketimines in virtually 100% yield:



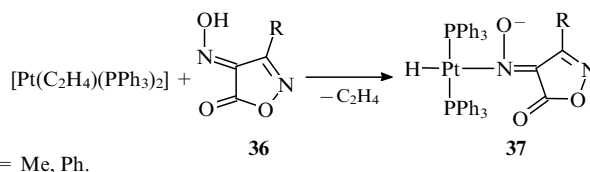
The mechanism of this process was not studied in detail. Taking into account the fact that *o*-benzylpropiophenone oxime and *o*-acetylacetophenone oxime are inactive in this reaction, it was suggested that the initial stage of the process is the reductive cleavage of the N–O bond.

7. Oxidative addition of oximes

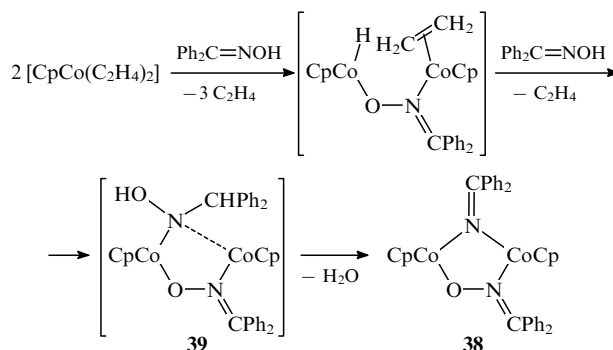
Oxidative addition of oximes to electron-rich metal sites may proceed with cleavage of both the O–H bond and the N–O bond resulting in complexes with bridging or monodentate ligands.

a. Oxidative addition of oximes as a result of the O–H bond cleavage

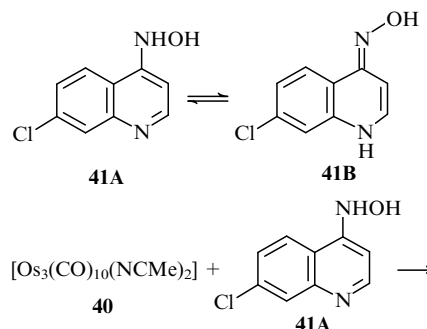
For the first time, the reaction of oxidative addition with cleavage of the O–H bond was performed by Beck and co-workers¹¹⁵ with heterocyclic oximes as examples. The platinum(0) complex $[\text{Pt}(\text{C}_2\text{H}_4)(\text{PPh}_3)_2]$ reacts with heterocyclic oxime **36** in toluene at room temperature yielding Pt(II) hydride-oximate complexes **37**. It has to be noted, that up to now this reaction is the only example of formation of monodentate N-coordinated oximate fragment in a complex formed as a result of the O–H bond cleavage.

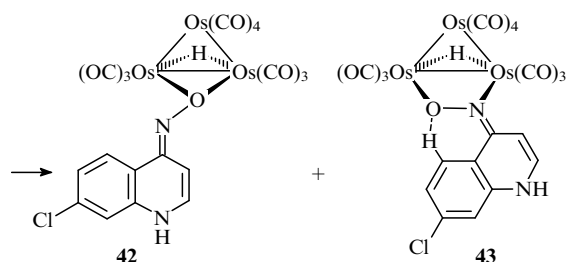


It was shown by Floriani and co-workers¹¹⁶ that the reaction of benzophenone oxime with the complex $[\text{CpCo}(\text{C}_2\text{H}_4)_2]$ in toluene at room temperature leads to the formation of the μ_2 -imidooximate cobalt cluster $[\{\text{CpCo}\}_2(\mu_2-\text{N}=\text{CPh}_2) \cdot (\mu_2-\text{ON}=\text{CPh}_2)]$ (**38**). The suggested reaction mechanism includes the following steps: oxidative addition of oxime to $\text{Co}(\text{I})$ with cleavage of the O–H bond, intramolecular nucleophilic addition of the hydride ion to the carbon atom of the second N-coordinated oxime moiety and dehydration of the intermediate **39** with formation of the complex **38**.



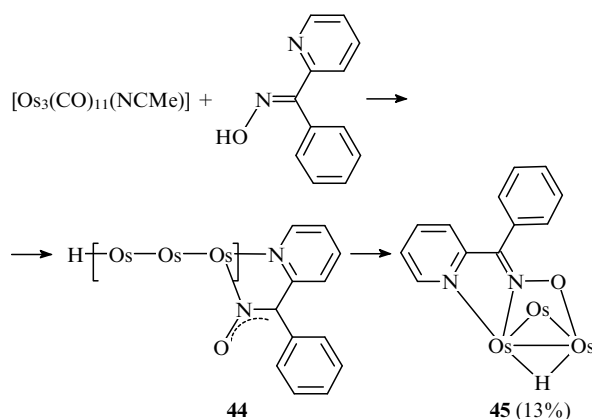
The reaction of the cluster $[\text{Os}_3(\text{CO})_{10}(\text{NCMe})_2]$ (**40**) with 7-chloro-4-(hydroxyamino)quinoline (**41**) existing in two tautomeric forms **A** and **B**, in a mixture of dichloromethane and acetone at room temperature produces the clusters $[\text{Os}_3(\mu_2-\text{H})(\mu_2-\eta^1-\text{OC}_9\text{H}_6\text{N}_2\text{Cl})(\text{CO})_{10}]$ (**42**) and $[\text{Os}_3(\mu_2-\text{H})(\mu_2-\eta^2-\text{ONC}_9\text{H}_6\text{NCl})(\text{CO})_{10}]$ (**43**) in 37% and 23% yields, respectively.¹¹⁷ The complex **42** is completely converted into the complex **43** when kept in acetone for two days at room temperature.



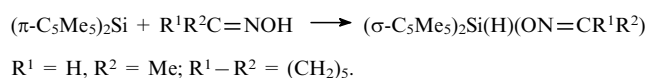


Acetone oxime reacts with the cluster **40** in the same way.¹¹⁸ The formed hydride-oximate complex $[\text{Os}_3(\mu_2\text{-H})(\mu_2\text{-ON}=\text{CMe}_2)(\text{CO})_{10}]$ isomerises into the hydroxo-imide complex $[\text{Os}_3(\mu_2\text{-OH})(\mu_2\text{-N}=\text{CMe}_2)(\text{CO})_{10}]$ on refluxing in octane. It was suggested¹¹⁸ that isomerisation proceeds with formation of the oxime intermediate $[\text{Os}_3(\mu_2\text{-HON}=\text{CMe}_2)(\text{CO})_{10}]$ (of the type **43**) in which the N–O bond cleavage takes place as a result of oxidative addition. This type of oxidative addition of oximes will be discussed in detail in the next Section of the review.

2-Benzoylpyridine oxime reacts with another osmium cluster $[\text{Os}_3(\text{CO})_{11}(\text{NCMe})]$ in dichloromethane at 25 °C yielding the complex $[\text{Os}_3\text{H}(\text{CO})_{11}\{\eta^2\text{-ON}=\text{CPh}(\text{NC}_5\text{H}_4)\}]$ (**44**) (carbonyl groups in formulas **44** and **45** below are omitted). Another cluster $[\text{Os}_3(\mu_2\text{-H})(\text{CO})_9\{\mu_2\text{-}\eta^3\text{-ON}=\text{CPh}(\text{NC}_5\text{H}_4)\}]$ (**45**) was obtained by refluxing the complex **44** for 3 h in toluene under argon.¹¹⁹



Oximato-silane complexes were obtained by heating $(\pi\text{-C}_5\text{Me}_5)_2\text{Si}$ with $\text{R}^1\text{R}^2\text{C}=\text{NOH}$ in toluene for several hours at 60 °C:¹²⁰



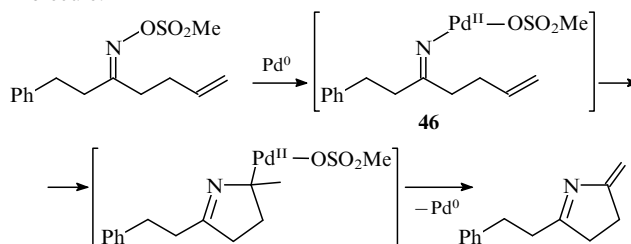
b. Oxidative addition of oximes with cleavage of the N–O bond

The first example of oxidative addition of acetone oxime to the rhodium complex *trans*- $[\text{ReCl}(\text{N}_2)(\text{dppe})_2]$ with cleavage of the N–O bond was described in 1998.¹²¹ The reaction was carried out in THF in the presence of TiHSO_4 . The hydroxo-complex *trans*- $[\text{Re}(\text{OH})(\text{NCMe}_2)(\text{dppe})][\text{HSO}_4]$ was obtained upon addition of the oxime to the Re(I) complex. Later, other oximes $\text{R}^1\text{R}^2\text{C}=\text{NOH}$ [$\text{R}^1 = \text{H}; \text{R}^2 = \text{Me}, \text{Ph}; \text{R}^1\text{--R}^2 = (\text{CH}_2)_4, (\text{CH}_2)_5$] were introduced in reactions with this complex.¹²²

Afterwards, Tillack *et al.*¹²³ have shown that reactions of titanocene derivatives with *O*-silylated oximes $\text{R}^1\text{R}^2\text{C}=\text{NOSiMe}_3$ [$\text{R}^1 = \text{R}^2 = \text{Me}, \text{R}^1\text{--R}^2 = (\text{CH}_2)_5$] in refluxing hexane for 5 h resulted in complexes $[\text{Cp}_2\text{Ti}(\text{N}=\text{CR}^1\text{R}^2)(\text{OSiMe}_3)]$ in 45% and 50% yields, respectively.

The oxidative addition of oxime derivatives to palladium catalysts was used to synthesise key intermediates in the preparation of various heterocycles.^{124–127} Thus unsaturated *O*-substituted ketoximes are converted into various nitrogen heterocycles (pyrroles, pyridines, isoquinolines, spiroimines and azaazulenes) on heating in DMF (110 °C, 30 min) in the presence

of catalytic amounts of $\text{Pd}(\text{PPh}_3)_4$ and triethylamine. It was suggested that these reactions occur *via* alkylideneaminopalladium intermediate of the type **46** (as a result of oxidative addition of the oxime to Pd^0) followed by intramolecular amination (similar to the Heck reaction) of the alkene fragment of the molecule.^{124–127}



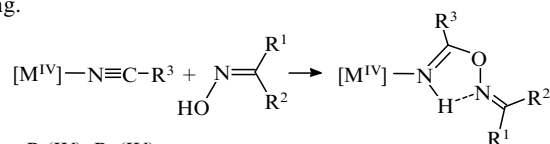
Thus, oxidative addition of oximes to a metal site, which occurs with cleavage of the O–H or N–O bond (depending on the character of the metal), may result in both hydride-oximate (N- or O-coordinated) and hydroxoalkylideneamine metal complexes.

III. Reaction with retention of the C = NOH fragment

1. Nucleophilic addition of oximes to multiple bonds

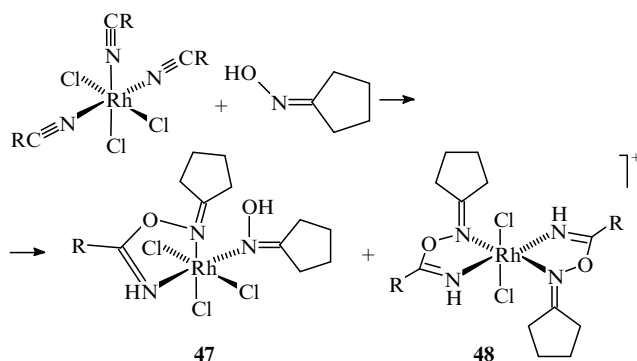
a. Metal-mediated addition reactions of oximes to nitriles

Vast amount of experimental data are known to date concerning metal-mediated nucleophilic addition of oximes to nitriles with formation of iminoacyl ligands.^{18, 19, 128} Reactions of nitrile complexes of metals in higher oxidation states $[\text{Pt}(\text{IV})]$,^{129–134} $[\text{Re}(\text{IV})]$ ¹³⁵ with various oximes in aprotic media (nitriles, chloroform, CH_2Cl_2) are highly selective and result in monodentate N-coordinated iminoacyl derivatives in high yields. *E*-Isomers of iminoacyl ligands are stabilised by an intramolecular hydrogen bond between the hydrogen atom of the imine and the nitrogen atom of the acyl fragment with formation of a 5-membered N–H–ring.



In these reactions, the metal centre activates the carbon atom of the nitrile ligand and then stabilises the coordinated imine formed.

In contrast to $\text{Pt}(\text{IV})$ and $\text{Re}(\text{IV})$ nitrile complexes, a $\text{Rh}(\text{III})$ nitrile complex, *viz.*, *mer*- $[\text{RhCl}_3(\text{NCR})_3]$, reacts with oximes (for example, with cyclopentanone oxime) yielding rhodium(III) *N,N*-mono- (**47**) and *N,N*-bis-chelate (**48**) iminoacyl complexes.¹³⁶



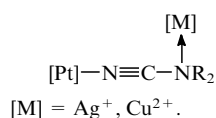
Bis-chelate complexes **48** were also obtained by a reaction of *mer*- $[\text{RhCl}_3\{\text{HON}=\text{C}(\text{CH}_2)_4\}_3]$ with acetonitrile in ethanol.³⁸ Previously, similar chelate iminoacyl compounds were formed on refluxing oxo-vanadium salicylaldoximate complex $[\text{VOL}_2]$

$$\text{PdCl}_2 + \text{R}^1\text{R}^2\text{C}=\text{NOH} \xrightarrow{\text{R}^3\text{CN}} \text{Product}$$

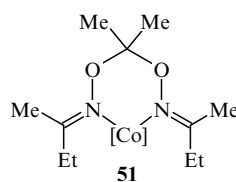
$$\begin{array}{ccc}
 \left[\begin{array}{c} \text{R}^3 \\ \diagup \\ \text{C} \equiv \text{N} \\ \diagdown \\ \text{OH} \end{array} \right] & \longrightarrow & \begin{array}{c} \text{H} \\ \diagup \\ \text{N} \\ \diagdown \\ \text{O} \end{array} \\
 \text{[M]} & & \text{[M]} \\
 \text{R}^1 \text{---} \text{C} \text{---} \text{R}^2 & & \text{R}^1 \text{---} \text{C} \text{---} \text{R}^2
 \end{array}$$

49 **50**

Platinum(II) cyanamide complexes, viz., *cis*-[PtCl(N≡CNR³)₂(PPh₃)₂][BF₄] and *cis*-[Pt(N≡CNR³)₂(PPh₃)₂].[BF₄]₂, react with oximes in the presence of Ag⁺ or Cu²⁺ salts (CH₂Cl₂, 20–25 °C) to form azametallacycles [Pt(NH=C(NR³)).ON=CR¹R²)(PPh₃)₂][BF₄]₂.¹⁴⁰ The oxime-cyanamide intermediate *cis*-[Pt(N≡CNET₂)(HON=CR¹R²)(PPh₃)₂][BF₄]₂ was isolated at R³ = Et, which serves as indirect evidence for the above-mentioned mechanism of formation of chelate iminoacyl complexes. It was suggested¹⁴⁰ that the Ag⁺ or Cu²⁺ ions favour additional electrophilic activation of the carbon atom of the cyanamide group and allow this reaction to take place even in the case of relatively inert Pt(II) complexes.

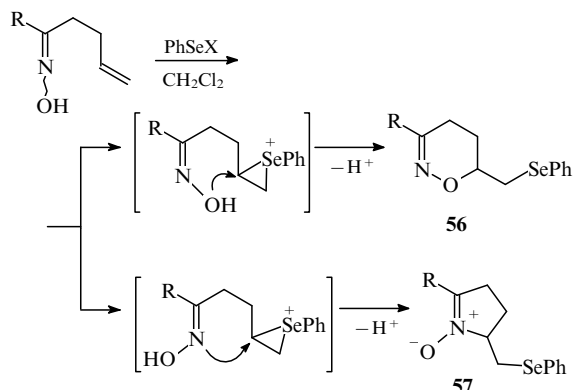


Complex **51** was obtained in the reaction of $\text{CoI}_2 \cdot 2\text{H}_2\text{O}$ with an excess of butan-2-one oxime in dry acetone in the presence of trimethyl orthoformate and its structure was determined by X-ray crystallography.¹⁴⁴

[illegible]

The intramolecular cyclisation of unsaturated alkenyl- and allenyl-oximes resulting in heterocyclic compounds (oxazoles and oxazines) and cyclic nitrones is one of the best studied and often employed reactions of this type. Thus it was shown^{146, 147} that α,β -unsaturated oximes $\text{HON}=\text{CR}^1-\text{CR}^2=\text{CR}^3\text{H}$ ($\text{R}^1 = \text{R}^3 = \text{Ph}$, $\text{R}^2 = \text{H}$; $\text{R}^1 = \text{Bu}^t$, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{Ph}$; $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{Me}$, $\text{R}^3 = \text{Pr}^i$) were converted into the corresponding isoxazoles by refluxing in benzene in the presence of equimolar amount of $[\text{PdCl}_2(\text{PPh}_3)_2]$ and a fivefold excess of NaOPh . Presumably,^{146, 147} a Pd σ,π -oxime complex, in which the palladium centre is linked to the nitrogen atom and the ethylene fragment, is formed in the initial stage of the reaction. The electrophilically activated $\text{C}=\text{C}$ bond then undergoes intramolecular nucleophilic attack by the oxygen atom of the oxime moiety resulting in closure of the isoxazole ring.

Depending on the configuration, γ -alkenyl oximes are converted into either 1,2-oxazines **56** or cyclic nitrones **57** in the presence of selenium compounds PhSeX (X = Cl, Br) at room temperature in acetonitrile or dichloromethane.^{148, 149}

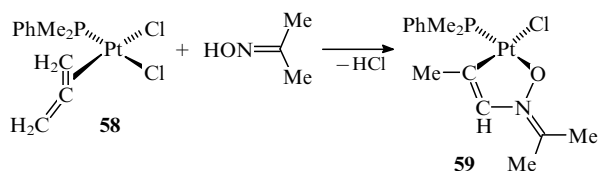


The structure of the final products depends on the spatial configuration of the starting oximes. The O-nucleophilic attack on the carbon atom of the C=C bond takes place in the case of *E*-isomers; in the case of *Z*-isomers, N-nucleophilic attack occurs.

Cyclic nitrones are also formed from *Z*-isomers of γ -alkenyl oximes in the presence of mercury(II) acetate in THF at 25 °C¹⁵⁰ as well as from *E*-isomers of δ -unsaturated oximes upon refluxing in THF in the presence of PdCl₂ or [PdCl₂(NCMe)₂].¹⁵¹ Allenic oximes are converted into unsaturated cyclic nitrones in high yields at room temperature in dichloromethane in the presence of Ag⁺.¹⁵²

Various oximes are converted into oxime ethers or cyclic nitrones in the presence of catalytic amounts of the complex [Pd(PPh₃)₄] or a system of reagents Pd(NO₃)₂–PPh₃ (1 : 4) as a result of intermolecular nucleophilic addition (O- or N-) to butadiene.¹⁵³ Presumably,¹⁵³ electrophilic activation of butadiene is a result of formation of a palladium π -allyl intermediate.

The reaction product of coordinated allene in *cis*-[PtCl₂(C₃H₄)(PMe₂Ph)] (**58**) with acetone oxime is the only example known so far of a stable complex obtained upon nucleophilic addition of the oxime to the C=C bond.¹⁵⁴

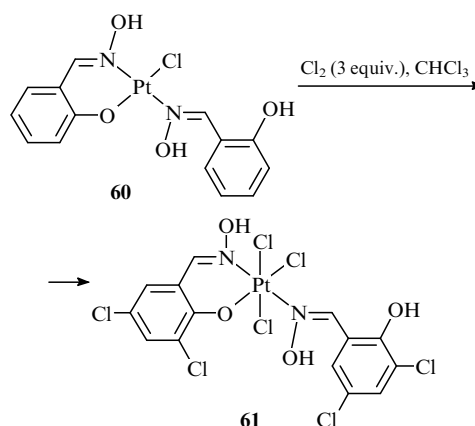


Allene electrophilically activated by coordination to Pt undergoes intramolecular nucleophilic attack by the nitrogen atom of the O-coordinated oximate ligand, which is accompanied by 1,3 prototropic shift and closure of a five-membered C,O-chelate ring giving rise to complex **59**.

2. Reactions of peripheral groups in oxime- and oximate complexes

Peripheral groups of coordinated ligands may undergo different transformations; such reactions are well known in coordination chemistry. However, there are very few examples of such processes in the chemistry of oxime and oximate complexes. These will be discussed in this Section.

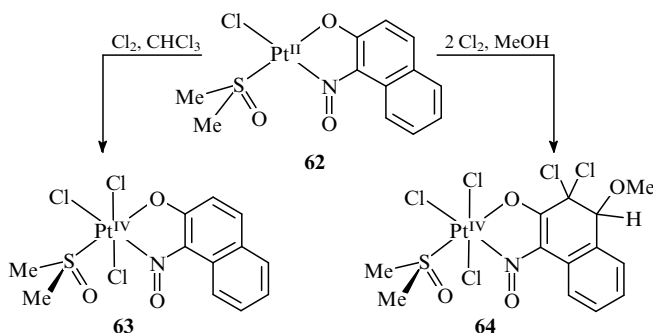
Chlorination of various platinum(II) salicylaldoximate complexes was studied in detail.^{155, 156} Thus chlorination of oxime-oximate complex **60** afforded the complex *trans*-(N,N)-[PtCl₃(3,5-Cl₂-2-OC₆H₂CH=NOH)(3,5-Cl₂-2-HOC₆H₄CH=NOH)] (**61**); its structure was determined by X-ray crystallography.



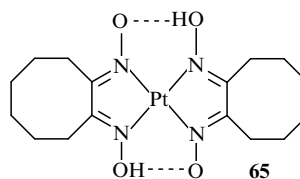
Other platinum(II) salicylaldoximate complexes, *e.g.*, the bis-chelate complex [Pt(*o*-OC₆H₄CH=NOH)₂]¹⁵⁷ and mixed-ligand complexes *trans*-(S,N)-[PtCl₂(*o*-HOC₆H₄CH=NOH)(Me₂SO)]·H₂O and *trans*-(S,N)-[PtCl(*o*-OC₆H₄CH=NOH)(Me₂SO)]¹⁵⁵ undergo similar transformations upon chlorination. The reactions of these complexes with an excess of Cl₂ are selective: the chlorine atoms in the products occupy *ortho*- and *para*-positions of the benzene ring relative to the OH group. Conversely, the chlorination of non-coordinated salicylaldoxime is non-selective and results in a large number of products.

Chlorination of complex **62** with an excess of Cl₂ in chloroform at room temperature yielded complex **63**. The same reaction in methanol afforded complex **64** in 24% yield.

Chlorination of non-coordinated 1,2-naphthoquinone 1-monoxime under the same conditions resulted in the corresponding methoxylated oxime in less than 3% yield. This suggests that the methoxylation is metal-mediated.¹⁵⁷ The following mechanism of formation of the complex **64** was suggested: oxidation of Pt(II) into Pt(IV), chlorination of the naphthalene fragment and subsequent methoxylation.



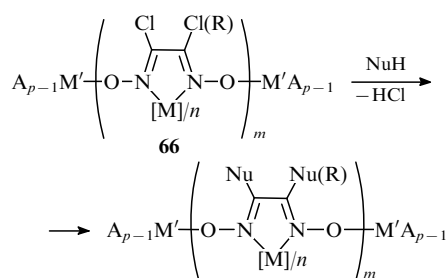
Chlorination of the platinum(II) bis-oximate chelate complex [Pt^{II}{C₈H₁₂(=NO)₂H₂}] (**65**) with PhICl₂ in CH₂Cl₂ produces the platinum(III) binuclear complex [Pt^{III}Cl{C₈H₁₂(=NO)₂H₂}]₂, which is converted into [Pt^{IV}Cl₂{C₈H₁₂(=NO)₂H₂}]₂ under the action of an excess of PhICl₂.¹⁵⁹



Oxidation of the platinum(II) *cis*- and *trans*-acetone oxime complexes [PtCl₂(Me₂C=NOH)₂] with excess chlorine in CHCl₃ yields [Pt(IV)Cl₄(Me₂C=NOH)₂].¹⁶⁰ In both cases,^{159, 160} chlorination affects only the platinum site with retention of the oxime and oximate ligands.

Thus, in spite of different chlorination conditions (different solvents and chlorinating agents) and various starting Pt(II) complexes, the oxime fragment was not changed upon chlorination. The metal site serves in all these reactions as a protecting group, which prevents the Piloty reaction¹⁵⁸ (chlorination of 'free' oximes) and/or oxidative deoxygenation (see Section II.4).

Voloshin *et al.*^{161–172} have shown that functionalisation (change of peripheral environment) of clathrochelate complexes with encapsulated metal ions (Fe^{2+} , Co^+ , Co^{2+} , Co^{3+} , Ru^{2+}) follows two principal pathways, *viz.*, incorporation of a substituent (*e.g.*, a chlorine atom) into chelating edge fragments of the cage (edge functionalisation) and substitution in tripod linking fragments. In the case of edge functionalisation of the macrobicyclic cage framework, the substituent and encapsulating metal site have substantial electronic and spatial impacts on each other, which are especially strong in the case of polyenic clathrochelate complexes of transition metals with a conjugated system of π -bonds in the chelating fragments. The presence of a system of σ - and π -bonds provides effective transfer of both inductive and mesomeric effects of functional substituents to the encapsulated metal ion. For instance, the presence of reactive chlorine atoms in molecules of tris-dioximate clathrochelates **66** enables their further functionalisation under mild conditions in the nucleophilic substitution with various H-nucleophiles (NuH) and synthesis of compounds with predetermined properties.



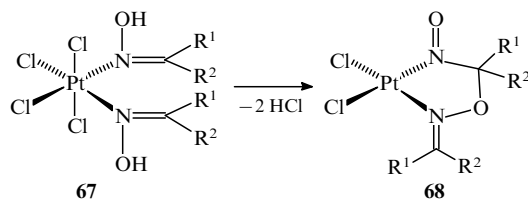
$M = \text{Fe}^{2+}$, Co^+ , Co^{2+} , Co^{3+} , Ru^{2+} ; $M' = \text{B}^{3+}$, Sn^{4+} ;
 $R = \text{Me}$; $A = \text{F}$, Bu^n , Ph ; NuH — O-, S- and N-nucleophiles.

Chemically stable cage structures with pendent substituents, highly biologically active materials,¹⁷³ new liquid-crystalline systems,¹⁷² luminescent labels¹⁷⁴ and selective reagents for sequencing of nucleic acids¹⁶⁸ have been synthesised by this method.

IV. Miscellaneous oxime reactions involving metal complexes

The reactions of oximes that do not comply with the classification used in the previous Sections are discussed in this Section.

Oxidation of platinum(II) oxime complexes *cis*-[PtCl₂·(R¹R²C=NOH)₂] with chlorine in CHCl₃ yields the platinum(IV) coordination compounds *cis*-[PtCl₄(R¹R²C=NOH)₂] (**67**), which are spontaneously converted into platinum(II) chelate derivatives [PtCl₂{N(=O)CR¹R²ON=CR¹R²}] (**68**) on storage in aqueous acetone for 3 h.

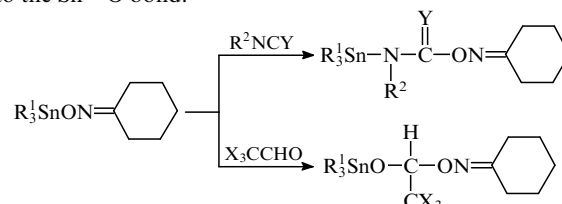


$R^1 = R^2 = \text{Me}$; $R^1 - R^2 = (\text{CH}_2)_4, (\text{CH}_2)_5$.

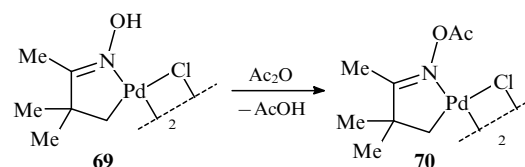
Complexes [PtX₂{N(=O)CR¹R²ON=CR¹R²}] isostructural to the complex **68** were obtained in the reaction of *trans*-[PtX₂(R¹R²C=NOH)₂] [X = Cl, Br; R¹ = R² = Me; R¹ - R² = (CH₂)₄, (CH₂)₅] with *m*-chloroperoxybenzoic acid in DMF at 40 °C.¹⁷⁵ While the formation of the chelate **68** is a result

of intramolecular two-electron redox interaction between Pt(IV) and the nitrogen atom of the oxime ligand, the formation of its isostructural analogue in DMF (see Ref. 175) occurs as an intermolecular oxidation of the nitrogen atom of the coordinated oxime with *m*-chloroperoxybenzoic acid.

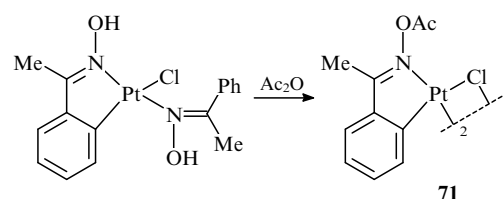
Reactions of *O*-trialkylstannyl oximes with alkyl and aryl isocyanates, their thia analogues and aldehydes result in compounds that can formally be regarded as the insertion products into the Sn—O bond.¹⁷⁶



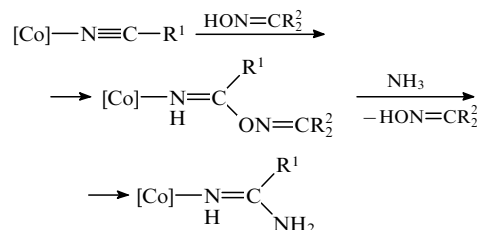
Refluxing of the palladium(II) dimeric bridged oxime complex [Pd(μ-Cl)(CH₂CMe₂CMe=NOH)]₂ (**69**) in acetic anhydride yields complex **70** with an *O*-acylated oxime.¹⁷⁷



A platinum(II) dimeric bridged complex **71**, *viz.*, [Pt(μ-Cl)·{*o*-C₆H₄C(Me)=NOAc}]₂ containing an *O*-acylated oxime fragment was obtained by refluxing [PtCl{*o*-C₆H₄C(Me)=NOH}·(HON=CPhMe)] in acetic anhydride for 1 h.¹⁷⁸



Reactions of nitriles with ketoximes in the presence of salts of 3d metals were studied.^{179–182} Thus nitriles R¹CN are converted into the corresponding amidines at 50 °C in 8 h on treatment with ketoximes R₂C=NOH in the presence of Co(NO₃)₂·6 H₂O in a molar ratio of 4:1. These amidines were isolated as nitrates [R¹C(=NH₂)NH₂](NO₃).¹⁷⁹ In the case of acetonitrile, a stable intermediate [Co(NCMe)₂(H₂O)₄](NO₃)₂ was isolated and structurally characterised. Acetic acid, which is a product of the two-step hydrolysis of the nitrile, was also detected. A suggested¹⁷⁹ reaction mechanism is based on iminoacylation of a nitrile (see Section III.1.a) coordinated to Co(II) followed by intermolecular nucleophilic attack of NH₃ on the imidate carbon atom (a product of two-step hydrolysis of R¹CN) and amidine formation.

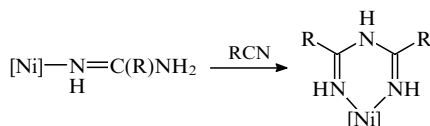


$R^1 = \text{Me}$, Et , Pr^n , Bu^n ; $R_2 = \text{Me}_2$, $(\text{CH}_2)_5$.

Catalytic hydrolysis of nitriles into the corresponding carboxamides R¹C(O)NH₂ was performed in the presence of a system ZnX₂ - R₂C=NOH [X = Cl, NO₃, CF₃SO₃; R₂ = Me₂, (CH₂)₄, (CH₂)₅; the molar ratio of the zinc salt to oxime being equal to

1:4].¹⁸⁰ The highest efficiency was achieved in the hydrolysis of *p*-methoxyphenylacetone nitrile in the presence of a system $\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O} - \text{Me}_2\text{C}=\text{NOH}$. In this case, the turnover number of the catalyst was equal to 1000. A zinc(II) oxime complex $[\text{Zn}(\text{NO}_3)_2(\text{Me}_2\text{C}=\text{NOH})_2]$ was the only stable intermediate isolated in the process. Presumably,¹⁸⁰ the formation of an imine complex $[\text{Zn}] - \text{NH}=\text{C}(\text{R}^1)\text{ON}=\text{CR}_2^2$ is the first step of the putative mechanism of the process. Hydrolysis of the imino-ligand into carboxamide in the coordination sphere of zinc and recovery of the catalyst due to hydration of the complex complete the catalytic cycle.

The nickel(II) imidoamidinate complexes $[\text{Ni}\{\text{NH}=\text{C}(\text{R}).\text{NHC}(\text{R})=\text{NH}\}_2]^{2+}$ (see¹⁸¹) were obtained in high yields (65%–91%) by refluxing $\text{NiCl}_2 \cdot 2\text{H}_2\text{O}$ in nitrile solvents in the presence of acetone oxime. As in the two previously described cases (see^{179,180}), the plausible mechanism of the reaction includes the formation of an $[\text{Ni}] - \text{NH}=\text{C}(\text{R})\text{ON}=\text{CMe}_2$ intermediate, which hydrolyses later with elimination of NH_3 . Ammonia formed reacts with another coordinated nitrile to give amidine. Nucleophilic addition of this amidine to the ligand RCN results in nickel imidoamidinate complexes.



A novel efficient method for the synthesis of industrially important symmetrical (**72**) and asymmetrical phthalocyanines and their complexes with Ni(II), Cu(II), Zn(II) and Cd(II) by reactions of substituted phthalocyanines **73** with the corresponding metal chlorides in the presence of an oxime $\text{Me}(\text{R}^2)\text{C}=\text{NOH}$ (Scheme 5, path *a*) was proposed.¹⁸²

Chelate **74** was obtained by refluxing $\text{NiCl}_2 \cdot 2\text{H}_2\text{O}$ in acetone for 24 h in the presence of an oxime and various phthalonitrile derivatives (the molar ratio oxime:phthalonitrile = 2:1). Complex **74** is the nucleophilic addition product of two oxime

molecules to one nitrile group (Scheme 5, path *b*) and this is the first example of such type of metal-mediated reactions of oximes. Nickel phthalocyanines **72** ($\text{M} = \text{Ni}$) can be obtained under 'mild' conditions (refluxing in methanol, 24 h) and in high yields (~60%) when complex **74** is used as a phthalogen (Scheme 5, path *c*).

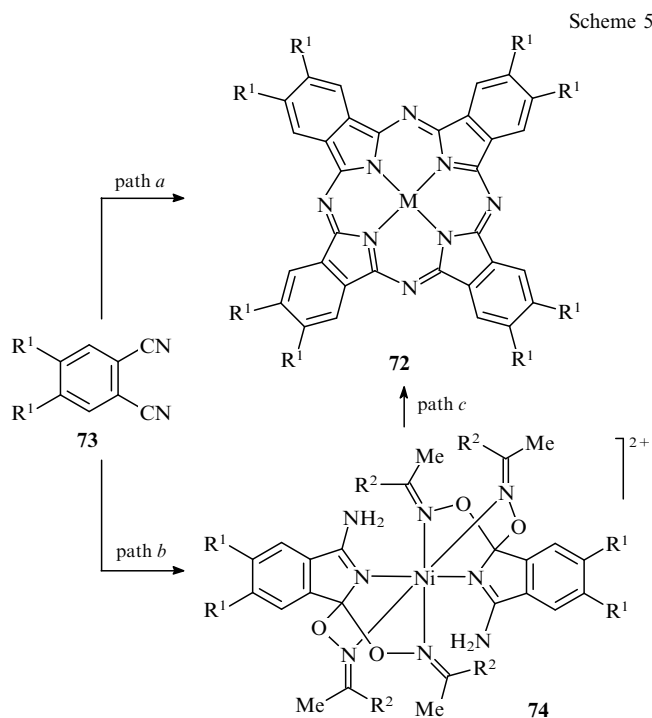
V. Conclusion

The data discussed in the present review on metal-mediated and metal-catalysed reactions of free and coordinated oximes and their derivatives show that nowadays the development of new methods of organic synthesis and design of new models for the interpretation of mechanisms of catalytic processes are in the focus of attention. Particularly, methods of dehydration and reductive deoxygenation of aldioximes in the presence of metal complexes giving nitriles in high yield have been developed; new reactions of oxidative and reductive deoxygenation resulting in carbonyl compounds have been discovered. The search for efficient catalysts of the Beckmann rearrangement is underway. It appeared that application of various rhenium(VII) derivatives allows smooth conversion of cyclohexanone oxime into industrially important ω -caprolactam. A new catalytic method of hydration of nitriles into amides in the presence of oximes and zinc nitrate as well as simple and inexpensive method of amidine synthesis from oximes and cobalt(II) nitrate in nitrile media were developed. A new efficient method for the synthesis of industrially important symmetrical and asymmetrical metal phthalocyanines by reactions of various phthalonitriles with an excess of oximes in the presence of Ni(II), Cu(II), Zn(II) and Cd(II) chlorides has been found.

Significant attention is still paid to metal-mediated reactions of oximes resulting in new ligand systems: loss of integrity of the $\text{C}=\text{NOH}$ fragment in reactions of reductive deoxygenation of oxime ligands leads to mixed-ligand imine-oxime complexes. New methods of synthesis of nitrile complexes of W, Ru and Os by dehydration of the starting oxime adducts as a result of cleavage of the $\text{N}-\text{O}$ bond of the oxime fragment are developed. Stable nitroso complexes of Mo(VI) and Ru(III) are obtained by hydrolytic and redox processes in aqueous media. Reactions of oxidative addition of oximes to electron-rich sites resulting in imide-oximate or hydride-oximate ligands have been studied. Hydroxo-alkylideneamine ligands, generated by oxidative cleavage of the $\text{N}-\text{O}$ bond, are regarded as the key intermediates of the palladium-catalysed Heck reaction in the synthesis of heterocycles. New types of imino-ligands have been synthesised by nucleophilic addition of oximes to coordinated nitriles. Depending on the character of the metal, either monodentate N-coordinated molecular complexes or N,N-chelate products are formed. Nickel(II) imidoamidinate chelates or phthalocyanines are obtained in oxime–nitrile template transformations in the presence of nickel(II) chloride.

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- (a) MX_2 [$\text{M} = \text{Ni(II)}, \text{Cu(II)}, \text{Zn(II)}, \text{Cd(II)}$]; 4 equiv. of $\text{Me}(\text{R}^2)\text{C}=\text{NOH}$ ($\text{R}^2 = \text{Me}, \text{Et}$);
 (b) $\text{NiCl}_2 \cdot 2\text{H}_2\text{O}$, boiling in Me_2CO , $\text{Me}(\text{R}^2)\text{C}=\text{NOH}$;
 (c) $\text{R}_2\text{C}_6\text{H}_2(\text{CN})_2$, boiling in MeOH , 24 h.

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^a — *Russ. J. Gen. Chem. (Engl. Transl.)*

^b — *Russ. J. Inorg. Chem. (Engl. Transl.)*

^c — *Russ. J. Coord. Chem. (Engl. Transl.)*

^d — *Dokl. Chem. (Engl. Transl.)*

^e — *Russ. Chem. Bull., Int. Ed. (Engl. Transl.)*

Multisensor systems of the electronic tongue type as novel opportunities in design and application of chemical sensors

Yu G Vlasov, A V Legin, A M Rudnitskaya

Contents

I. Introduction	125
II. Multisensor systems	125
III. Certain analytical applications of multisensor systems of the electronic tongue type	129
IV. Conclusion	131

Abstract. The main types of modern multisensor systems of the electronic tongue type as well as the sensitive materials and sensors (transducers) employed in such systems are considered. The most commonly used analytical applications of the electronic tongue including recognition and classification of various liquid media, quantitative analysis, process monitoring and taste assessment of foodstuffs are discussed. The bibliography includes 84 references.

I. Introduction

A challenge for the development of new analytical methods and instruments consists of the quest for the highest possible selectivity with respect to a given component or components. To meet this goal, a great number of electrochemical (particularly, potentiometric) sensors such as ion-selective electrodes (ISE), ion-selective field transistors (ISFT), *etc.* were developed. The first multisensor systems, as well as many systems of the electronic tongue type proposed to date, are based on the use of ISE or sensors of a similar nature.^{1,2} This is why the way from individual sensors to the electronic tongue is traced in the present review by the example of ISE, although many arguments are equally valid for other types of chemical sensors.³

The first potentiometric chemical sensor, *viz.*, the ion-selective electrode with an oxide glass membrane, was proposed for the determination of the activity of hydrogen ions in aqueous solutions.⁴ Later, a great number of various membrane materials for ISE were developed, *viz.*, oxide glass, single crystals, pressed polycrystalline blends of inorganic active components, liquid and plasticised organic polymeric compositions containing ion-exchange resins or neutral carriers, chalcogenide glass (for the determination of heavy metal ions). The membrane materials were used in both bulk sensors and various thin-film electrodes and microsenors. For the comprehensive description of the existing ISE and sensors of other types, see books and reviews.^{4–9}

Short time of analysis, the possibility of miniaturisation of instruments and automation of the procedure as well as the simplicity and rather low cost of sensors make them an attractive

tool for the analysis of solutions. The use of ISE for these purposes is limited, as a rule, to the cases where the concentrations of interfering ions are low and the electrode response is described by the Nernst equation. In addition, the use of ISE for the analysis of real objects is often hampered due to the insufficient selectivity with respect to the detected ion in the presence of other substances.

The most impressive progress in the field of sensor materials is associated with the synthesis of new organic substances employed as ionophores in polymeric plasticised membranes. However, it is the glass pH-electrode that still possesses the highest selectivity and is most popular, because the use of other sensors based on other detection principles often faces the same problem of insufficient selectivity in multicomponent media, which hinders their analytical application. The development and application of multisensor systems of the electronic tongue type offers a possible way towards the solution of this problem.

II. Multisensor systems

1. The role of biology and chemometrics in the development of multisensor systems

Two fields of knowledge had the greatest effect on the development of multisensor systems. These are, on the one hand, the new achievements in biology, namely, understanding of the structure and operation of the human sensory system, and, on the other hand, the new possibilities and approaches to the processing of multidimensional data that were proposed within the framework of chemometrics.

The development of chemical multisensor systems was largely an attempt to mimic the structure and properties of biological sensory systems, namely, the mammalian olfaction and taste systems.¹⁰ Initially, such an approach was realised in gas analysing systems, *i.e.*, electronic noses; later, similar principles were used for the development of liquid analysers — electronic tongues. In the course of evolution, olfaction became the most efficient sensory system due to the high sensitivity of the human nose with respect to certain substances (one can identify up to 10 thousands of substances in the amount of down to 40 molecules).¹¹ The detection limit of the human nose with respect to certain substances is several ppb, while that of animals' noses may be even lower. Such possibilities of olfaction are attributed to the large number of different types of poorly selective receptors in combination with the specific way the signals from the set of receptors are processed in the peripheral and central nervous systems. The sense of taste is organised in the same way as the olfaction, although the number of taste receptors in humans is smaller.¹¹ Traditionally, the following four basic taste sensations are distinguished: sweet, salty, sour and bitter. Recently, an

Yu G Vlasov, A V Legin, A M Rudnitskaya Department of Chemistry, St Petersburg State University, Universitetskaya nab. 7/9, 199034 St Petersburg, Russian Federation. Fax (7-812) 328 28 35, tel. (7-812) 328 95 95, e-mail: vlasov@KL13930.spb.edu (Yu G Vlasov), tel. (7-812) 328 28 35, e-mail: andrew@KL13930.spb.edu (A V Legin), alice@KL13930.spb.edu (A M Rudnitskaya)

Received 25 March 2005

Uspekhi Khimii 75 (2) 141–150 (2006); translated by T Ya Safonova

additional (fifth) taste characteristic, *viz.*, umami, was introduced, which is determined in particular by sodium glutamate and isocyanate.¹² Five major taste characteristics and their combinations are used to describe and quantitatively assess the taste of foodstuffs by additionally invoking such characteristics as taste sharpness, food texture, mouthfeel, taste duration, *etc.*

At present, the relationship between the structure (and chemical properties) of many substances and their taste is insufficiently studied, as well as many other interesting effects, *e.g.*, the interaction of substances with different taste kinds or the increase in the sensitivity limit (desensitising) due to the synergistic effect of substances with different taste kinds.¹¹ The detection limit is usually higher for tastes as compared with scents, with one exception of alkaloids (for instance, quinine). However, the differential sensitivity of biological sensory systems of tasting and smelling is comparable. Thus, the mechanisms of operation of the taste and olfaction sensory systems are similar, although olfaction is a more sophisticated sense in animate nature (for example, for mammals and people).

The potentials of biological sensory systems based on a great number of nonspecific receptors led to the idea of using their structural principles in the development of artificial sensory systems. The latter were initially intended for the analysis of gases and identification of scents.

The development of electronic noses, *i.e.*, multisensor systems for the gas analysis, was initiated by the studies by Moncrieff¹³ and Persaud and Dodd;¹⁴ later, different research teams all over the world made their contribution to the solution of this problem.¹⁰ A typical electronic nose consists of a set (array) of non-selective sensors (most often, semiconducting sensors based on tin dioxide with different additives) and a system for processing multivariate data (for instance, on the basis of artificial neural networks). Electronic noses are applied for the identification of various gas mixtures and/or individual gases (for example, in leakage of chemicals).

The same organisational principles (arrays of low-selective sensors and multidimensional methods of data processing) were used in the development of multisensor systems for the analysis of liquids, the so-called electronic tongues. Like its biological prototype, the electronic tongue operates in various liquid media. However, the sensitivity and detection limits of artificial 'tongues' may substantially surpass the parameters of biological prototypes, because the materials of these sensors are capable of far extending the analytical potential of the system.

A common typical feature of electronic noses and tongues consists of combining the arrays of low-selective sensors with the data processing that employs pattern recognition methods. However, the sensor materials used in noses and tongues have virtually nothing in common, the sensors used in tongues being more plentiful both in the number and type. This offers certain advantages, for example, the electronic tongues are used not only for recognition and identification but also for the multicomponent quantitative analysis. In contrast to its biological prototype, the electronic tongue can be employed in the measurements in any media including hazardous and even lethal for living organisms.

What is important is that despite the similar organisational principles one cannot draw parallels between the potentials of artificial and biological systems and must take into account the significant differences between the sensors used for electronic tongues and noses, which leads to different approaches to the development of new sensors and the methods of their application. In the present review, we consider the studies devoted to multisensor systems for the analysis of liquids, *viz.*, electronic tongues. The majority of such systems were developed on the basis of potentiometric sensors.

As was mentioned above, most ISE (and also most of sensors based on different principles) exhibit low selectivities in multicomponent solutions. In the case of ISE, the effect of interfering

ions on the electrode response is conventionally described by the Nikolsky equation (or similar equations)

$$E = E^\circ + \frac{RT}{z_i F} \ln \left(a_i + \sum_j K_{ij} (a_j)^{z_i/z_j} \right), \quad (1)$$

where E is the potential difference (emf) of the electrochemical cell that consists of a reference electrode and ISE; E° is the standard potential; R is the gas constant; T is the absolute temperature; F is the Faraday constant; z_i and z_j are the charges of the primary and interfering ions, respectively, a_i and a_j are the activities of the primary and interfering ions, respectively; K_{ij} is the coefficient of selectivity of ISE with respect to the primary ion i in the presence of an interfering ion j .

Thus, the response of a low-selective electrode is determined by the concentrations of the primary ion and the interfering ion (or ions). If two terms in parentheses in Eqn (1) are comparable, the electrode response becomes non-linear. A non-linear calibration curve, as long as it is reproducible, can also be used for analytical purposes; however, more than one electrode should be used for the determination of parameters in Eqn (1). Apparently, the number of electrodes should not be smaller than the number of ions to be determined. Within the framework of such an approach, it was proposed to use ISE arrays rather than separate sensors to overcome the insufficient selectivity of ISE in the presence of interfering ions. It was assumed that the response of each electrode in multicomponent solutions is described by the Nikolsky equation. Solving the system of such equations allows certain parameters of the electrode response in multicomponent solutions to be determined, namely, the standard potential, the selectivity coefficients and/or the slope. The mentioned parameters can further be used for the determination of concentrations of ions in solutions of unknown composition. It is well known that many parameters of the ISE response (for instance, the detection limit or the selectivity coefficient) depend on the conditions and methods of their determination. Numerous attempts to develop standard methods for their determination failed. Thus, the fact that all parameters of sensors are determined directly in multicomponent solutions with compositions close to those of analysed solutions pertains to advantages of the approach described above, in addition to the possibility of taking into account the effect of interfering ions. The calculated parameters of the response are more adequate than the theoretical parameters and make it possible to enhance the accuracy of the analysis, even being far from versatile. Various mathematical methods were proposed for solving the system of the Nikolsky equations, including different versions of regressions (Multi Linear Regression, Non-linear Regression, Partial Least Squares) and artificial neural networks.^{15–23}

The next step involved abandoning the Nikolsky equation in favour of the methods that do not require any *a priori* information on the functional dependences between the potentials of sensors and the activities (concentrations) of determined substances. Thus, a new direction in the application of chemical sensors, which substantially differs from the use of conventional ion-selective electrodes and is known as the 'electronic tongue', was developed.

The electronic tongue is an analytical instrument that comprises a set (array) of chemical sensors of relatively low selectivity, being simultaneously sensitive to several components in the analysed solution (cross-sensitivity), and employs a suitable method for the processing of multidimensional data from the array of sensors (*e.g.*, the methods of pattern recognition and multivariate calibration). A system that uses sensors with reproducible analytic response and employs, if necessary, an adequate calibration procedure (calibration as such, training) is capable of the recognition (identification, classification) of various liquid media and the multicomponent quantitative analysis of inorganic and organic constituents.

2. Requirements to sensors for electronic tongue-type systems

It is evident that the array of sensors forms the key part of the electronic tongue. Sensors with relatively low selectivity or cross-sensitivity rather than highly selective sensors are most promising candidates for these systems.^{18–20} Reproducibility of their characteristics is the necessary condition. Thus, an electronic tongue requires sensors with reproducible analytical characteristics and high cross-sensitivity. Although the term ‘cross-sensitivity’ is generally accepted for describing the properties of sensors in the literature devoted to multisensor systems, to date we have no its unambiguous definition. Quite a number of terms to describe the same phenomenon are used as synonyms (*e.g.*, non-selectivity, cross-reactivity, low selectivity, partial selectivity and even global selectivity). Hereinafter, we will use the term ‘cross-sensitivity’.

At present, there is no generally accepted method for the assessment of cross-sensitivity. The use of the selectivity coefficient [Eqn (1)] or its reciprocal value seems to be a poor choice, because it contains no information on the sensitivity itself and its value strongly depends on the determination procedure (there is no standard method). When determining the selectivity coefficient, it is assumed that the response of a sensor to both primary and interfering ions corresponds to the theoretically calculated value, which is rarely the case. Moreover, the selectivity coefficient is by definition a value that characterises a binary system (which consists of one primary and one interfering ion), whereas for the case of a complex solution that contains several interfering ions, the question of the primary ion remains open and the selectivity coefficient value is far from real.

The authors of this review have put forward²⁴ an empirical method for assessing the cross-sensitivity. For this purpose, the following three parameters were used: the average slope, the reproducibility factor and the non-selectivity factor, which describe the sensitivity and reproducibility of a sensor's response and also its selectivity with respect to the studied ions. These parameters were originally determined for sensors with chalcogenide glass membranes with respect to a group of transition metal cations.²⁴ Later, the proposed approach was applied for assessing the cross-sensitivity of other sensor materials (*e.g.*, polymeric) with respect to other groups of ions.²⁵

The calculation of the parameters mentioned above involves the use of experimental data obtained in calibration measurements in a solution of a selected set of substances (ions) using the previously determined sensor materials the cross-sensitivity of which is to be studied. Even the most ‘non-selective’ sensor materials are sensitive only to a certain group of substances rather than to all ions in the solution.

The first and most important parameter of the cross-sensitivity is the average slope (S), which is determined in individual solutions of a selected set of substances as follows:

$$S = \frac{1}{n} \sum_i S_i,$$

where S_i is the slope of the sensor electrode response in calibration solutions that contain individual substances, with respect to which the cross-sensitivity of the sensor is studied, n is the number of substances studied. Thus, this parameter represents the averaged sensitivity of a sensor material toward a certain group of substances (ions).

The second parameter is the stability factor (K), which represents the signal-to-noise ratio for the sensor material averaged over all studied substances

$$K = \frac{1}{n} \sum_i K_i = \frac{1}{n} \sum_i \frac{S_i}{s_i^2},$$

where S_i is the slope of the sensor electrode response in solutions of chosen substances, s_i is the standard deviation of the electrode response in solutions of chosen substances. Apparently, the standard deviation is calculated in parallel measurements and characterises the reproducibility of the electrode characteristics of the sensor material in the solutions under study.

The third parameter, *viz.*, the non-selectivity factor (F), characterises the uniformity of the distribution of sensitivity of a sensor material with respect to the set of substances chosen for studies

$$F = \frac{S}{s^2},$$

where S is the average slope, s is the standard deviation of the average slope, which is calculated based on the slopes of the electrode response in solutions of individual substances.

The larger is the average slope, the higher is sensitivity of a sensor to the studied set of substances. The optimum value of this parameter is estimated in each particular case. Assume that the cross-sensitivity of a sensor material with respect to a set of doubly charged ions is considered. In this case, the electrode response slope is most likely to vary from 0 (the absence of sensitivity) to 29 mV (pX)^{−1} (a response corresponding to the Nernst equation). Thus, the average slope close to 29 mV (pX)^{−1} suggests the equally high sensitivity with respect to all ions under study. In practice, the same sensitivity with respect to a wide set of ions is virtually unknown. Therefore, it can be assumed that sensor materials with an average slope > 25 mV (pX)^{−1} exhibit high cross-sensitivity and may be included into the multisensor system for determination of this set of ions. However, in certain cases the average slope of a material sensitive with respect to a set of doubly charged ions can exceed 30 mV (pX)^{−1}, which is associated with the supersensitivity with respect to one or several ions. In this situation, to assess whether the sensor has cross-sensitivity, one has to consider the non-selectivity factor, which describes the uniformity of distribution of sensitivity over ions. A factor of non-selectivity below 0.1 is typical of highly selective sensors that exhibit high sensitivity to only one primary ion. The factor equal to 0.1 points to the sensitivity with respect to several ions among those studied. For the materials with relatively uniform sensitivity with respect to all ions, this value should exceed unity. As a rule, it is assumed that the non-selectivity factor of 0.5 and higher suggests the presence of cross-sensitivity of a given sensor material with respect to the studied set of ions. It is evident that both parameters, the average slope and the non-selectivity factor, should be taken into account in practice. Thus a sensor that exhibits equally low sensitivity with respect to all studied ions will have a high factor of non-selectivity but a low average slope.

The stability factor is used for assessing the reproducibility of electrode characteristics of sensor materials. Although it is measured in solutions of individual substances, it is evident that the reproducibility of electrode characteristics of sensor materials in these solutions correlates with their reproducibility in mixed solutions containing these substances. The higher the stability factor the higher the reproducibility. It is shown that sensors with the stability factor ≥ 2 can be used in a multisensor system.^{24, 25}

This set of parameters is representative and suitable, although other sets exist.

Summarising, it is essential to note that within the framework of the proposed approach no *a priori* assumptions are drawn on the mechanism of the response of sensors; therefore, this approach can be applied for assessing the cross-sensitivity of not only potentiometric sensors but also chemical sensors of other types.

3. Sensors used in the electronic tongue systems

Systems of the electronic tongue type can comprise any chemical sensors for analysing liquids regardless of what physical principle they are based on.

The ‘taste sensor’ was the first multisensor system analogous to the electronic tongue.²⁶ It included eight potentiometric sensors with the so-called lipid membranes^{2, 27, 28} that exhibited cross-sensitivity with respect to substances of different tastes. The membranes had a polymeric (PVC) matrix. Thin-film sensors were also manufactured, with the aim of miniaturisation, by applying Langmuir–Blodgett films on semiconducting supports, based on the same sensor materials but using a different principle

of signal detection. Different authors used field effect transistors,²⁹ light-addressable potentiometric sensors (LAPS) and sensors based on the method of surface photovoltage (SPV)^{30,31} as the sensitive elements (transducers).

An electronic tongue based on arrays of various potentiometric sensors including inorganic membranes was developed;³² its measuring circuit and photograph are shown in Figs 1 and 2. It is the authors of this study who, together with their Italian colleagues from the University Tor Vergata (Rome), were the first to propose the term 'electronic tongue' as applied to cross-sensitive sensors in combination with the data processing based on pattern recognition methods.³³ The sensors were fabricated using a wide assortment of membrane materials, which included chalcogenide glass doped with different metals, plasticised polymers containing various active substances and also polycrystalline compositions.^{1,24,25,32} Several hundred different sensors were studied, from which the compositions with the highest cross-sensitivity were selected. As a rule, an electronic tongue comprises from 5 to 30 sensors depending on the analytical problem. Microsensors based on thin nanofilms of chalcogenide glasses were prepared using pulsed laser deposition (PLD).³⁴ The composition and properties of the film materials and systems differed little from those of the parent chalcogenide glasses.

A flow-injection version of the electronic tongue system with multisensor detection was developed, which included from 3 to 11 sensors.³⁵ The possibility of performing repeated measurements including those in the automatic mode (due to the multichannel actuator) and the small sample volume (as a rule, 150–500 μL , which can be decreased to 50 μL) are among the advantages of flow-injection multisensor systems.

It was proposed to use electronic tongues built of potentiometric sensors the preparation of which involved the application of metalloporphyrins with different central atoms [Mn(III), Fe(III), Co(II), Ni(II)], and also tetraphenylporphyrin onto glassy

carbon supports by means of the electropolymerisation technique.³⁶ An electronic tongue based on already existing and commercially available ISE was produced.^{37,38}

The measurements using arrays of potentiometric sensors are by and large similar to those using individual ISE. In both cases, the emf of electrochemical cells formed by sensors of the array taken in turn and the reference electrode is measured. In these measurements, multichannel voltmeters with high input impedance ($\geq 10^{12} \Omega$) are used. As a rule, a computer controls the measurements and data recording.

In addition to potentiometry, it was proposed to use voltammetry in multisensor systems,^{3,39–41} which is also based on a similar combination of measurements of non-specific electrochemical signals and their processing by pattern recognition methods. The polarographic wave becomes a non-selective analytical signal in those cases where several solution components are oxidised at the same or similar potentials. To resolve such a signal and retrieve certain analytical information, one has to use several working electrodes rather than one electrode, as in the classical scheme. Noble metals (platinum, gold, iridium, rhodium, rhenium) are used as the working electrodes.

A multisensor system based on electrodes modified with monophthalocyanine complexes of cobalt and copper, bis(phthalocyanine) complexes of europium, gadolinium, and lutetium and octakis(*tert*-butyl)-substituted bis(phthalocyanine) complex of praseodymium is described.⁴² The modified electrodes were prepared either by applying Langmuir–Blodgett films on glass supports or with the use of the graphite paste electrode technology (by mixing 15 vol.% phthalocyanine with a graphite paste). Measurements with such voltammetric multisensor systems are carried out using a classical three-electrode circuit, which contains a reference electrode, a steel counter electrode, an array of working electrodes and a commutator for switching from one electrode to another. Large amplitude pulse voltammetry (LAPV) was chosen for the measurements with an array of electrodes made of noble metals. The potential was scanned in the range from -0.4 to $+0.6$ V with 100-mV steps.³ Cyclic voltammetry with a scanning rate of 0.1 V s^{-1} was used⁴² in the measurements with an array of modified electrodes.

An electronic tongue design was proposed that mimicked the biological prototype despite being based on optical sensors.⁴³ Sensors that mimicked taste receptors consisted of grains of poly(ethylene glycol)–polystyrene resin (PEG-PS) with various indicator molecules. The latter represented fluorescein, *o*-cresolphthalein complexone, alizarin complexone and resorufin-substituted galactoside boronate. The response of sensors was measured with respect to a control sensor, which represented a grain of a resin with acetylated terminal amino groups. The grains were located in microcavities fabricated by the micromachining technology in silicon/silicon nitride plates, which mimicked the arrangement of taste buds on the tongue. The changes in the light absorption by the grains in different solutions were detected using CCD (Charge-coupled Devices). The study was aimed at merely demonstrating the possibilities; therefore, the analytical applications of this tongue are yet unknown.

Different conducting polymers such as polyaniline, polypyrrole, stearic acid and their mixtures are used in the preparation of sensors for electronic tongues.^{44,45} Langmuir–Blodgett polymeric films are applied on metal supports. Measurements are carried out using the method of impedance spectroscopy at room temperature (20 ± 3) °C in a frequency range from 20 to 10^5 Hz. The use of impedance spectroscopy is based on the fact that the low frequency range of such a spectrum describes the properties of the electrical double layer formed as a result of adsorption of substances from the analysed solution on the surface of a sensor.

Obviously, the possible sensor materials and detection methods are not limited to the versions mentioned above, and one can expect the appearance of reports on the use of other types of sensors.

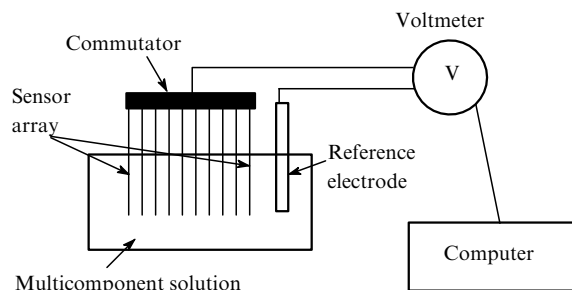


Figure 1. The measuring circuit of an electronic tongue based on potentiometric chemical sensors.³²



Figure 2. A photograph of a laboratory prototype of the electronic tongue based of potentiometric chemical sensors.³²

4. Data processing

Although chemical sensors form the most important part of the multisensor system, the adequate methods of data processing also play an important role. The response of a cross-sensitive sensor in a multicomponent solution is complex and contains information on different components present in the medium. To gain this information, it is necessary to analyse the overall response of all sensors in the system. Under these conditions, the correct choice of the method of data processing and its application are of great importance. Different approaches including the methods of pattern recognition and multivariate calibration are used.

The choice of a particular method for the data processing depends on both the analytical problem and the parameters of sensitivity of sensors, *i.e.*, the non-linearity of the response, the degree of correlation between the responses of different sensors in the array, *etc.* The following three main problems are known in the data processing: the studies on the data structure and recognition; the classification and identification; the quantitative analysis (determination of concentrations of substances or other quantitative parameters).

The first stage of data processing always involves the data recognition and the studies on their structure, which allows one to initially assess the reproducibility and detect outliers, to visually study the data structure, detect data clusters, *etc.* For these purposes, the methods of unsupervised learning such as the principal component analysis and certain kinds of artificial neural networks are used.

The problems of classification and quantitative analysis are solved, as a rule, by the methods of supervised learning. For classification, such methods as (Soft Independent Modeling of Class Analogy) SIMCA, linear discrimination analysis, multi-dimensional regressions and artificial neural networks are used. In those cases where *a priori* information on the studied samples is absent, the classification can be accomplished by the methods of unsupervised learning. To obtain calibration curves for the determination of concentrations of solution components, multivariate calibrations are used, the most popular of which involve principal components regression and partial least squares as well as artificial neural networks. The detailed descriptions of the main methods of chemometrics, which are used to process the results of measurements with multisensor systems, are available in the literature.^{46–48}

5. Advantages of sensor systems over individual sensors

Even the first studies devoted to the use of sensor arrays have demonstrated that the use of chemometrics for processing the response of sensors makes it possible to compensate to a certain extent the insufficient selectivity of ISE and quantitatively determine the activities of ions in multicomponent solutions. Subsequent experimental data implied that sensors with moderate selectivities or cross-sensitivities should be preferred for constructing the arrays.¹⁹ Such arrays allow one to carry out quantitative measurements with smaller errors as compared with arrays including only highly selective sensors. Thus, there appears a possibility for extending the range of analysable substances or solution components.

In addition to the compensation of insufficient selectivity of sensors, the arrays of sensors with cross-sensitivity in relatively simple solutions make it possible to reduce the detection limit (with respect to concentration) by an order of magnitude.⁴⁹ In solutions of complex composition, this effect can even be more pronounced.

Yet another practically important feature of arrays of sensors is the possibility of carrying out potentiometric measurements without recourse to the reference electrode. In this case, the potential differences between all the pairs of sensors in the array are measured.⁵⁰ Evidently, some of potential differences obtained in this way will be excessive and should be rejected in the course of data processing. The analytical characteristics of the electronic

tongue are shown to be independent of the reference electrode during the measurements.

The capability of systems of the electronic tongue type to recognise and identify multicomponent solutions in almost the same way as people do is very promising. In the literature, this is usually referred to as the fingerprint technique. Such an analysis is totally untypical of not only ion-selective electrodes but also all other conventional analytical methods. As a result, a multisensor system may produce an integral estimate, a chemical pattern of the analysed liquid, *i.e.*, its 'fingerprint'. This pattern either coincides or differs for different analysed liquids. This allows a conclusion to be drawn on their identity or difference. What is most unusual is that the electronic tongue can recognise liquids of unknown composition without any preliminary information on the qualitative or quantitative composition of samples. Apparently, the classification and identification by means of an electronic tongue require preliminary calibration of the instrument with respect to a series of known samples. This is a new and promising approach to the analysis of the quality of many foodstuffs and determination of its compliance with a chosen quality standard.

The ability of multisensor systems to recognise and quantitatively assess tastes is their most unusual property, which is the reason for their title 'electronic tongue'. The system is calibrated (trained) over a series of standard solutions or food samples, which have been characterised by professional tasters as regards the taste type and intensity. If a system can detect the key substances and the features that determine the taste, then, after such a training, the electronic tongue acquires the capability to analyse unknown food samples, producing the type and intensity of their taste as the result. The demand for the determination of taste by means of an analytical tool is the highest in the food and drug industries, which probably represents one of the most interesting practical applications of electronic tongues in future.

III. Certain analytical applications of multisensor systems of the electronic tongue type

To date, a great number of studies devoted to various applications of the electronic tongue multisensor systems are documented.^{1,32,51} Many of them describe how to recognise different foodstuffs, determine the quality of one and the same foodstuff, confirm their correspondence to the quality standard and their authenticity and reveal counterfeit products. Currently, great attention is paid to the use of electronic tongues for monitoring industrial processes and the quality control, which involves the determination of concentrations of key components and the assessment of the correspondence of the overall quality of a process or a foodstuff to the standard. The taste of foodstuffs is assessed. For calibration of the system, the taste estimates made by professional tasters are used.

Electronic tongues are used most often in the analysis of foodstuffs. The performance of systems for the analysis of fruit juices,^{3,31,52,53} mineral water,^{54–56} soft drinks,⁵⁶ coffee,^{56,57} tea,^{58–60} milk and dairy products,^{3,39,61,62} wine,^{55,63,64} miso (Japanese soy paste),⁶⁵ sake,^{66,67} vegetable oils,⁶⁸ fruit,⁶⁹ vegetables,⁷⁰ meat,⁷¹ fish⁵⁶ is described. As a rule, the electronic tongue was used for recognition and classification of listed foodstuffs, less often, for their quantitative analysis. For instance, the use of the electronic tongue for recognition of different coffee brands was described.⁵⁶ Figure 3 shows the results of recognition for eight individual brands of coffee and three commercial mixtures. Data were processed by the Principal Component Analysis (PCA). As is seen, all the samples differ from one another except for samples 2 and 6, which represent one and the same coffee sample. This sample strongly differs from the rest samples in both the results of the analysis using the electronic tongue and its taste and scent.

The response of an electronic tongue towards the dilution of fruit juice with water or sugar solution was studied.⁵⁴ This problem was topical due to the appearance of faked foodstuffs obtained by excessive dilution of fruit juices with water, sugar

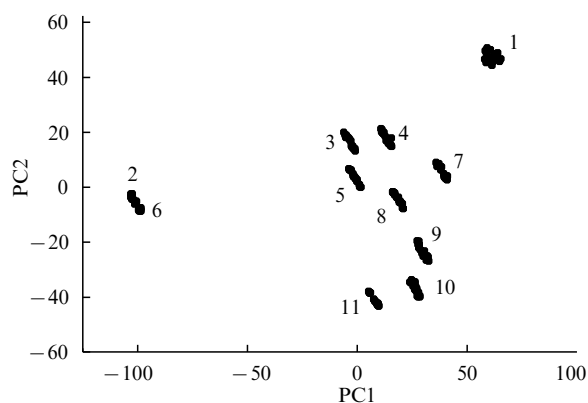


Figure 3. Results of measurements with an electronic tongue for eight individual brands of coffee (samples 1–8) and three commercial mixtures (sample 9–11). Data were processed using the principal component analysis.⁵⁶ PC1 and PC2 are the first and the second principal components.

solution, or similar solutions. Figure 4 shows the results of measurements with a multisensor system for two samples of orange juice (freshly squeezed and prepared from a concentrate). The data were processed using the principal component analysis technique. The points in the upper part of the plot correspond to pure juice, those in the bottom part correspond to diluted juice. It was found that the multisensor system allows determination of just 1% water added to orange juice.

The use of the electronic tongue for the determination of concentrations of inorganic cations and anions, organic acid anions, amino acids, polyphenols, and also such parameters as the total and titratable acidity^{55, 56, 64} and the number of bacteria in spoilt milk³⁹ is described. The electronic tongue can be used for the monitoring and determination of concentrations of key components in biotechnological processes for the synthesis of such substances as enzymes used in the production of cheese,⁷² miso⁶⁵ and sake.⁶⁷ To evaluate this method in assessing the taste, solutions of substances with typical tastes were tested both separately and in mixtures with different foodstuffs and drugs. As a rule, several parameters were assessed in the taste, which were important for a given foodstuff, for example, the flavour, acidity,

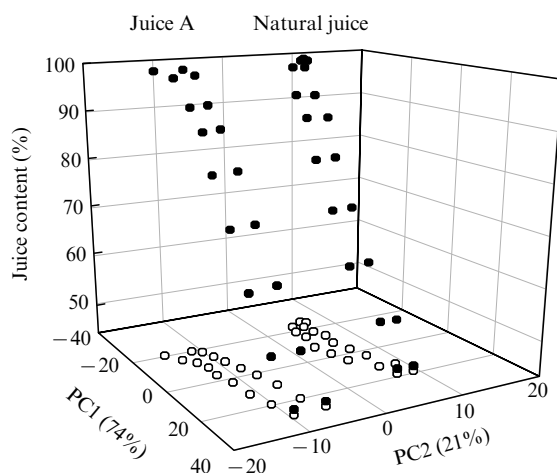


Figure 4. Monitoring of the dilution of orange juice with water carried out using a multisensor system.

The results of measurements with the electronic tongue for two orange juice samples: prepared from concentrate (juice A) and freshly squeezed (natural). Data were processed by the principal component analysis.⁵³ PC1 and PC2 are the first and the second principal components. Open circles represent projections of the experimental points on a plane.

and texture of coffee,⁵⁶ the taste richness and the baked-milk flavour in milk,⁶² 'dietness' (the difference between regular and light versions of beverages) of Pepsi-Cola,⁵⁶ *etc.* The main problem in the assessment of the taste of drugs was to measure the bitterness intensity in active substances and effectively mask it by different sweeteners and flavourings.^{73–75} An electronic tongue (e.t.) based on potentiometric chemical sensors was used for the determination of taste characteristics of eight brands of coffee (Table 1).⁵⁶ The calibration was carried out using organoleptic estimates of the flavour and scent of coffee, which were made by professional tasters and provided by the manufacturing company. Four parameters were assessed on a ten-point scale. The calibration model was calculated using a neural network with back propagation of errors. A part of samples were used for calibration, the other samples were used in the tests. Table 1 shows the organoleptic estimates made by tasters and the values obtained by applying the calibration model to the control samples. All the cases demonstrate good agreement. The possibility of drawing correlations between the response of an analytical tool and human perception can be of great practical importance.

Table 1. Organoleptic tests of coffee made by tasters and calculated by applying the calibration model to the test samples.

Parameter	Method of estimate	Sample			
		5	6	7	8
Flavour	e.t.	4.8±0.2	7.8±0.1	3.1±0.3	4.1±0.4
	tasters	3–7	7–9	1–2	2–4
Acidity	e.t.	4.8±0.1	3.6±0.3	5.7±0.3	5.4±0.3
	tasters	5–8	2–5	5–8	5–8
Body	e.t.	7.0±0.1	8.5±0.01	8.4±0.1	6.0±0.1
	tasters	5–9	8–9	8–9	5–7
Smell	e.t.	5.3±0.2	8.4±0.01	3.8±0.3	4.7±0.3
	tasters	4–7	8–9	2–3	3–5

The application field of the electronic tongue is not limited to foodstuffs. Multisensor systems were used for the monitoring and determination of the principal components in the growth media used for growing microorganisms,⁷⁶ for recognition of various growth media,⁷⁷ for monitoring of cleaning of drinking water,⁷⁸ for determination of the contents of inorganic anions and transition-metal cations in model ground, mine and sea water,^{24, 25, 79–83} and also in the smoke from incineration plants (after the absorption of smoke by a liquid);³⁵ for the quantitative analysis of the dialysis solutions used in the devices such as 'artificial kidney',⁸⁴ *etc.* The use of electronic tongues for simultaneous determination of iron and uranium in different oxidation states in model mine water is described.^{81, 82} The need for such tests is associated with the control over the composition of water in deserted uranium mines in order to undertake timely measures on the radiation safety. Uranium in different oxidation states exhibits different solubility and, hence, the different ability to migrate under natural conditions. This is why the determination of the contents of uranium(VI) and uranium(IV) and also of iron(II) and iron(III), which accompany uranium, is among the most important problems in the analysis of mine water. Table 2 shows the results obtained by means of an electronic tongue. The possibility of simultaneous determination of the contents of iron and uranium in different oxidation states was also demonstrated.

The idea of simultaneously using liquid and gas sensors for the analysis of foodstuffs was born in analogy to the fact that people simultaneously assess tastes and smells. The sensitivity and selectivity of sensors used in electronic noses and tongues substantially differ from the characteristics of biological receptors; therefore, the role of artificial sensory systems and their contribu-

Table 2. Results of determination of the contents of iron and uranium in different oxidation states in solutions that model mine water (the results shown correspond to test solutions only).

The form of the element	Found /mol litre ⁻¹	Added /mol litre ⁻¹	Standard deviation
U(IV)	2.5×10^{-5}	3.0×10^{-5}	2×10^{-6}
	5.0×10^{-5}	5.4×10^{-5}	4×10^{-6}
	2.5×10^{-5}	2.7×10^{-5}	3×10^{-6}
	5.0×10^{-5}	5.0×10^{-5}	1×10^{-6}
	2.5×10^{-5}	2.9×10^{-5}	1×10^{-6}
	5.0×10^{-5}	5.5×10^{-5}	2×10^{-6}
	7.5×10^{-5}	6.4×10^{-5}	2×10^{-6}
U(VI)	5.0×10^{-5}	4.4×10^{-5}	7×10^{-6}
	7.5×10^{-5}	7.3×10^{-5}	7×10^{-6}
	1.0×10^{-4}	8×10^{-5}	1×10^{-5}
	5.0×10^{-5}	5×10^{-5}	1×10^{-5}
	7.5×10^{-5}	7×10^{-5}	1×10^{-5}
	1.0×10^{-4}	9.9×10^{-5}	3×10^{-6}
	2.5×10^{-5}	3.6×10^{-5}	3×10^{-6}
	5.0×10^{-5}	4.4×10^{-5}	3×10^{-6}
	7.5×10^{-5}	8.3×10^{-5}	7×10^{-6}
Fe(III)	1.0×10^{-5}	1.6×10^{-5}	3×10^{-6}
	3.0×10^{-5}	3×10^{-5}	1×10^{-5}
	5.0×10^{-5}	5×10^{-5}	2×10^{-5}
	1.0×10^{-5}	6.5×10^{-6}	2×10^{-6}
	3.0×10^{-5}	2×10^{-5}	2×10^{-5}
	5.0×10^{-5}	3×10^{-5}	3×10^{-5}
Fe(II)	1.0×10^{-5}	1.1×10^{-5}	2×10^{-6}
	3.0×10^{-5}	1.4×10^{-5}	4×10^{-6}
	5.0×10^{-5}	2.6×10^{-5}	4×10^{-6}
	1.0×10^{-5}	1.5×10^{-5}	1×10^{-6}
	3.0×10^{-5}	3.5×10^{-5}	6×10^{-6}
	5.0×10^{-5}	5×10^{-5}	2×10^{-5}

tions to the final result can differ from those of their natural prototypes. Nonetheless, the hybrid systems 'electronic nose + electronic tongue' were used in recognition of wines,⁶³ fruit juices,⁴¹ milk and even urine samples.⁶¹ The idea of using hybrid systems looks interesting, although to date it demonstrated no real advantages over the use of electronic tongue alone.

IV. Conclusion

Multisensor systems of the electronic tongue type represent a rapidly developing and promising interdisciplinary scientific field. At present, there is a possibility of using such systems for the quantitative analysis, quality control, recognition and classification in the food and pharmaceutical industries, medicine and also for environmental control. The existence of a correlation between the response of an electronic tongue and the human perception of taste is both unusual and promising from the viewpoint of practice. Today, the first commercial systems of the electronic tongue type are available.

Unfortunately, the knowledge in this young scientific direction is still largely empiric. The use of only limited number of sensor materials is a significant drawback of multisensor systems. In many cases, only a single type of sensors is used. For example, in certain studies only metalloporphyrins³⁶ or phthalocyanine complexes⁴² or some other substances are used as the active components of sensor membranes. Naturally, the differences in the electrode characteristics of sensors containing homologues as the active substances are not great, and, in effect, such a multisensor system can be used for determination of only a limited group of substances and shows no serious promise for its extending. Consequently, the development of new sensor compositions and materials gains in importance. It is also necessary to extend

the range of substances detectable by electronic tongues. For example, there are numerous problems on the determination of organic substances in mixtures. Without solving these problems, the extension of the application fields of this method and its further development are impossible.

Insufficient attention is also paid to studying the mechanism of the response of sensor materials used in multisensor systems. As a rule, the studies devoted to sensors are descriptive and empirical. The in-depth, more fundamental knowledge of the mechanism of the sensor response is the second prerequisite for the development of new compositions and the extension of the range of detectable substances.

An important task yet insufficiently reflected in the literature is the development of the objective criteria of the formation of a multisensor system to solve a given analytical problem. In particular, no methods exist which would allow one to *a priori* determine how many sensors and what sensor characteristics are required for the analysis of a given mixture of substances. At present, two major approaches to the formation of multisensor systems are distinguished. It is possible to take a redundant set of sensors sensitive to the analysed substances and then, in the stage of data processing, select those sensors that provide the greatest body of information, *i.e.*, exhibit the highest sensitivity with respect to the analytes and good reproducibility. Here, the requirement for the wide initial set of sensors is the key problem. Another approach consists of the use of a standard set of sensors. The weight of information provided by them is also assessed in the stage of data processing. It is evident that this approach is not always the optimum one.

Insofar as the electronic tongue represents an analytical tool, a question arises on its complex application. Despite the appearance of the first commercial instruments, most analytical results obtained with the electronic-tongue multisensor systems merely demonstrate their potentials rather than their practical analytical applications. There is the demand for the thorough development of the methodical grounds, in particular, aimed at providing the reproducibility of the responses of sensors, on the methods of calibration, conditioning and washing of sensors, *etc.*

Summarising, note once again that serious efforts should be undertaken in the studies of the mechanism of the sensor response to different analysed substances, in the development of new sensor compositions and also in the elaboration of methods for practical application of electronic tongues to solving particular problems. It is probable that rapid progress will be observed in this field in the near future.

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^a — *Russ. J. Anal. Chem. (Engl. Transl.)*^b — *Russ. J. Appl. Chem. (Engl. Transl.)*^c — *Radiochemistry (Engl. Transl.)*

Polymer degradation and its role in nature and modern medical technologies

A Yu Bilibin, I M Zorin

Contents

I. Introduction	133
II. General concepts of polymer degradation	133
III. Natural polymers contributing the most to the formation of the biosphere	134
IV. Synthetic biodegradable polymers. Chemical structures and preparation features	135
V. Degradation of natural and synthetic polymers in the environment	136
VI. Biomedical technologies based on polymer degradation	137
VII. Conclusion	142

Abstract. The published data on the degradation of natural and synthetic polymers in the environment are analysed. The use of polymer degradation in the most advanced biomedical technologies is considered. The bibliography includes 221 references.

I. Introduction

Degradation of polymers is a global process occurring in the biosphere of the Earth, which has an enormous impact on its formation and human activity. In nature, polymer degradation determines the material balance in the biosphere. It was estimated¹ that at least 10^{15} kg of cellulose, the most abundant plant polymer, is produced on Earth annually by photosynthesis. Multiple catabolic–anabolic conversions of cellulose yield a variety of other products. As a result, the major part of the cellulose formed undergoes degradation with the formation of low-molecular-mass (predominantly, gaseous) products, while the other part is stored in the uppermost layers of the Earth's crust where it makes the major contribution to the formation of the topsoil or undergoes partial mineralisation.

Considering the role of polymeric materials in the development of material and spiritual culture of Mankind, it may be conjectured that polymer degradation is a critical factor in this process. Polymeric materials constitute the basis of clothing, building, shipbuilding and, which is even more important, of recording, reproduction and storage of information (paper and book- printing, cine- and magnetic films, *etc.*). However, the degradation of polymeric articles that are vitally important for human life reduces critically their service lives. Therefore, since ancient times the Man considered polymer degradation as an inevitable evil and did his best to prevent or retard this process without even getting an insight into its physical meaning. It is not therefore surprising that degradation and stabilisation of polymers were among the first subjects of investigation in polymer chemistry. However, the discoveries made in the past few decades

enabled the utilisation of degradation processes in modern technologies.

The ecological equilibrium formed over the course of millenia was disturbed drastically in the past century as a result of anthropogenic activity, particularly due to conversions of natural substances (mineral oil, gas, carbon) into novel, non-natural materials, such as Teflon, polystyrene, polypropylene, *etc.* No efficient mechanisms of the degradation of these polymers exist in nature, therefore their stock on the Earth is steadily increasing, which threatens severe, hardly predictable changes in the environment. The ever increasing output of synthetic polymeric materials is a challenge to Mankind as regards the maintenance of the global equilibrium (sustainable development).

This review surveys the papers devoted to studies on the degradation of natural and synthetic polymers in the environment as well as the use of this process in modern technologies.

II. General concepts of polymer degradation

Deterioration of polymeric materials occurs much faster than that of other substances (metals, minerals, *etc.*) resulting in the loss of their strengths and elasticities up to spontaneous decomposition of polymeric articles even in the absence of external forces. Degradation of the constituent polymers is the reason for such behaviour of polymeric materials.

Degradation of polymers, *i.e.*, cleavage of chemical bonds in the main chain of a macromolecule, is usually classified according to two parameters, *viz.*, the mechanism of chain degradation and the type of energy that brings about the degradation. The former involves chain reactions (depolymerisation) where monomeric molecules are eliminated successively from the reactive site of the macromolecule under the action of energetic factors. An alternative mechanism consists of random degradation where those chemical bonds are cleaved under the action of energy factors, which experience the maximum strain by virtue of fluctuation.²

Virtually all energy types cause degradation of polymers. This can be induced by thermal, radiation-chemical (photochemical), chemical (hydrolysis, ammonolysis, oxidation), mechanochemical, *etc.*, factors. In most cases, the degradation is induced simultaneously by several factors and the contribution of each of them cannot always be established. One of the most common types of polymer degradation, *viz.*, biodegradation, occurs in polymers under the action of different enzymes. In a broad sense, biodegradation implies the destruction occurring under the influence of environmental factors, such as water, soil, bio-

A Yu Bilibin, I M Zorin Department of Chemistry, St Petersburg State University, Universitetsky pr. 26, Petrodvorets, 198504 St Petersburg, Russian Federation. Fax (7-812) 428 69 39, tel. (7-812) 428 68 40, e-mail: alex_bilibin@mail.ru (A Yu Bilibin), tel. (7-812) 428 40 75, e-mail: ivan_zorin@mail.ru (I M Zorin)

Received 16 May 2005

Uspekhi Khimii 75 (2) 151–165 (2006); translated by R L Birnova

logical fluids, *etc.* Many synthetic polymers, especially carbochain polymers, *i.e.*, those built exclusively of carbon atoms in the main chain, are not subject to biodegradation and remain in the environment over the course of years. In contrast, biopolymers (natural polymers and their synthetic analogues) undergo biodegradation being converted into low-molecular-mass compounds.

The degradation rate is an essential feature of the process. However, its true rate constant can seldom be established and this can be done only under model, strictly specific conditions. In real situations with numerous factors influencing the degradation, the rate of the overall process has to be determined by indirect methods.

The most popular methods for the estimation of the degradation rate are as follows:²

(1) Estimation of changes in masses and linear sizes of samples. This approach is used for determining the degree and rate of degradation by measuring the reduction of the mass per unit time. If the surface area is known, the reduction of the mass per unit area per unit time can easily be calculated and the corresponding rate constants can be determined. The dimensional characteristics of the samples can be established in a similar way.

(2) Estimation of changes in the average molecular mass and molecular-mass distribution of the polymer employed in the preparation of a sample. In this case, determination of molecular characteristics of the original sample (as a rule, by gel-permeation chromatography) is followed, after a definite period of time, by determination of molecular characteristics of the sample subjected to degradation. However, the heterogeneity of degradation over the bulk of the sample prevents correct interpretation of the results.

(3) Estimation of changes in the concentrations of the degradation products. This approach is used for the determination of diverse miscellaneous characteristics, *e.g.*, total volume of gaseous products, concentration of the monomer or the degradation products of a particular polymeric material, changes in pH, *etc.* This method usually gives reliable results provided that the degradation of the tested sample is complete.

(4) Estimation of changes in the concentrations of low-molecular-mass products included into the tested sample. Dyes and radiolabelled substances are used as the most reliable 'markers'; in practice, drugs can also be employed.

(5) Determination of the rates of changes in the mechanical characteristics of degradable polymeric articles. As a rule, these studies are confined to films or fibres.

(6) Determination of the rates of changes in the thermal characteristics of polymers used as starting materials for the preparation of tested articles (*e.g.*, melting and glass-transition temperatures).

The above-described methods are not absolute and the results obtained depend critically on the experimental conditions. Therefore, a comparison of experimental results obtained by different groups of researchers who employ different methods is not always justified. To make the experimental results comparable, the methods used for the study of polymer degradation should be standardised.

The methods for estimating the changes in the molecular masses or concentrations of degradation products in the tested samples provide the most reliable information about the rates of these reactions. Such characteristics can be used for the assessment of the average degree of degradation of the sample at large. However, taking into account the heterogeneous nature of the process the surface/volume ratio of the sample should be considered in each specific case

III. Natural polymers contributing the most to the formation of the biosphere

In nature, biopolymers are represented by several major classes which differ in the types of the chemical bonds in the main chains. These include hydrocarbons (rubber, gutta-percha), carbo-

hydrates (cellulose, starch, chitin, *etc.*), proteins, nucleic acids, aliphatic polyesters and polyphenols (lignin).

Structure-forming polymers of plants and animals constitute the major part of high-molecular-mass organic substances synthesised on the Earth annually. The structural function of biopolymers underlies the ability of the living beings (from bacteria to higher organisms) to take definite shapes which is changed depending on the situation. In plants, the structure-forming function is fulfilled by polysaccharides, first of all, by cellulose. In animal organisms, this role is played by both polysaccharides (*e.g.*, chitin, the main constituent of invertebrate's exoskeletons) and proteins (*e.g.*, collagen and keratin, the main structure-forming elements of vertebrates). Biochemical conversions of these polymers are crucial for the formation of the biosphere.

1. Polysaccharides

Cellulose (poly-1,4- β -D-glucopyranose) is the main constituent of algae, herb and shrub stalks and stems. Biosynthesis of cellulose seems to be among the most ancient biochemical processes on the Earth. Recent studies have shown that cyanobacteria (blue-green algae), one of the oldest life forms on our planet, synthesise cellulose.^{3,4} There is evidence⁵ that cellulose can also be synthesised by some animal organisms. It is interesting to note that cellulose underlying a vast array of food chains of higher animals is not digested by their organisms due to the absence of the corresponding enzymes (cellulases). In herbivores, its primary degradation to easily digestible oligo- and monosaccharides is effected by symbiotic microorganisms.⁶

From the chemical point of view, cellulose degradation represents hydrolysis of the polysaccharide to oligo- and monosaccharides. In nature, this reaction is predominantly catalysed by the enzyme cellulase.

Studies of cellulose degradation are of special importance for a number of reasons.

— Owing to its large-scale synthesis in nature, cellulose represents the main material factor responsible for the formation of soils and deposits (carbon, shale oils). As to the origin of oil fields, this is still open to question. These problems constitute the subject of an interdisciplinary science, biogeochemistry.

— The cellulose-based articles (*e.g.*, fabrics, wood) that came down to us from ancient times are of tremendous interest for archeochemistry, a science that evolved at the interfaces between archeology, history, chemistry, microbiology, mycology and some other sciences.

— Cellulose is a basic component of paper. Therefore, studies of cellulose degradation are underway on the (i) development of methods for conservation, protection and restoration of paper and articles thereof and (ii) determination of the rates and mechanisms of degradation of cellulose (including paper) under the action of external factors in compost, soil, river- and seawater, *etc.*

— Of particular importance is thermal degradation of cellulose concomitant with inflammation of degradation products. Studies in this area make the subject of thermochemistry and those branches of chemistry that are concerned with reduction in the combustibility of cellulose materials.

Among other polysaccharides, mention should be made of a structural isomer of cellulose, *viz.*, poly- α -D-glucopyranose (starch, glycogen and amylose). They are synthesised in plants and animals as reserve sources of carbon and energy and are easily hydrolysed by the corresponding enzymes. Of tremendous importance in this group of biopolymers is starch, which has been widely used since the 1990's for the preparation of biodegradable polymeric materials as a constituent of mixtures with polyethylene, polypropylene and other large-scale non-biodegradable synthetic polymers.

Chitin [poly(*N*-acetyl-1,4- β -D-glucosamine)] occupies a special place in polysaccharides. It is present in small amounts in fungi and some algae. In the biosphere, chitin is predominantly localised in the external skeletons of invertebrates, particularly of

Arthropoda. It was calculated⁷ that the total mass of chitin in the oceans amounts to 1.5×10^{12} kg. Its annual production by krill alone exceeds 10^8 kg. Enormous amount of chitin-containing waste products formed upon its processing is considered to be a valuable raw material for the commercial production of a vast array of chemical substances.⁸

A partly N-deacetylated chitin derivative chitosan presents particular interest for medicine. Chitosan is one of the few biopolymers that contain basic groups, which determines its ability to form interpolyelectrolyte complexes upon interaction with negatively charged biomacromolecules. The problems of biocompatibility, biodegradation and practical application of chitin and chitosan are considered in detail by Kumar.⁹

2. Proteins and polypeptides

This group includes both natural polymers (collagen, fibroin) and synthetic polypeptides based on one or several amino acids.

In mammalian tissues, collagen constitutes up to 30% of the protein mass. Collagen is an extracellular matrix protein and contains predominantly glycine, proline and hydroxyproline; three separate polypeptide chains form helical structures, which combine in more complex microfibrils. Being a constituent of connective tissues, cartilages and vascular walls, collagen plays the role of a structure-forming element in the organism. Besides, it is the main protein component of a bone tissue. More than 10 types of collagen can be distinguished depending on the type and function of the parent tissue.

3. Polyhydroxyalkanoates

Polymers pertaining to this group occur in nature as organelles of some fungi and bacterial cells and serve as the reserve energy and carbon sources.¹⁰ The first compound of this series, poly(3-hydroxybutyrate) (PHB), was discovered in 1927. In its properties, it is similar to synthetic thermoplastics, such as polyethylene or polypropylene, but, in contrast to the latter, it is decomposed in biological media into non-toxic products. This property attracted keen attention of investigators in PHB and its structural analogues as promising biodegradable plastic materials for medical purposes. In addition, these polymers present substantial interest as biodegradable packaging materials. Although PHB is itself a brittle material, its mechanical properties can significantly be improved if employed as a co-polymer with other monomers, *e.g.*, 4-hydroxyvaleric acid.^{11–14} The industrial production of PHB and a co-polymer of 3-hydroxybutyric and 4-hydroxyvaleric acids (PHBV) under the tradename Biopol by microbiological synthesis using the widespread soil bacteria *Alcaligenes eutrophus* began in the 1980's. Whereas in 1980 the cost of PHB was ~2000 USD per kilo, by 1995 it dropped to 10 USD per kilo (*cf.* the cost of ordinary polyethylene-type thermosets, 1 USD per kilo).¹⁵

The possibility to synthesise polyhydroxyalkanoates using transgenic plants was widely explored in the past decade. The first report on such a synthesis in a transgenic cruciferous plant (*Arabidopsis thaliana*) appeared in 1992.¹⁶ It is expected that the cost of natural polyhydroxyalkanoates will soon reach that of large-scale products, such as sugar or starch.

Degradation of PHB and PHBV *in vivo* occurs under the action of intracellular and extracellular enzymes (depolymerases) to yield digestable hydroxybutyric and hydroxyvaleric acids. Their further aerobic conversions yield water and carbon dioxide. Under anaerobic conditions, methane is also formed. The metabolic pathways in organisms that produce polyhydroxyalkanoates and prospects of their biotechnological manufacture are discussed in detail.^{17–19}

The problems related to environmental pollution by synthetic polymers and the increasing cost of crude oil the reserves of which will sooner or later be depleted have recently become especially acute. In this connection, special attention is given to the production of materials based on either natural polymers or polymers prepared from natural renewable raw materials. These include traditional natural polymers (wood, cotton, silk, wool, leather,

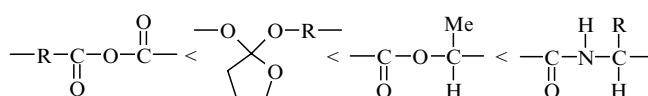
etc.) and their analogues or hitherto unknown polymeric materials prepared by genetically modified microorganisms in common biosynthetic routes.²⁰ So far, these polymeric materials are much more expensive than the synthetic polymers. Moreover, studies in this area come up against the resistance of oil-producing companies which supply raw materials for the production of synthetic polymers.

4. Polyphenols

Lignin is the most important representative of this class of polymers. In addition to cellulose, it is an essential component of wood; in soft woods, its content reaches 50%. This amorphous non-toxic polymer is widely available as a side product from paper-making; however, it has a limited market²¹ and it is mainly used as a fuel. Lignin macromolecules have complex structures: in softwoods, the main monomeric fragment of lignin is 2-methoxy-4-propylphenol (guaiacol), while that in hardwoods is 1,5-dimethoxy-4-propyl-phenol (syringol). In the environment, lignin is rapidly decomposed into low-molecular-mass phenols and is regarded as a very promising material for the preparation of biodegradable polyalkene-containing mixtures.

IV. Synthetic biodegradable polymers. Chemical structures and preparation features

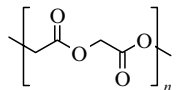
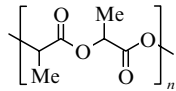
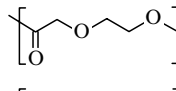
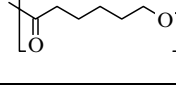
The onrush of the field of polymer chemistry related to the synthesis and utilisation of biodegradable polymers is observed in the past decades. As a rule, it is the ester and amide bonds that undergo hydrolytic degradation under biotic and abiotic conditions. Other bond types, *e.g.*, anhydrides, also cleave easily. The stabilities of the corresponding chemical groups against hydrolysis increase in the following order:



The discovery of bacterial polyhydroxyalkanoates stimulated the search and synthesis of novel polymers related to this class.²² Polymers of glycolic and lactic acids (polyglycolides and polylactides, respectively) are the most known and most abundant representatives of synthetic polyhydroxyalkanoates. High-molecular-mass polymers were obtained for the first time in the 1950's.²³ They are usually synthesised by ionic polymerisation in a melt of a monomer under the action of organometallic catalysts, *e.g.*, tin octanoate.^{24–26} Properties of the polymers thus prepared strongly depend on the nature of the catalyst;^{27,28} therefore, a search for novel efficient catalysts is a topical trend in studies aimed at the synthesis of biodegradable polyhydroxyalkanoates.^{29–40}

Some examples of polyhydroxyalkanoates prepared by chemical synthesis are listed in Table 1.²²

Table 1. The main synthetic polyhydroxyalkanoates.

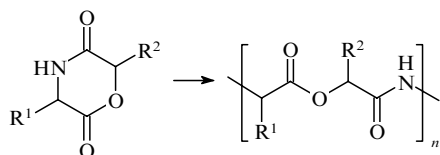
Name	Structure
Poly(oxymethylenecarbonyl) (polyglycolide, polyglycolic acid)	
Poly(oxyethylidenecarbonyl) (polylactide, polylactic acid)	
Poly(oxymethyleneoxyethylenecarbonyl) [poly(1,4-dioxanone)]	
Poly(oxypentamethylenecarbonyl) [poly(6-caprolactone)]	

Polyglycolide is a crystalline polymer with the melting temperature 225–230 °C.⁴¹ Its half-life varies from 60 to 90 days depending on the shape and size of the tested sample and the degradation conditions.^{42–49}

In contrast to polyglycolide, polylactides differ in structures and, correspondingly, in properties. The presence, in lactic acid, of a chiral carbon atom points to the existence of two stereoisomers (D and L); therefore, polylactide chains can be built of D- or L-isomers or of a racemic mixture of both. Poly-D-lactide and poly-L-lactide are crystalline polymers. Poly-D,L-lactide is an amorphous polymer; its properties are determined by the microstructures of its chains, namely, by the distribution of the D- and L-isomers,^{50–54} which varies from random to highly blockwise. This, in turn, determines physical (crystallisability) and chemical (degradation rate) properties of the polymer.⁵⁵

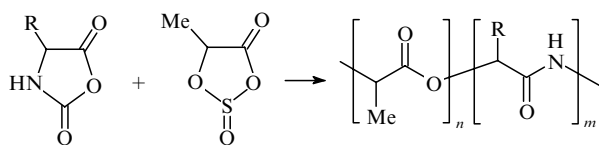
Both polyglycolide and polylactides can be regarded as the basic polymers of a family of polymeric products; in their hydrolysis, the $-O-C(O)-$ bond is cleaved. One of the groups of this family is represented by polyhydroxyalkanoates with a long-chain side alkyl substituent at the α -carbon atom.^{56–67} Yet another prominent group contains linear ω -polyesters among which poly(6-caprolactone) presents the greatest practical interest.^{68–73}

In addition to polyesters containing only ester hydrolysable groups, of great industrial importance are polymers containing other functional groups in the main chain, *e.g.*, ether groups, obtained by polymerisation of dioxanones.^{74–78} Such polymers are more hydrophilic than polyhydroxyalkanoates. Mention can be made of polymers containing alternating ester and amide bonds in their chains. They are prepared by polymerisation of morpholine-2,5-diones.^{79–83} Essentially, these compounds represent alternating copolymers of α -hydroxy and α -amino acids. They possess enhanced hydrophilicities; in addition, side functional groups that can undergo polymer-analogous transformations can be incorporated into the polymeric chains.



Synthesis of such polymers is rather complicated and labour-consuming; therefore, copolymers of lactide with the corresponding morpholinediones are prepared instead.^{84–91}

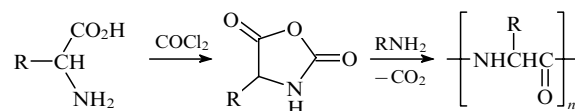
An interesting and efficient approach to the synthesis of copolymers of hydroxy and amino acids has been developed by Deng and co-workers.⁹² It is based on the copolymerisation of amino acid *N*-carboxy anhydrides with α -hydroxy acid anhydrosulfites.



The physical and chemical properties of polymers (including degradation rates) can be changed substantially by varying their chemical structures. The degradation rate depends critically on the nature of the monomers. Thus polyesters derived from oxalic acid are characterised by the highest degradation rates and are rapidly (within several hours) decomposed in weakly alkaline media (*e.g.*, in saturated solutions of sodium bicarbonate).^{93–95} Polyanhydrides^{94–104} prepared by polycondensation of aliphatic dicarboxylic acids in the presence of acetic anhydride¹⁰⁵ or by polymerisation of cyclic anhydrides^{106,107} undergo very fast hydrolytic degradation. However, polyoxalates and polyanhydrides have one common disadvantage: their degradation yields abiotic products.

Yet another type of biodegradable polymers is represented by polyamides including synthetic protein analogues, *viz.*, poly- α -amino acids (polypeptides). Their degradation rates in biological media are significantly lower than the degradation rates of structurally similar polyesters. As a rule, the degradation of polyamides requires the presence of the corresponding proteases in the reaction medium.^{108–112}

Polypeptides are prepared by various methods, among which polymerisation of *N*-carboxy anhydrides of α -amino acids has been studied in detail.



Recently, procedures for the polymerisation of these monomers have been developed that yield living polymers. This allowed preparation of polypeptides with a very narrow molecular-mass distribution.^{113,114}

The amino acid units in synthetic polymers based on natural amino acids can be linked into polymeric chains in both α - and other positions. Along with amino and carboxylic groups, other functional groups (*e.g.*, the hydroxy groups of serine, threonine or tyrosine) can be involved in the chain formation, which enables the access to polymers with predetermined properties.¹¹⁵

V. Degradation of natural and synthetic polymers in the environment

Studies of degradation of natural and synthetic polymers in the environment may conventionally be classified into several groups:

— ‘Archeochemical’ studies of polymeric articles dating back to ancient times. As a rule, such investigations are concerned with archeological finds. Thus the paper¹¹⁶ describes the results of an analysis of more than 6000-year-old wood specimens from some Egyptian tombs in comparison with other ancient specimens discovered in different parts of the world. Special attention is given to the dependence of the action of fungi and microorganisms on the specimens in the local environmental conditions (humidity, soil characteristics, *etc.*).

— ‘Full-scale’ studies of polymer degradation in soil, sea- and river water, compost, *etc.* Such studies usually have only limited, regional significance, since the factors responsible for the degradation of polymers are highly region-specific. The objects for such studies include newsprint paper, natural and synthetic packaging materials, *etc.*^{117–122}

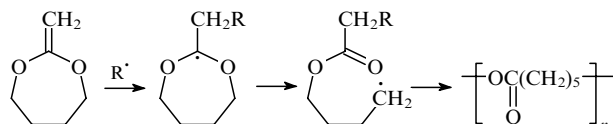
— Laboratory studies where the effects of one or several quantitatively describable factors able to induce degradation of polymers in nature (light, oxygen, water, definite bacterial strains, *etc.*) are simulated.^{123–125}

Studies of polymer degradation *in vivo* occupy a prominent place.

The search for synthetic polymeric materials that are decomposed in the environment at fast rates without the formation of large amounts of harmful products are underway in many countries. A key trend is the increase in the degradation rates of materials based on carbochain polymers, such as polyethylene, polypropylene, poly(vinyl chloride), which contribute the most to the environmental pollution, since they are not very prone to oxidative and photochemical degradation, nor they are decomposed by enzymes, microorganisms or fungi. Polyethylene, which is especially dangerous for soils, is an example. It was calculated¹²⁰ that the decomposition of low-density 60 μ m-thick polyethylene films lasts 300 years! IR spectroscopic studies have shown that the main degradation mechanisms of this material include oxidative and photooxidative degradation, which is accompanied by the introduction of hydroxy groups and double bonds in the polymeric chain. Enhanced hydrophilicity of polymeric films favours their attack by microorganisms.

The main pathways to increase the decomposition rates of polyethylene and related polymeric compounds include the incorporation, into the polymeric chain, of units susceptible to degradation. This can be performed by copolymerisation of the basic monomer with a small amount of a 'degradable' co-monomer or by preparation of composite biodegradable materials from blends of carbochain polymers with natural biodegradable polymeric compounds, *e.g.*, starch.

2-Methylidene-1,3-dioxepane, which is easily homo- and copolymerised under various conditions, is a promising degradable co-monomer. Upon its incorporation into polyethylene¹²⁶ or other vinyl polymers,¹²⁷ the monomeric units are formed that contain an aliphatic ester bond which undergoes cleavage in the hydrolytic degradation of the copolymer macromolecule.



However, the majority of these studies are aimed at the production of blends of carbochain polymers with biodegradable (both natural or synthetic) polymers. A prominent position among natural polymers used as additives to polyethylene or polypropylene is occupied by starch. Blending of starch with polyethylene in certain proportions under various conditions affords thermoplastic polymeric materials. The articles prepared from them are only slightly inferior to those prepared from the free polymer in mechanical characteristics, but they decompose in the environment by factors of tens faster.¹¹⁹ A series of such polymeric materials (Mater-Bi) have been developed recently in Italy.¹²⁸ The interest in their manufacture is especially high in southern countries where the production of starch from various local sources, *e.g.*, rice, is especially well-established.¹²⁹ In some cases, hydrophilic polysaccharides are subjected to chemical modification in order to enhance their hydrophobic properties and to improve their compatibilities with hydrophobic polyolefins.¹³⁰

Composite degradable polymeric materials were also developed on the basis of other polymeric combinations, *e.g.*, poly(vinyl alcohol)–starch¹³¹ and polycaprolactone–lignin.¹³² The main advantages of this approach include relative simplicity, low cost and possibility to use basic polymers produced on a large scale and inexpensive degradable additives (starch, lignin). The disadvantage consists of low mechanical characteristics of ready articles, predominantly due to the poor compatibility of the components.

The manufacture of polymeric articles that preserve high mechanical characteristics throughout the operation period and undergo rapid degradation afterwards without release of harmful products is yet another promising trend in the design of environmentally friendly polymeric materials. As regards their functions, this group refers primarily to packaging materials. The aliphatic polyesters of synthetic and microbiological origin described above present the greatest practical interest in this respect. Such polymers can be used as such in single-component systems and as degradable components in blends with large-scale manufactured polymers.

VI. Biomedical technologies based on polymer degradation

Natural polymers (*e.g.*, cellulose and silk fibres) have been used in medicine as suture and dressing materials since the time of its origin by virtue of their high durability, flexibility and ability to absorb moisture. The advent of novel polymeric materials (natural rubber and gutta-percha) favoured the development of novel medical products. The discovery of the macromolecular origin of polymers and the subsequent explosive development of the synthetic polymer chemistry has led to closer interactions between

these areas of knowledge. Biodegradable polymers were also in great demand in clinical medicine. A variety of novel, in principle, biomedical technologies developed in the past decades are based on degradation of polymers in aqueous physiological media.

The biodegradable polymeric materials used in the medical practice differ in the phase states of their constituent polymers (solutions, gels, solids), shapes [*viz.*, one-dimensional (fibres, tubes), two-dimensional (films, fabrics), three-dimensional (large-size articles some of which have rather complex shapes)] and in decomposition rates in biological media. This Section deals with the description of three lines of research in this area, *viz.*, preparation of biodegradable suture and dressing materials, development of biodegradable polymers for the targeted delivery of medicinal drugs and the use of biodegradation in tissue engineering.

1. Biodegradable polymeric suture, fastening and dressing materials

The problem of bioresorbable (biodegradable) suture materials is as old as the surgery itself. Whereas suture removal after external wound healing does not present significant difficulties, in the case of intracavitary operations this procedure may require additional surgical intervention.

Traditionally, fibrous materials of cellulose fibres are used in the clinical practice as dressings due to their high moisture-absorbing properties. Filaments of cellulose and natural silk have been used as suture material; they do not induce rejection, but are resorbed in the organism for a time exceeding manifold that required for the regeneration of tissues. Therefore, practitioners in medicine are on a continuous search for bioresorbable suture materials. The catgut, *i.e.*, a filament prepared from dried intestinal membranes of young cattle, is now forbidden for use in the surgical practice in many countries of the world because of the problem of 'mad cow disease' (bovine spongiform encephalopathy).

Suture materials (fibres and filaments) prepared from polylactide, polyglycolide and their copolymers are currently widely used in intracavitary operations. These polymers are readily converted into fibres by extrusion at temperatures below their thermal degradation temperature, which excludes the presence of foreign degradation products in the extrudates. The time required for the complete decomposition of these materials in the human organism can be controlled by the composition of the copolymers. Commercial production of such suture materials (mono- and polyfilamentous fibres)¹³³ is currently underway in some European companies. Each type of filaments has advantages and disadvantages of its own. Monofilamentous threads have smoother surfaces and are sterilised more easily. Their main disadvantage is higher stiffness, which creates additional problems during the operation. Polyfilamentous threads are more convenient, however their less smooth surfaces create complications and do not always meet the requirements for high sterility.^{133–138} In Russia, surgical suture filaments based on biodegradable polymers (Vycril, Dexon) are mainly produced from imported raw materials.

The adequate use of ware for union and fastening of bone fragments in reconstructive surgery presents a serious problem. While metallic (titanium) staples, pins and screws are very convenient surgical tools, their removal after consolidation of fractured bones demands additional surgical operation. Therefore, leaving metallic fasteners in the patient's organism is considered admissible. Within the organism, these are gradually overgrown with connective tissue and after a while they are no longer recognised by the organism as foreign bodies. However, the difference in the deformation characteristics of the bone tissue and titanium may create serious problems for patients. Moreover, redistribution of load in favour of the metallic element increases the risk of osteoporosis.

Some manufacturers produce polylactide fasteners for bone fragments. The adequate choice of chemical structures of poly-

mers enables the synchronisation of the time of their degradation and that of bone consolidation, which varies from several weeks to several months. Such materials are usually made of poly-L-lactide, a polymer with a regular structure and high degree of crystallinity. Due to the regular crystalline structure, the diffusion coefficients of the destructive reagents inside the fasteners decrease, which makes the latter more stable than those made of amorphous materials. Of particular importance is the sizes invariability of polymeric fastenings in the earliest steps of bone consolidation, *i.e.*, these materials should not swell in biological media.¹³⁹

2. Biodegradable polymers for targeted delivery of medicinal drugs

The problem of drug formulations is one of the main challenges to modern pharmacology. On entering the organism (especially, upon oral administration) drugs are exposed to the action of highly active biological media containing enzymes. This results in partial or complete inactivation of the drug before it reaches the small intestine and is absorbed by blood. Therefore, one has to increase the drug dose, which increases the risk of side effects. Direct administration of medicinal drugs into the circulating blood is not always efficient due to functioning of protective mechanisms from drugs as foreign compounds. Therefore, the therapeutic effects of drugs administered in this way are short-lasting (Fig. 1).

In the 1950's, it has occurred to use polymers for the modification of medicinal drugs. Initially, biologically active substances were chemically immobilised on polymeric macromolecules as supports.¹⁴⁰ This approach was thought to prevent drug inactivation in the organism (especially, upon oral administration) and to prolong their therapeutic effects. Studies aimed at perfecting the functioning of drugs follow two major lines, *viz.*,

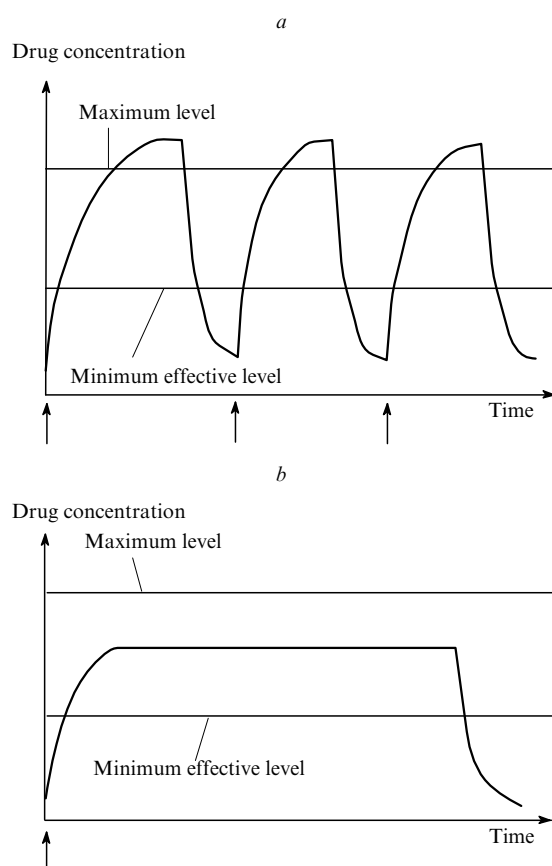


Figure 1. Time dependences of the concentration of a free drug (a) and of a drug included into biodegradable polymeric microgranules (b). The time of drug administration is marked by arrows.

(i) maintenance of constant drug levels over sufficiently long periods of time and (ii) efficient (without inactivation) delivery of drugs to damaged cells, tissues or organs with subsequent release of the active substance in the target organ or tissue (targeted drug delivery).

Various approaches are known to reach this goal, including the use of thermo- and pH-sensitive hydrogels¹⁴¹ and biodegradable polymers. Chemical and physicochemical aspects of drug design for targeted delivery of active substances based on the use of biodegradable polymers are considered below. The main principle in the design of such formulations consists of the encapsulation of medicinal drugs into matrices of biodegradable polymers and administration of these compositions. In the organism, the polymer undergoes gradual degradation with liberation of the active substance. Obviously, invariability of the drug upon the production of such compositions is a necessary condition.

Biodegradable films and macroscopic plates are among the simplest formulations of this kind where the active substance is dispersed more or less uniformly in the bulk. Such articles are implanted into the area of the injured tissue or organ and function as 'drug depots'. The controlled release of the drug from the polymeric matrix occurs continuously, in the course of its degradation.

The methods for the manufacture of such articles depend on the physicochemical properties of the constituents. If the drug and the polymer are soluble in the same solvent (*e.g.*, dichloromethane), films of required thickness are cast from a solution of the components and are cut into plates or rods. If the components have no common solvent, they are finely dispersed into a mechanical blend and thermal compacting affords films, plates or rods. In the case of thermal inactivation of a drug, an inert solvent is added to the dispersed blend until a thick paste is formed. This is dried to give plates of a biodegradable polymer–drug composite. This method was used¹⁴² to obtain composites of the antibiotics Sulperazone or Duocide with a copolymer of 3- and 4-hydroxybutyric acids employed in the therapy of osteomyelitis.

Microencapsulation is a more complex process for the production of compositions of biodegradable polymers with drugs. Usually, it includes emulsification of a solution of a biodegradable polymer in water in the presence of a surfactant or a stabiliser, *e.g.*, partly hydrolysed poly(vinyl acetate). In these technologies it is important that the polymer and the drug be soluble in the same solvent. In this case, the polymer and the drug are dissolved in this solvent (*e.g.*, dichloromethane) and are emulsified in water in the presence of a surfactant (an 'oil-in-water' emulsion) using vigorous stirring or sonication. On gentle heating, the solvent is evaporated from the emulsion droplets to afford a suspension of microgranules. Their sizes depend on the stirring rate, the surfactant concentration and other factors; they vary from 10 to 60 μm . Such granules represent homogeneous systems the active drug in which is evenly distributed in the bulk.

This method was used by Langer and co-workers¹⁴³ for the preparation of microgranules from copolymers of lactic acid with lysine containing side polypeptide chains grafted to the NH_2 groups of lysine. Rhodamine B was used as a model of the encapsulated drug. Such copolymers present considerable interest, since the presence of side amino acid functional groups and the active substance in the grafted polypeptide chains allows covalent binding of this or any other drug to the surface of the microgranules (in addition to encapsulation) or its binding through electrostatic forces.

The situation is more complex where the drug is water-soluble and the polymer is soluble in a low-polar solvent. In this case, microgranules are prepared by the double emulsion method ('water-in-oil' in water). The first step includes the preparation of an aqueous solution of the drug in a solution of the polymer in a low-polar solvent ('water-in-oil'). In the second step, the resulting emulsion is poured into an aqueous solution of a surfactant with vigorous stirring or sonication (Fig. 2) to yield a double emulsion ('water-in-oil' in water). The last step includes

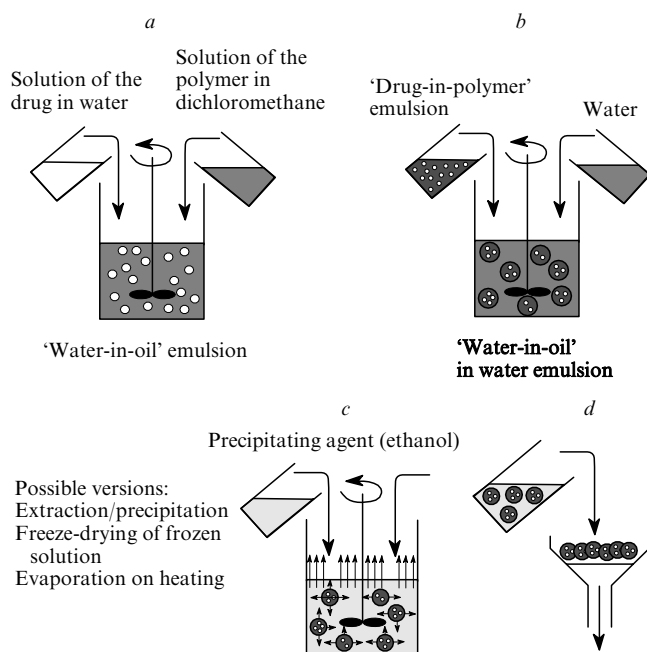


Figure 2. A chart of manufacture of drug-loaded polymeric microgranules.

(a) Loading of the polymer with the drug; (b) preparation of a polymer dispersion; (c) removal of an organic solvent; (d) isolation of the microgranules.

removal of the low-polar solvent and solidification of the microgranules with the encapsulated droplets of the aqueous drug solution by evaporation of the solvent with constant stirring or by addition of a solvent that precipitates the polymer. The microgranules can be filtered off or isolated by centrifugation. If required, water can be removed from the frozen granules by lyophilisation. The product obtained represents a microheterogeneous system where the drug (as an aqueous solution or as such) is dispersed in the bulk of the degradable polymer. Surface erosion of such granules results in the release of the drug into the organism.

The features of the manufacture of microgranules based on a copolymer of D,L-lactide with glycolide by the double emulsion method is described in detail.¹⁴⁴ In this study, ¹⁴C-mannitol was used as the included compound; its content in the granules and the rate of its liberation upon polymer degradation were established by radioactivity measurements.

More sophisticated techniques for the manufacture of microgranules with drugs included have been developed. For example, according to the ProLease[®] technology,¹⁴⁵ a solution of a polymer in dichloromethane containing dissolved or dispersed additives is sonicated in a vessel with liquid nitrogen. On the vessel bottom, frozen ethanol is present meant for polymer precipitation. Thawing of ethanol as the temperature is increased results in extraction of the solvent from the granules. This approach was used¹⁴⁶ for the manufacture of polylactide microgranules containing human growth hormone; their degradation and the concomitant liberation of the hormone were studied both *in vitro* and *in vivo*.

Production of nanoparticles with included medicinal drugs was the next step in the miniaturisation of degradable polymer granules. These technologies are based on the formation of micelles of diphilic block-copolymers, one of the blocks being biodegradable. Immobilisation of lipophilic drugs is achieved by their solubilisation in micelle cores. The structures of micelles can be stabilised by polymerisation of the functional groups localised either in the micelle core or on its surface. A series of papers devoted to polymeric core-shell micelles were published by

Kataoka and co-workers.^{147, 148} One of the first reports on 'surface cross-linked' micelles was published by Wooley and co-workers.¹⁴⁹ Micellar 'nanodepots' for drug delivery are reviewed in detail.^{150, 151}

3. The use of biodegradable polymers in tissue engineering

Tissue engineering is a novel, rapidly developing trend in the biomedical science which is concerned with the methods for the growth of fragments of tissue or organ injured as a result of a disease or an accident, from patient's own cells and further implantation of the tissues into the organism. Quite naturally, the immunocompatibility problem is not critical in this case. This approach was developed in the 1980's by the American surgeon Vacanti in collaboration with the chemist Langer. The first publications on this subject appeared in the early 1990's.^{152, 153}

Currently, cell therapy is often used for the treatment of some severe diseases resulting from injuries of tissues of internal organs and including myocardial infarction. A suspension of living cells of the corresponding tissue are commonly administered to the patient, they find the target site themselves and favour fast healing of the injured tissue. Unfortunately, this approach is not always efficient; moreover, it demands the use of a large excess of cell cultures.

In the approach developed by Langer and Vacanti, the cell culture of the corresponding tissue is plated onto a special porous scaffold made of a biodegradable polymeric material. After adsorption on the inner surface of the scaffold pores, the cells begin to proliferate, which results in fusion of an integrated tissue. In a biological medium, the scaffold undergoes gradual degradation (Fig. 3). After a while, a fragment of the integrated tissue is formed instead of the polymeric scaffold with sown cells. Its shape is the same as the shape of the original scaffold and is not foreign for the organism.

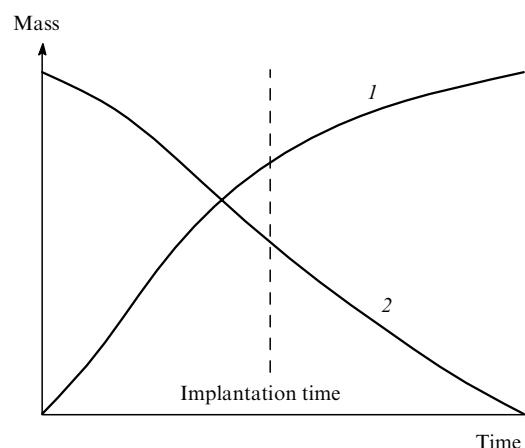


Figure 3. Time dependences of the mass of an integrated cultured tissue (1) and the polymeric material of the scaffold (2).

At present, the muscle, bone and connective tissue engineering has reached the clinical level.^{154–159} Studies on culturing of skin,^{160, 161} nerve,^{162–165} parodontium^{166, 167} and eyeball (including crystalline lens) tissues^{168–170} are in the research stage. Needless to say, each tissue type has its own peculiarities and requires original approaches. Thousands of papers devoted to tissue engineering have appeared since the first publication (see, for example, Refs 171–187). The use of polymeric materials in tissue engineering has been reviewed^{188, 189} (the data are as of 2000).

Further progress in this area depends on the solution of a great number of diverse problems. Here we briefly discuss the major problems related to the use of biodegradable polymers in tissue engineering (for the design of scaffolds) and their interactions with the cellular material, *viz.*,

- chemical nature of the polymer;
- types of polymeric scaffolds and technologies for their manufacture;
- dependence of cell behaviour on chemical, energetic and morphological characteristics of the polymer surface;
- cell interaction with the polymeric surface of the scaffold and the principles for improving its efficiency by surface modification.

a. Chemical nature of polymers used in scaffold manufacture

Polymers used for the manufacture of scaffolds should meet a number of demands:

- (i) they should not be toxic, nor induce rejection, *i.e.*, be biologically compatible with body tissues;
- (ii) their degradation rates should correlate with the rates of formation of the integrated tissue;
- (iii) their degradation products should not be toxic; moreover, it is desirable that these products served as nutrients for the growing tissue cells;
- (iv) the chemical structures of the polymers should create the most favourable conditions for the cell growth on the scaffold surface.

A series of natural and synthetic biodegradable polymers meet these requirements. Among the natural polymers, various types of collagens, chitosan, hyaluronic acid, starch and some other polysaccharides can be distinguished. Being a matrix protein formed by living cells sown onto a foreign surface, collagen would be an ideal material for the scaffolds. However, its physicochemical properties do not always match the technology of scaffold manufacture. In addition, the rate of its degradation in the organism is often too low for the solution of many practical tasks of tissue engineering. Chitosan is a product of partial or complete deacetylation of chitin. Its physicochemical properties are determined by the degree of deacetylation, which allows their adaptation for the solution of specific tasks.^{9, 190} For this reason, chitosan and its derivatives can be regarded as promising polymeric materials for the manufacture of scaffolds.^{191–195}

However, the majority of studies aimed at the design of scaffolds deal with synthetic biodegradable polymers, predominantly polyhydroxyalkanoates and related materials. Poly-D,L-lactide, poly-L-lactide and their copolymers are used as the basic polymers; they are the most thoroughly studied as regards their synthesis, degradation and behaviour *in vivo*. The use of polylactides for the preparation of medicinal products is authorised in the majority of industrially developed countries. Non-toxicity of these polymers and their degradation products is their main advantage.

The degradation rate of poly-D,L-lactide meets the requirements for the polymeric materials used for the manufacture of scaffolds. These materials are easily processed by molding from

melts or casting from solutions in organic solvents.¹⁹⁶ The broad range of properties of lactide-based copolymers allow their extensive use in the design of macromolecular constructions.

A family of novel copolymers based on polylactide have been developed.¹⁹⁷ These include depsi-peptides with side groups containing ionogenic groups; comb-like and branched polylactides; polylactides grafted to polysaccharide chains. Polylactide copolymers grafted to dextran as the main chain have been described.¹⁹⁸

b. Types of polymeric scaffolds and technologies of their manufacture

A key problem in the construction of a tissue or an organ fragment is related to the structure of the polymeric scaffold used as a biodegradable matrix for cell seeding. As a rule, they are two- or three-dimensional constructions containing an array of interconnected pores of definite sizes and configurations. These may include truly porous (*e.g.*, foam-like or sponge-type) or quasi-porous objects made of woven or non-woven moulded materials with fibres of various diameters prepared from biodegradable polymers. The manufacture of the latter type of scaffolds utilises the most advanced technologies, such as, for instance, multilayer deposition of fused fibres with the help of a special programming device (Fusion Deposition Modelling). The approaches to the formation of such scaffolds are given in detail in a review.¹⁵⁵

Of particular interest are the technologies used for the manufacture of genuinely porous scaffolds where the cells are bound to the polymer on the inner surface of a pore rather than on the outer surface of a fibre or a disc. In contrast to foams where the pores are isolated from one another, sponges contain a well-developed system of interconnected pores. Sponge-like systems are the most suitable for tissue engineering, the bimodal pore size distribution being optimal, with large pores having diameters $\geq 100 \mu\text{m}$ and small ones having diameters of tens to hundreds nanometres. It is on the inner surface of large pores that the cells attach to the polymer, proliferate and then integrate into the tissue. The supply of nutrients and the removal of metabolites occur through the biological fluid that circulates through the system of small pores. Porosity, *i.e.*, the ratio of the pore volume to the total volume of the polymeric article, is an important characteristics of a scaffold. This is directly related to its mechanical properties including the ability to preserve its shape during the time required for the formation of an integrated tissue. In this situation, it is important to maintain the balance between the mechanical strength and the resistance of the scaffold to external factors, on the one hand, and the minimum content concentration of the structure-forming polymer in the total volume of the scaffold, on the other hand. The main methods for the manufacture of porous scaffolds and their characteristics are listed in Table 2.^{155, 199}

Table 2. The main approaches to the manufacture of polymeric scaffolds.

Method	Average pore size / μm	Degree of porosity (%)	Structural features
Foaming with a gas	0.1 – 1000	—	open and closed isotropic pores
Phase stratification in the system polymer – solvent induced by temperature changes with subsequent removal of the solvent (by lyophilisation or extraction)	< 200	97	open isotropic pores
Preparation of a 'water-in-oil' emulsion with subsequent freezing and lyophilisation (removal of water)	< 200	97	the same
Preparation of mechanical blends of a polymer and fractionated salt crystals with subsequent extraction of the latter with water	< 100	85	closed and open pores having the shapes of porogen particles (cubic in the case of NaCl crystals)
Construction of a pore system using a three-dimensional template with subsequent removal of the latter	45 – 150	60	open pores of any predetermined shape
Phase stratification of two incompatible polymers with subsequent removal of one of the polymers by selective solubilisation or degradation	200 – 300	80 – 90	open pores

A novel approach to the formation of porous structures based on the use of blends of two incompatible polymers and subsequent selective degradation of one of them has been developed by the authors of the present review.⁹⁵ Its essence is as follows:

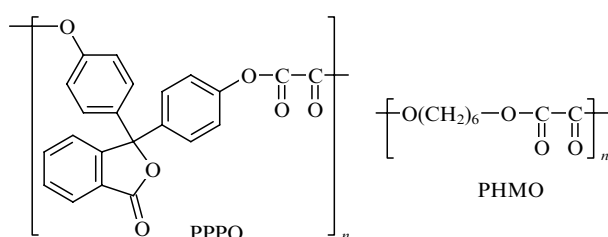
(1) The degradation rates of two polymers one of which is a matrix-forming component and the other is a pore-forming component should be essentially different (by no less than 1 to 2 orders of magnitude).

(2) The polymers should undergo phase separation in solution or in a melt to form biphasic continuous systems.

(3) The heterogeneous structure formed is stabilised by precipitation of the polymer or by cooling of the melt.

(4) The pore-forming polymer should be selectively extracted.

The feasibility of this approach was demonstrated in experiments with blends of a polylactide (PLA) and polyoxalates [poly(phenolphthaleine oxalate), PPPO and poly(hexamethylene oxalate), PHMO], which possess high degradation rates in alkaline media.



Highly porous polylactide discs (the degree of porosity $\sim 90\%$) were prepared by sedimentation of a heterogeneous polymeric blend from a solution with subsequent compacting and degradative removal of the polyester.²⁰⁰ The micrographs show the general view of a porous disc (optical microscopy) (Fig. 4) and its microstructure (electron microscopy) (Fig. 5).

Porous films prepared by casting from both the melts and the solution with subsequent degradative polyester removal are shown in Fig. 6.²⁰¹ A similar approach to the formation of porous structures was developed recently by Favis and co-workers^{202, 203} and by Langer and co-workers.²⁰⁴

Other characteristics of inner surfaces of the scaffold pores including the character of the inner surface of pores and its topography, free surface energy, charge, the presence of func-

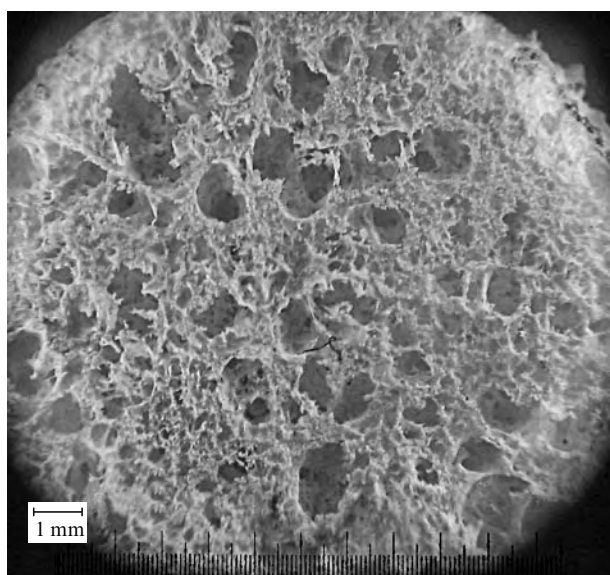


Figure 4. A porous disc manufactured from a heterogenous system PLA–PPPO in the solution by precipitation of the emulsion, extrusion and degradative removal of PPPO.

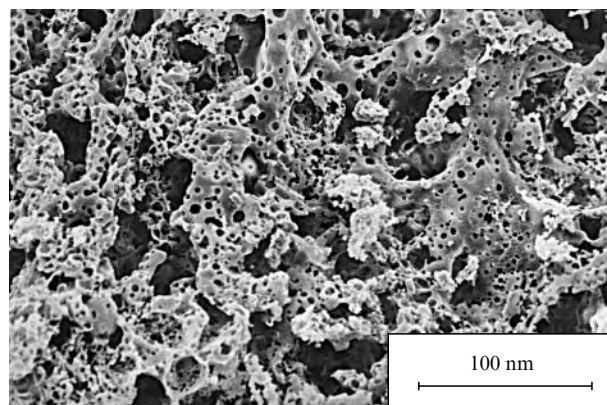


Figure 5. Microstructure of a porous disc ($\times 300$ magnification).

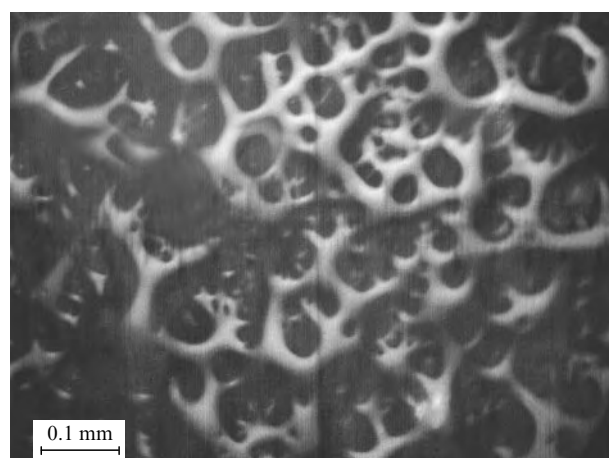


Figure 6. A porous film manufactured from the PLA–PHMO melt after the degradative removal of PHMO.

tional groups, hydrophobicity–hydrophilicity ratio, *etc.*, also play a prominent role.

c. Cell interactions with scaffold polymeric surfaces

The interactions of living cells with polymer surfaces present a serious problem in many areas of biology and medicine, particularly with respect to donor blood storage, organ and tissue prosthesis, *etc.* However, it is in tissue engineering that the interactions of cells designed for tissue growth with polymer surfaces are especially critical. These cells ought to manifest specific behaviour over the whole period of tissue growth beginning with the plating of the cells onto the scaffold up to the moment of their implantation into the organism. In the first step, the cells are to be adsorbed on the surfaces of polymeric articles. In this step, the forces that determine their adsorption should be strong enough to ensure their binding to the surface without causing their deformation. In subsequent steps, the cells begin to synthesise extracellular matrix proteins (collagen, fibronectin, *etc.*) and thus create convenient surfaces for subsequent active proliferation and formation of integrated tissues. These processes occur in parallel with the disintegration of the polymeric material of the scaffold.

The interactions that determine the adsorption of cells on the scaffold surface can be classified into several groups:

(1) non-specific weak non-covalent interactions that are largely determined by the free surface energy of the polymeric material (or, more exactly, by the free interphase energy at the polymer–physiological medium interface);

(2) electrostatic interactions of negatively charged cells with the polymer surface;

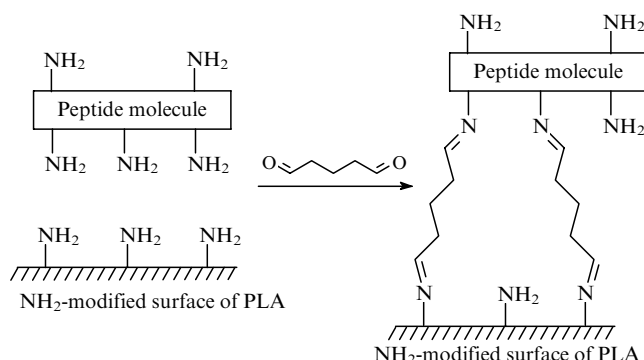
(3) highly specific interactions of cell receptors with binding chemical structures, most commonly, of the peptide nature, immobilised on the surface of the polymeric material.

In addition to physicochemical and biospecific factors, cell binding to polymeric surfaces strongly depends on their morphology.^{205–208} The majority of cell adsorption experiments were carried out with films, since three-dimensional samples present problems as regards formation of certain surface structures and their analysis. Polymeric materials with predetermined surface morphology can be obtained in different ways, *e.g.*, using various combinations of a polymer and a solvent (or solvent mixtures)²⁰⁹ or by preparing films from polymer blends followed by thermal or chemical treatment of the preformed films.^{210, 211} It was found²⁰⁷ that polyhydroxyalkanoate films prepared under special conditions had coral-like surfaces with low cell adsorption. The structures of such surfaces become smoother upon treatment of films with lipase, which increases cell adsorption 40-fold.

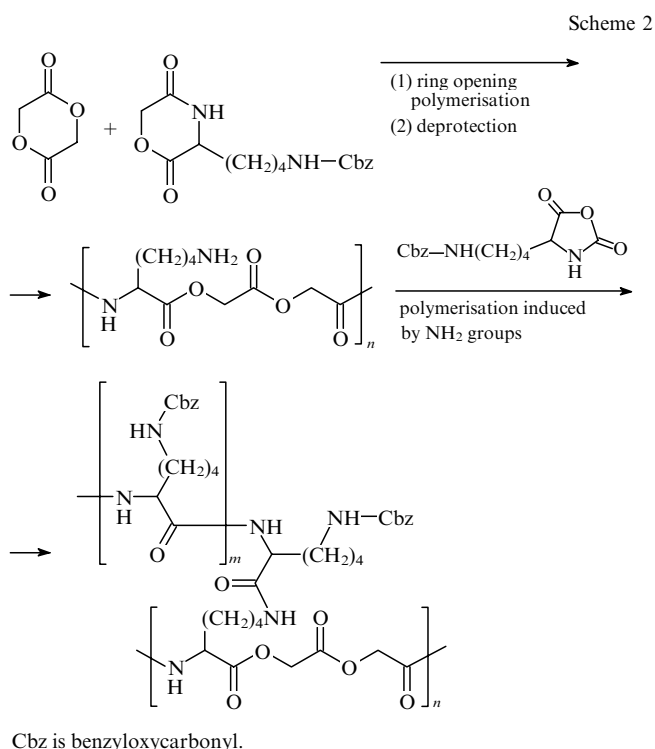
The free energy of a surface is largely determined by the nature of the polymeric material. The lowest values of this parameter are characteristic of perfluorinated polymers. For example, the free surface energy of Teflon is 18 mJ m^{-2} . The interactions of such surfaces with cells are negligibly weak, which allows their use for the storage of donor blood and for other similar purposes. Higher values of free energy are required for more efficient adsorption of cells on the scaffold surface.²¹² Surface hydrophilicity is yet another important related factor, since the majority of cells (with the exception of adipose tissue cells) function in aqueous media and possess high affinity for hydrophilic surfaces. Polyhydroxyalkanoates, the most popular scaffold material, have hydrophobic surfaces, which reduces cell adsorption on them.

The hydrophilicities of polyhydroxyalkanoate-based scaffold surfaces can be increased by different methods. One of the most popular techniques includes treatment of scaffold surfaces with solutions of extracellular matrix proteins. This procedure has a dual effect, since it increases both the hydrophilicity and the biocompatibility of the scaffold surface. The use of collagen-treated films for cell adsorption allows one to increase significantly the number of cells adsorbed per surface unit.^{213, 214} Moreover, these cells are able to proliferate spontaneously (without additional adaptation). The main disadvantage of this approach is that collagen and other matrix proteins are very quickly desorbed from the polymer surface in physiological media. To prevent desorption, these proteins are covalently bound to the polymer, *e.g.*, using glutaraldehyde (Scheme 1).¹⁸⁴

Scheme 1



However, the practical realisation of this approach requires the use of polymeric materials with surface amino groups, *e.g.* chitosan the number of amino groups in which is easily controlled by the extent of hydrolysis of the acetamido groups.²¹⁵ Lysine units can be introduced into polyhydroxyalkanoates, the most suitable material for the manufacture of scaffolds, by copolymerisation of the lactide with the corresponding morpholinedione.⁸⁸ Removal of the protective benzyloxycarbonyl groups in the side chains liberates amino groups.



The role of positively charged amino groups on the scaffold surface is not confined to the covalent binding of matrix proteins. These groups enhance cell adsorption due to electrostatic interactions with the negatively charged cell surface.²¹⁶ In order to further enhance this interaction, Langer and co-workers⁸⁹ employed the amino groups of lysine in the copolymer chains for graft-polymerisation of N^α -carboxy- N^ϵ -benzyloxycarbonyl lysine (Scheme 2).

Covalent attachment of the so-called binding peptides is one of the most interesting approaches to increasing the affinity of the scaffold surfaces to the cells to be adsorbed. The tripeptide arginyl-glycyl-aspartyl (RGD-peptide) able to interact with cell-binding receptors has been studied in most detail.^{217–221} The incorporation of even very small amounts of this peptide resulted in a significant increase in the surface adsorption of the cells. The works devoted to biospecific adsorption of cells on the surfaces of polymeric materials under the action of binding peptides were published quite recently. There is still no data on which of the methods for grafting of the peptide to the scaffold surface ensures the best results. However, further studies may culminate in significant achievements in the physicochemistry and biochemistry of interactions of living cells with various surfaces.

Obviously, very soon novel tissue engineering technologies will occupy a prominent place not only in reconstructive surgery, but also in treatment of diseases that are still beyond the control of modern medicine. The development of novel biodegradable polymeric materials will surely make a weighty contribution to the attainment of this goal.

VII. Conclusion

In the past few decades, the branch of chemistry of high-molecular-mass compounds concerned with the degradation and stabilisation of polymers has developed into a vast area of knowledge that involves diverse sciences and technologies — from chemistry to microelectronics, biogeochemistry, ecology, medicine and even archeology. The conventional views on the polymer degradation and its role in nature and in modern technologies also changed considerably. For a long time, the main efforts were focussed on the protection of polymeric articles from degradation;

however, more recent trends are towards investigation of the role of polymer degradation in sculpturing the appearance of our Planet and functions of living organisms, natural transformations of low-molecular-mass compounds into polymers and *vice versa* and the 'fate' of polymeric articles that have served their time in the environment. However, the most important result in studies of polymer degradation is that this phenomenon has found novel, quite unexpected applications in the most advanced technologies.

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^a — *Polym. Sci. (Engl. Transl.)*

Charge transfer processes in conducting polymer films

V V Malev, V V Kondratiev

Contents

I. Introduction	147
II. Method of equivalent circuits	148
III. Homogeneous film model	151
IV. Experimental results on the impedance of modified electrodes	154
V. Conclusion	159

Abstract. The available models of charge transfer processes in electroactive polymer films are considered. Examples of interpretation of the data of electrochemical measurements using model approaches are given. The emphasis is placed on the interpretation of the results on the impedance of modified electrodes. On this basis, conclusions concerning the most topical research problems and the description of the processes in question are drawn. The bibliography includes 122 references.

I. Introduction

The laws of electrode processes in electroactive polymer films have been the subject of intensive research in recent decades. At present, this is an individual investigation direction called electrochemistry of modified electrodes. Research in this field became particularly intensive since the discovery of the so-called 'synthetic metals' (conducting polymers with conjugated bonds) in the late 1970s.¹ Incessant interest in such polymers is due to prospects for their practical use as materials for power sources, various electrochromic and optoelectronic devices, *etc.*^{2–10} Until very recently, most studies in this field concerned the search for novel systems in order to fabricate films whose properties will fulfill practical demands. Studies on the laws of transport processes in such systems are scarce. The fact that the kinetics and mechanisms of charge transfer in electroactive polymer films have been poorly studied is due to the lack of information on their structural features. The stoichiometry and products of the electrode reactions are sometimes unclear. Often, it is unknown which proportion of potentially active film fragments is involved in the electrode process and whether or not are the film properties changed with the film thickness. The authors of the present review do not pretend to highlight all aspects of research in this field. Here, it is appropriate to place the emphasis on theoretical approaches to the description of charge transfer in various polymers and on generalisation of quantitative data on the kinetics of these processes.

V V Malev, V V Kondratiev Department of Chemistry, St Petersburg State University, Universitetsky pr. 26, Petrodvorets, 198504 St Petersburg, Russian Federation. Fax: (7-812) 428 69 39, tel. (7-812) 428 69 00, e-mail: malev@ech.chem.spb.ru (V V Malev), vkondrat@rbcmail.ru (V V Kondratiev)

Received 12 April 2005

Uspekhi Khimii 75 (2) 166–182 (2006); translated by A M Raevskiy

A polymer-modified (from this point on, 'modified') electrode is a conducting substrate coated with an organic or inorganic electroactive polymer film contacting an electrolyte solution. Usually, two main classes of such films include electron-conducting (or simply conducting) polymers and redox polymers.^{8–10} The first class comprises organic polymers with a conjugated system of π -bonds. Here, the conductivity is due to delocalisation of electrons or 'holes' that appear upon the oxidation (doping) of the polymer. Typical conducting organic polymers with conjugated bonds include, *e.g.*, polymers based on aniline and its derivatives, polymers based on simple and substituted five-membered heterocycles (polythiophenes, polypyrroles), *etc.* A feature of this class of organic polymers is the ability to undergo reversible redox transitions involving the so-called dopants (anions, hydrogen ions). Redox transitions induce abrupt changes in the polymer conductivity, from quasi-metallic conductivity to semiconductor one.

The class of redox polymers comprises polymer structures containing immobilised redox active centres. Electron transfer between these centres determines relatively low electronic conductivity of such polymers. Electroactive centres can be constituents of the polymer chain or be bound to functional groups of the polymer. Typical redox polymers include polynuclear complexes based on metal hexacyanoferrates, polyoxotungstates and polyoxomolybdates as well as ion-exchange polymers with incorporated (electrostatically bound) redox active cations or anions.

In most cases electroactive polymer films are synthesised on the surface of electron-conducting substrates by electrochemical polymerisation of monomeric organic compounds or metal complexes.

Electrochemically active centres in the redox polymers are metal ions, which can change the oxidation state and thus participate in electron exchange processes. The conductivity of a redox polymer is governed by the product of the electron donor concentration by the electron acceptor concentration and reaches the maximum value at the formal potential of the redox system.

The electrochemically active fragment of conducting polymers is the double bond. Elimination of an electron from the double bond (oxidation) leads to the formation of a radical cation in the initial stage. Experimental EPR studies of conducting polymer films confirm the presence of unpaired electrons in the films.^{2,3}

A radical cation that formed is partially delocalised over a polymer chain fragment of size of a few (usually, 4–6) monomer units. This leads to deformation of the polymer structure and polarisation of the environment (this gave the name 'polaron' to the chain fragment containing the radical cation). Polarisation of the environment and interaction with counterions lead to stabi-

sation of the radical cation. If the next electron is removed from the same polymer chain fragment, a dication or bipolaron is formed. At present, the polaron theory of conductivity has been recognised as the main model for explanation of the electronic conductivity of polymers with conjugated bonds. According to this theory, the electronic conductivity is due to the motion of polarons and bipolarons along the polymer chain in an electric field and occurs by reorganisation of the double and single bonds and by electron hopping between chains.

In spite of some distinctions between these classes of polymers, common to both of them is a mixed electronic-ionic mechanism of conductivity. Indeed, a negative or positive charge injected into a film should be compensated by injection or removal of electrolyte ions absorbed in the film in order to meet the electrical neutrality condition for the entire film. Therefore, in both cases theoretical description of charge transfer has much in common; in essence, it uses the same model of electron hopping mechanism of charge exchange between adjacent redox centres (or delocalised holes and electrons in conducting polymers), accompanied by transfer of counterions.^{4–10} Considering the concepts underlying the interpretation of data on the electrochemical properties of electroactive polymer films, two approaches to construction of theoretical models of these systems should be pointed out. The first approach has been best developed and treats the film as a system possessing homogeneous properties.^{5, 11–19} Analysis of the response of a metallic electrode (conducting substrate) coated with such a film and contacting an electrolyte solution involves the division of the overall process into certain stages, namely, charge transfer in adjacent electrolyte and charge injection into and charge transfer inside the film. The second approach, which has been intensively developing recently, takes into account inhomogeneous structure of the film and, in particular, microcrystallite structure of the film, *i.e.*, the presence of pores filled with electrolyte.^{20–28} Apparently, electrolyte ions can be absorbed in (and removed from) such inhomogeneous film not only from the outer interface with the solution but also from the inner interfaces corresponding to pore–polymer interfaces.

From the aforesaid it follows that modified electrodes should be studied by various methods. Apparent correspondence between the electrochemical properties of the modified electrodes and the structure and morphology features of the modifier films requires the use of various structural-physical methods. At the same time it is desired that the structure and properties of films be changed in a target fashion using chemical techniques. Often an electrode process is accompanied by changes in the spectral characteristics of the films; this makes spectroelectrochemical methods of investigation necessary (see *e.g.*, reviews^{29, 30}). An important role is also played by the quartz microbalance method,^{31–36} which in many cases helps to reliably determine the nature of counterions incorporated into polymer film and the degree of changes in the viscoelastic properties of the film in the course of the electrode process. The most widely used electrochemical methods of investigation of modified electrodes include cyclic voltammetry (CV) and Electrochemical Impedance Spectroscopy (EIS). Chronoamperometry (CA) is somewhat more rarely used. Multistage character of electrode processes in such systems, the presence of at least two interfaces (film–solution and film–metallic electrode or another conducting substrate, *e.g.*, semiconductor, graphite, glassy carbon) complicate the interpretation of experimental data.

Both the use of methods of investigation of modified electrodes and processes occurring in them and the difficulties in the interpretation of measurement results require elaboration of relevant theoretical concepts. A broad spectrum of problems and methods make it impossible to correctly describe all aspects of research in the field of modified electrodes in the framework of a small review article. Therefore, in this work we will restrict ourselves to consideration of electrochemical aspects of this avenue of research (*i.e.*, the available models for the description of charge transport in the systems under study and illustration of

the use of such models in studies of electrode processes occurring in particular systems).

Electrochemical impedance spectroscopy is the most efficient method of studying charge transfer processes. However, the use of this technique often faces some difficulties³⁷ that are usually due to the need of taking into account a large number of factors responsible for charge transfer in real systems (*i.e.*, to multiparametric character of analysis). Studies on the impedance of the redox polymer and conducting polymer films carried out to 1989 were briefly outlined by Musiani.³⁸

The possibility of using different models of the systems under study and different transport schemes *a priori* makes the interpretation of the results obtained somewhat ambiguous. Therefore, often a particular interpretation is predetermined by the choice of a certain equivalent electric circuit as a model for the system under study or by introducing a number of additional elements corresponding to peculiar features of the impedance spectra into the available circuits. This manner of data interpretation is highly popular and can be treated as a specific approach involving the use of analogue electric circuits. Since the approach uses no particular model, it can be employed for analysing the electrical responses of modified electrodes in the case of both homogeneous and inhomogeneous films and, in particular, porous polymer films.

II. Method of equivalent circuits

As mentioned above, electroactive polymer films exhibit a mixed electronic-ionic conductivity, *i.e.*, electron transfer in a film is accompanied by transfer of counterions. To visualise this process, Albery *et al.*^{20–23} proposed an equivalent circuit (Fig. 1) comprised of transmission lines corresponding to the system's con-

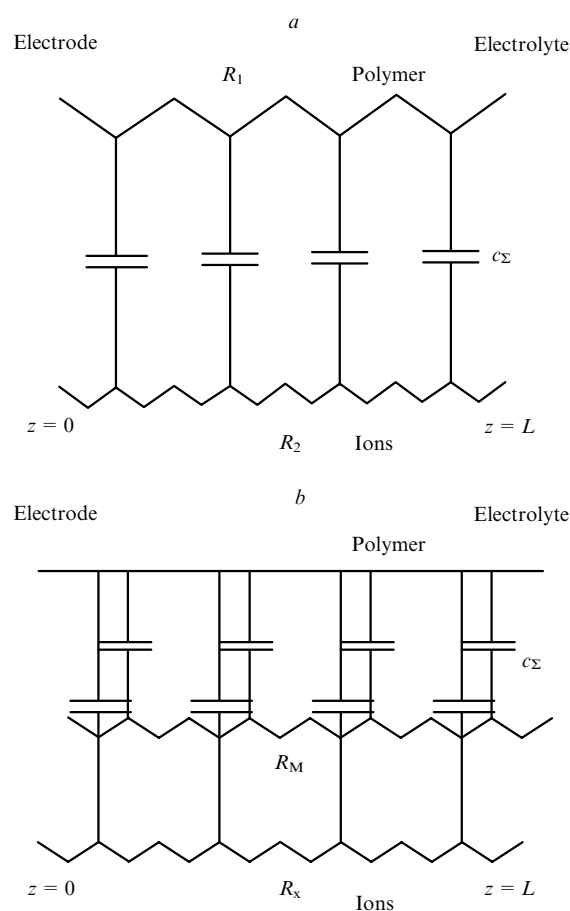


Figure 1. Transmission lines for two particles (electron and ion) (a) and for three particles (electron, cation M^+ and anion X^-) (b).²²

ductivity with respect to each type of particles and connected by capacitors. The capacitors take into account the possibility of redox process in the film upon injection of a negative or positive charge and compensation of this charge due to incorporation (removal) of corresponding ions. Initially, this equivalent circuit was proposed for the description of porous electrodes. Albery *et al.* considered two phases of the film, namely, the polymer and pores. The film-related impedance is represented by a finite transmission line consisting of two resistors, R_1 and R_2 , and one capacitance (see Fig. 1a). Here, R_1 is the resistor describing the motion of electrons in the polymer and R_2 is the resistor describing ion transfer in pores. Consideration of this circuit shows that if $R_1 \ll R_2$ (electronic conductivity is much higher than ionic conductivity) the charge 'leaks' from the polymer with the higher conductivity towards the electrolyte surface. The exchange reaction begins at the film–solution interface and propagates through the film (porous coating) into the interior to the electrode. Otherwise, if $R_1 \gg R_2$ (ionic conductivity is much higher than electronic conductivity), the charge leaks along more conductive pores, and oxidation begins at the electrode–polymer interface and gradually propagates into the interior of the polymer coating. The Albery theory allows the pore-to-polymer volume ratio, diffusion coefficient and thickness of the coating to be determined. Qualitatively, the model of infinite or (in simplified form) finite transmission lines describes conducting polymer films irrespective of their structure (porous or not). However, this only indicates the correctness of representation of films by this equivalent electric circuit. Physical meaning of the model is still to be clarified, in particular in the cases of frequency-dependent elements of the circuit (see below). Often, for the sake of simplicity the transmission lines in the equivalent circuit shown in Fig. 1a are replaced by an element called the Warburg impedance (Z_W) or diffusion impedance (Z_d).

In addition to charge transfer in bulk film, which is characterised by the transmission lines, the EIS spectrum of modified electrodes is affected by the charge injection processes at the conducting substrate–film and film–solution interfaces. This effect is usually included by introducing the so-called RC-chain (element consisting of a resistor R_{ct} and capacitor C_{dl} connected in parallel) into corresponding equivalent circuit. The resistor describes hindered injection of charge carriers through a certain interface and the capacitor describes the need of charging the electric double layers for the injection to occur. The equivalent circuits often include a resistor R_s responsible for the resistance of the region of the bathing electrolyte solution from the film to the tip of the electrolytic salt bridge. Therefore, the simplest equivalent circuit of a homogeneous electroactive film, which takes into account the effect of one interface and charge transfer in bulk film, has the form shown in Fig. 2a.

Figure 2a also shows an ideal spectrum of this circuit in the complex coordinates ($-iZ_{Im}$, Z_{Re}) that are usually called the Nyquist coordinates. If the relaxation times characteristic of different stages of charge transfer differ appreciably, the overall impedance diagram reveals different frequency domains corresponding to each electrode process included. In the high-frequency limit one should expect the electrolyte solution resistance equal to R_s . At relatively lower frequencies, the impedance is due to a process at the electrode–film and/or film–electrolyte interface and the spectrum exhibits a semicircle (sometimes, two semicircles). The time constant τ (relaxation time or 'characteristic time') of the semicircle is governed by the product of the charge transfer resistance by the double layer capacitance

$$\tau = R_{ct}C_{dl}.$$

These two parameters can be determined using the diameter, D , and frequency, ω_{max} , at the maximum of the semicircle (see Fig. 2a).³⁷

$$D = R_{ct};$$

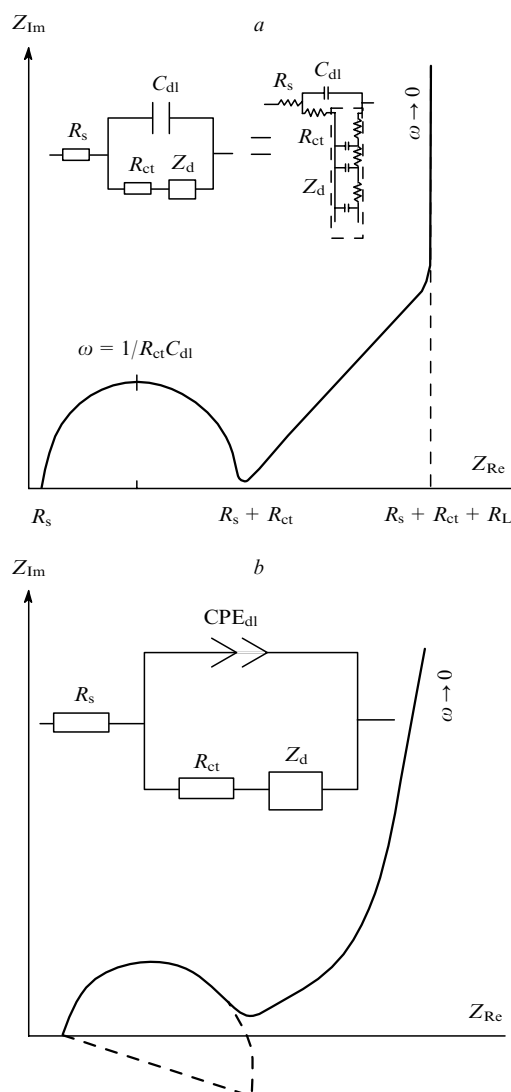


Figure 2. Simplest equivalent circuits for interpretation of the impedance of modified electrodes: conventional Randles circuit (a) and modified circuit (b) corresponding to the limiting effect of charge injection into film and the corresponding impedance spectra plotted in the complex coordinates (negative imaginary component of the impedance $-iZ_{Im}$ vs. real component Z_{Re}).

$$C_{dl} = \frac{1}{\omega_{max} R_{ct}}.$$

At lower frequencies, the major contribution to the frequency characteristic of the impedance comes from diffusion. Here, two regions can be considered, a linear region with a phase angle of $\pi/4$ corresponding to semi-infinite diffusion and treated as the Warburg impedance, Z_d , and a second linear region at more lower frequencies with a phase angle of $\pi/2$. Considering that the diffusion of ions in solution occurs much faster than in the film (*i.e.*, in the solid), it is reasonable to assume that mass transfer is governed by the diffusion of current carriers in the film. The region of very low frequencies with a phase angle of $\pi/2$ can be treated as a pure capacitive response of the system. In this region the diffusion is gradually limited by charge accumulation within the film as the frequency decreases, which leads to the limiting capacitance C_{lf} that can be calculated from the equation³⁷

$$C_{lf} = \frac{L^2}{3D_{eff}R_L},$$

where L is the film thickness, D_{eff} is the effective coefficient of diffusion in the film and R_L is the limiting resistance (intercept on the real axis of the impedance).

It should be noted that in practice the impedance spectra are often inconsistent with the simplest model mentioned above;^{39–43} sometimes they exhibit a bent semicircle centred below the real axis (see Fig. 2b). In addition, the pure capacitive behaviour predicted by the model (see above) is not observed even at very low frequencies. In many practically used models this deviation from the ideal behaviour is taken into account by replacing the capacitance by the so-called constant phase element (CPE)³⁷ whose impedance is given by

$$Z(\omega) = \frac{1}{T(i\omega)^\varphi},$$

where T is a constant measured in $\Omega^{-1} \text{ s}^\varphi$ and the exponent φ ($|\varphi| \leq 1$) determines the phase shift equal to $(\pi/2)\varphi$. The smaller the φ value ($0 < \varphi < 1$), the larger the shift of the semicircle. The CPE corresponds to a capacitor with the capacitance T at $\varphi = 1$, to an induction coil at $\varphi = -1$, to a resistor at $\varphi = 0$ and to the Warburg impedance Z_W at $\varphi = 1/2$ (see below).

The introduction of the CPE for the description of experimental data is a formal procedure, because the physical meaning of this element is still unclear, except for the particular cases mentioned above. The CPE is more likely introduced to simplify calculations rather than understand the actual nature of the processes occurring in the film. Nevertheless, the use of the CPE in equivalent circuits has been a routine step for many authors,^{41–43} in particular, in the description of the frequency-dependent capacitance of polymer films. The reasons for this dependence (frequency dispersion of capacitance) have been the subject of extensive literature based on the concepts of structural-chemical inhomogeneity in films, high roughness of interfaces and possible trapping effects (presence of mobile charge carrier traps in the form of certain film fragments). In these cases the frequency-dependent capacitance $C(\omega)$ is usually described by the semi-empirical relation

$$C(\omega) = \frac{C_0}{1 + (i\omega\tau)^{1-\alpha}}. \quad (1)$$

Here C_0 is a constant capacitance, τ is the characteristic time of the process responsible for the observed frequency dispersion of capacitance and α is an empirical exponent. It should be noted that as a rule the use of expression (1) is based on the De Levie theory for porous electrodes.⁴⁴ In this theory and its more recent versions the capacitance $C(\omega)$ does obey the relation of type (1). Experimental criteria for validation of the use of the porous film model include effects of film thickness and concentration of the bathing electrolyte, specific to these systems. Numerous investigations showed that variation of the film thickness usually leads to a change in the film morphology. As a rule, the degree of film porosity increases with the film thickness, thus affecting the magnitudes of the parameters to be determined. The contribution of ion transfer also changes, namely, increases on going to more porous films. Therefore, in such films one can expect an increase in the effective diffusion coefficient of current carriers with an increase in the concentration of the bathing electrolyte. Practical convenience of the use of the transmission line model lies in that it allows one to divide the impedance spectrum into characteristic regions [high-frequency semicircles and the diffusion (Warburg) impedance and low-frequency capacitance regions] responsible for different stages of charge transfer in films and thus to make qualitative conclusions about the mechanism of this process. At the same time quantitative interpretation of experimental data using the model mentioned above is impossible, because this requires the use of corresponding theoretical results.

Prior to going to a brief outline of the results for a homogeneous modifying polymer film a circumstance not discussed above

should be pointed out. The case in point is the choice of the fashion in which different elements of an equivalent circuit are connected to one another. Indeed, according to the Albery model, there are at least two transmission lines describing transfer of electrons and counterions in the film. Apparently, in the case of the substrate–film interface the RC -element corresponding to injection of electrons into the film (or *vice versa*) should be connected to the electron transmission line. But at the same interface, the transmission line for counterions should be connected to the substrate through a capacitor, because the charging of the interface will to a greater or lesser extent be determined by the dynamics of these ions in the electric double layer surrounding the substrate (see Ref. 45 and Fig. 3). A similar connection should also correspond to the film–solution interface (or polymer–pore interface in the case of porous film structure), but the difference is that now the RC -element is connected to the counterion transmission line and placed before the resistor R_s . In the absence of electron transfer at this interface the electron transmission line should terminate with a capacitor (see Fig. 3) or with the second RC -element in the presence of electron acceptors in the solution.

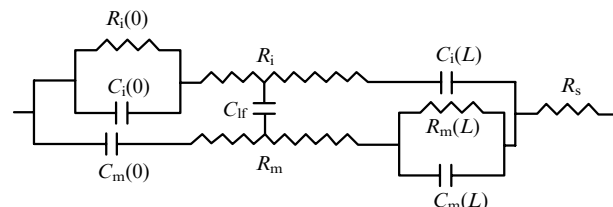


Figure 3. Equivalent circuit representing an electric model of polymer film with two charge carriers.

R_k is the bulk film resistance with respect to the k th current carrier, $R_k(z)$ and $C_k(z)$ are respectively the resistance and capacitance of the film interfaces at the coordinate z ($z = 0$ at the metal–film interface and $z = L$ at the film–solution interface); $k = i$ for electrons and $k = m$ for counterions; C_{if} is the low-frequency film capacitance; and R_s is the resistance of the bathing electrolyte.

Thus, detailing of the equivalent circuit of the modified electrode suggests the need of introducing at least three parameters (two capacitors and a resistor) for each interface in order to correctly describe its charging. Actually, yet another, fourth parameter should be added to the three ones, as was shown by Vorotyntsev *et al.*^{16,17} and will be considered below. Therefore, in the general case processing of experimental data using corresponding theoretical results can face certain problems. Even with a certain set of necessary parameters, the results of experimental data processing will cast some doubt. The reason is the lack, up to date, of a correct theory that would provide a basis for the interpretation of experimentally observed changes in such relatively simple parameters as the charge transfer resistance R_{ct} and interface capacitance C_d with the potential and other variable experimental parameters. To make no naked assertion, note that experimental C_{dl} values (usually, a few $\mu\text{F cm}^{-2}$, see below) have no comments. At best, mention is made that these values are small compared to the double layer capacitances in electrolyte solutions. The situation with interpretation of the R_{ct} values is somewhat different. They are often interpreted using the Butler–Volmer equation in order to write the expression for the rates of injection of current carriers into the film.¹² However, this equation does not include the effect of the electric double layer on the rates of heterogeneous charge transfer (the so-called Frumkin correction). Therefore, application of the Butler–Volmer equation to conducting polymers is at least a moot question. The expressions for injection currents used by Vorotyntsev *et al.*^{16,17} and Láng and Inzelt⁴⁶ were linearised with respect to small deviations of the concentrations and potential jumps. This representation of the injection currents is correct if small-amplitude methods (in partic-

ular, EIS) are used, but consideration of the shape of the R_{ct} -vs.-electrode potential plot (provided that relevant data are available) in this case is impossible. It seems obvious that correctness of data interpretation can only be confirmed by attaining agreement between the observed changes in the measured parameters of the impedance spectra as functions of the electrode potential and some theoretical concepts. Such an agreement is even more necessary in the case of multiparametric processing of impedance data, as often occurs in studies of modified electrodes (see below).

From the aforesaid it follows that research on charge transfer in the systems in question involves a particular investigation line, viz., elaboration of theoretical concepts appropriate for minimisation of the number of descriptor parameters.

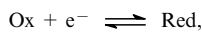
III. Homogeneous film model

A correct formulation of the problem of the impedance of a modified electrode and its solution for homogeneous conducting polymer films were reported by Vorotyntsev¹⁶ and then extended¹⁷ to the case where the bathing electrolyte contains a redox pair that provides the possibility for electrons to leak from the film surface. The importance of these results is not limited to the case of homogeneous conducting films separating the substrate and solution (or two metallic substrates or two solutions, see Refs 16 and 17). We believe that they should be taken into account, in one form or another, when using the porous models of such films. However, up to date general character of the analysis performed in these studies prevents the use of the results obtained. In this connection it seems appropriate to dwell here on some important aspects of the analysis,¹⁶ restricting ourselves to the case of modified electrode. In contrast to the non-model approach¹⁶ in this review we will employ a model one in order to find out the possibility of obtaining analytical expressions for some parameters reported by Vorotyntsev *et al.*^{16,17}

For a homogeneous electroactive film containing only two types of current carriers the electron and counterion flux densities j_{im} and j_m , respectively, are given by the following equations:¹¹

$$\begin{aligned} j_{im} &= -D_{im} \left\{ \frac{\partial C_R}{\partial z} - C_R(1 - \theta_R) \left[\frac{\partial \Phi}{\partial z} - \alpha_0 \frac{\partial \theta_R}{\partial z} \right] \right\}, \\ j_m &= -D_m \left\{ \frac{\partial C_m}{\partial z} + z_m C_m \frac{\partial \Phi}{\partial z} \right\}, \end{aligned} \quad (2)$$

where D_{im} and D_m are the electron and counterion diffusion coefficients, respectively; C_R is the concentration of the reduced fragments (sites); z is the distance from the substrate–film interface; $\theta_R = C_R/C$ is the coverage of the film fragments involved in electron transfer following the reaction



with the reduced form. Here $C = C_R + C_{Ox} \neq f(z)$ is the total concentration of such fragments; C_{Ox} is the concentration of oxidised fragments (sites); α_0 is a dimensionless (in units of RT) attraction constant determined by the energies of the interactions between film fragments and the nearest environment; C_m and $z_m = \pm 1$ are respectively the concentration of counterions in the film and the charge of these mobile charge carriers; $\Phi(z) = F\varphi(z)/RT$ is the dimensionless electric potential (vs. adjacent bulk electrolyte) and $\varphi(z)$ is the dimension value of this potential (see also Ref. 19 and references cited therein). Conditions for conservation of current carriers (electrons localised on the reduced fragments and counterions) in the film are given by the equations

$$\begin{aligned} \frac{\partial C_R}{\partial t} + \frac{\partial j_{im}}{\partial z} &= 0, \\ \frac{\partial C_m}{\partial t} + \frac{\partial j_m}{\partial z} &= 0, \end{aligned} \quad (3)$$

which correspond to the absence of chemical reactions (e.g., binding of counterions to film fragments) in the bulk film under study. The expression for the resulting current density, $I(z,t)$, due to the electron and counterion fluxes (j_{im} and j_m , respectively) is obvious:

$$I(z,t) = F(z_m j_m - j_{im}). \quad (4)$$

Equations (2)–(4) are supplemented with the Poisson equation

$$\frac{\partial^2 \Phi(z)}{\partial z^2} = -\frac{4\pi F^2}{\epsilon_f RT} \{ z_m C_m(z) + (z_0 - 1) C_R(z) + z_0 C_{Ox}(z) \}, \quad (5)$$

where z_0 is the charge of the oxidised form and ϵ_f is the dielectric permittivity of the film. An analogous Poisson equation

$$\frac{\partial^2 \Phi(z)}{\partial z^2} = -\frac{4\pi F^2 C_s}{\epsilon_s RT} \{ \exp[-\Phi(z)] - \exp[\Phi(z)] \} \quad (6)$$

should also be written for the bathing electrolyte, *i.e.*, for the distances $z > L$, where L is the film thickness, C_s is the volume concentration of a solution of symmetric (1–1-charged) electrolyte and ϵ_s is the dielectric permittivity of the electrolyte. Writing Eqn (6) also implies zero concentration gradients in the bulk electrolyte during measurements.

Gabrielli *et al.*,¹² Deslouis *et al.*⁴⁷ and the Mathias and Haas¹¹ solved Eqns (2)–(5) ignoring the electric double layers at film interfaces. Lång and Inzelt⁴⁶ have found an approximate solution to the problem taking into account the deviation from electrical neutrality. In contrast to these studies the derivation^{16,17} of the expressions for the impedance seems to be very correct. In particular, it was assumed that the equilibrium potential and current carrier concentration distributions are retained within the diffuse parts of the electric double layers of the film even when the potential applied to the electrode is altered at relatively high frequencies. Indeed, relaxation of these distributions should occur almost instantaneously, because the Fourier parameters, $(1/\kappa_f)^2/D_{eff}$, of these layers are very small [$1/\kappa_f$ is the thickness of the diffuse part of the electric double layer (EDL) of the film at the left or right boundary, D_{eff} is the effective diffusion coefficient of charge carriers in the film]. Therefore changes in the concentration and potential in these layers should occur under quasi-stationary conditions. Grafov and Chernenko^{48,49} first showed that in this case the potential and concentration distributions within diffuse layers should be equilibrium in character. This allowed the thermodynamic theory of interfaces (in particular, the Gibbs adsorption equation) to be employed^{16,17} for the description of the charging of the EDL in electroactive polymer films. Some important aspects of this analysis will be considered in detail in the text below. At the same time we will show the possibility of decreasing the number of description parameters.

It is convenient to begin with the determination of the injection rates of current carriers into the film. Let us make some simplifications, namely, assume that injection of counterions into the film is limited by partial desolvation of the counterions at the film–solution physical border. With this assumption the equation for the injection rate $J_m(L,t)$ of these ions has the form

$$J_m(L,t) = z_m F [\sigma_m C_M(L,t) - \rho_m C_m^s(L,t)], \quad (7)$$

where $C_M(L,t)$ is the concentration of counterions at the film surface as viewed from the adjacent solution, $C_m^s(L,t)$ is the concentration of the same counterions at the film surface as viewed from the film and σ_m and ρ_m are respectively the rate constants for injection. Since this stage is assumed to be the limiting stage for the incorporation (removal) of ions into the film, the concentrations $C_M(L,t)$ and $C_m^s(L,t)$ should respectively be related to the concentration, C_0 , of injected ions at the end of the diffuse layer in the solution and the concentration, $C_m(L,t)$, at the end of the diffuse layer in the film on the same side of the film by some equilibrium relationships. Taking into account these interrelations, Eqn (7) can be rewritten in the form

$$\begin{aligned}
& \times \left\{ 1 + \exp \left[\frac{F\{\varphi_s(0) - \varphi(0)\}}{RT} + \alpha_0(\theta_R^0 - \theta_R^f) \right] \frac{\theta_R^0}{1 - \theta_R^0} \right\}^{-1} = \\
& = -F\rho_e^0 \exp \left[\frac{F\{\alpha\varphi_s(0) + \beta E - \varphi(0)\}}{RT} + \alpha_0\theta_R^0 - \alpha\alpha_0\theta_R^f \right] \times \\
& \quad \times \frac{\theta_R^0}{1 - \theta_R^0} \left\{ 1 + \exp \left[\frac{F\{\varphi_s(0) - \varphi(0)\}}{RT} + \right. \right. \\
& \quad \left. \left. + \alpha_0(\theta_R^0 - \theta_R^f) \right] \frac{\theta_R^0}{1 - \theta_R^0} \right\}^{-1}, \quad (15)
\end{aligned}$$

where the superscript '0' denotes the equilibrium values of corresponding variables (this is also indicated by the absence of the symbol 'δ'); besides, for the equilibrium state of the system, which is assumed in derivation of Eqns (14) and (15), one has $\varphi(0) = \varphi(L)$ and $\varphi_s = 0$.

Although the relations derived are in essence phenomenological (in the sense that they include the rate constants σ_e^0 and ρ_e^0 determined only from measurements), the dependences of the exchange currents on the electrode potential, E , and concentration, C_0 , following from Eqns (14) and (15) can be checked experimentally. By comparing this type of theoretical dependences with experimental results it is possible to assess the correctness of the models used in processing of corresponding data. As an example, it is appropriate to analyse the simplest situation, *viz.*, insignificance of short-range effects ($\alpha \approx 0$) and applicability of the Gouy model to the substrate–film interface. In this case one has $\varphi_s(0) = E$ and from two alternative definitions of the exchange current of electron injection (15) the expression follows:

$$\frac{\theta_R^0}{1 - \theta_R^0} = \frac{\sigma_e^0}{\rho_e^0} \exp \left\{ \frac{F[\varphi(0) - E]}{RT} \right\}, \quad (16)$$

where $\sigma_e^0/\rho_e^0 = k_e$ apparently has the sense of the partition coefficient of electron between the film under study and the substrate. As should be expected, Eqn (16) follows from the first equation of the system (2) at j_{im} and α_0 equal to zero. Substituting Eqn (16) into Eqn (15) suggests that for this model of the film–substrate interface the exchange current I_{im}^0 is independent of the electrode potential:

$$I_{im}^0 = -F\sigma_e^0 \text{ at } \varphi_s(0) = E \text{ and } \alpha_0 \approx 0.$$

We can also make certain that the exchange current I_{im}^0 depends on the potential E if the same interface can be described by the Stern model. The form of this dependence will be reported elsewhere. Seemingly, the possibility of deriving, in the framework of the model approach employed, relationships for other impedance parameters of the modified electrode, namely, the film interface capacitance, transference numbers for the diffuse layers and the asymmetry factors does not require special comments. We will only point to this possibility.

In describing the impedance of the systems considered by Vorotyntsev *et al.*^{16,17} an important role was played by the choice of convenient variables to be analysed, namely, the charges

$$\delta q_s(k) = Fz_s \int_{1/k_f(k)} \delta c_s dz$$

in the diffuse layers of the film [$1/k_f(k)$ is the thickness of the diffuse layer at the k th interface ($k = 0, L$), $s = m, R$ is the index of the charge carriers under consideration]. A local change in the concentration of the s th sort of current carriers, $\delta c_s(z)$, due to application of an ac voltage, δE , to the system corresponded to the division^{16,17} of the total concentration, C_s , of this sort of particles into two components, $C_s = \delta n_s + \delta c_s$. The first component corresponds to the concentration that fulfils the condition for local electrical neutrality, that is, $z_m \delta n_m(z) = \delta n_R(z)$, while the second component corresponds to the deviation of the concentration of these particles from the 'electrically neutral' value δn_s . Clearly, the second component differs from zero only within the bulk charge regions (diffuse layers of the film in the vicinity of the film–

substrate and film–electrolyte solution interfaces). If we know the dependence of the charges $\delta q_s(k)$ in the diffuse layers on the increments of the concentration $\delta n_R(k, t) = z_m \delta n_m(k, t)$ and the potential jump in the k th diffuse layer $\delta \Delta \varphi(k)$, Eqns (2)–(6) can be solved correctly.^{16,17} Eventually, this makes it possible to derive the expression for the impedance of the system under study. Without dwelling on details of the solution we will note that the $\delta q_s(k)$ values were determined^{16,17} owing to the use of the Gibbs equation at the film interfaces

$$d\sigma(k) = q(k)d\delta \Delta \varphi(k) + \sum_{s=R}^{s=m} \Gamma_s(k)d\mu_s(k).$$

Here, summation was performed over two components (electrons localised on the reduced fragments of the film and counterions) ignoring a possible contribution of solvent molecules incorporated into the film. Since, owing to the condition for electrical neutrality, the increments of the chemical potentials $d\mu_s(k)$ are interrelated

$$\delta n_R(k) = z_m \delta n_m(k),$$

the tension $\sigma(k)$ (at the k th interface) depends on only two variables [$\delta \Delta \varphi(k)$ and $\delta n_R(k)$]. Based on the fact that the derivative $\partial^2 \sigma(k)/\partial[\delta \Delta \varphi(k)]\partial[\delta n_R(k)]$ is independent of the order of differentiation with respect to the variables $\delta \Delta \varphi(k)$ and $\delta n_R(k)$, expressions relating the charges $\delta q_s(k)$ to the total charge increments $\delta q(k) = \delta q_m(k) + \delta q_R(k)$ and $\delta n_R(k)$ were obtained:^{16,17}

$$\delta q_m(k) = \eta_m(k)\delta q(k) - C_f^{(k)} \left[\frac{d\mu_m(k)}{z_m F} - \frac{(-1)^{z_m} d\mu_R(k)}{F} \right],$$

$$\delta q_R(k) = \eta_R(k)\delta q(k) - C_f^{(k)} \left[\frac{d\mu_m(k)}{z_m F} - \frac{(-1)^{z_m} d\mu_R(k)}{F} \right].$$

Derivation of these relations requires the introduction of the (i) transference numbers for the diffuse layers [$\eta_m(k)$, $\eta_R(k)$] with respect to corresponding current carriers and (ii) asymmetry factor $C_f^{(k)}$, which are generally different for different film interfaces. The introduction of the $\eta_m(k)$ and $\eta_R(k)$ numbers is due to the necessity of taking into account the contributions of the $C_i(k)$ and $C_m(k)$ capacitors (see circuit in Fig. 3) to the resulting capacitance, $C(k)$, of the k th interface, whereas the factor $C_f^{(k)}$ describes the effect of the concentrations of both types of current carriers [at $z = 1/\kappa_f(0)$ and $z = L - 1/\kappa_f(L)$] on the charging of this interface. Since the sum of the transference numbers for the diffuse layers with respect to electrons and counterions equals unity^{16,17} [$\eta_R(k) + \eta_m(k) = 1$], the total number of phenomenological parameters for the description of each interface appears to be equal to four (with inclusion of the interface capacitance and exchange current for one or another stage of injection). This means that in the general case the overall expression for the impedance of a modified electrode

$$\begin{aligned}
Z(\omega) = & R_f + R_s + Z(0, \omega) + Z(L, \omega) + \\
& + Z_f(t_m, D_{eff}, A_0, \eta_m(k), C_f^{(k)}, C(k), I_{im}^0, I_m^0, \omega) \quad (17)
\end{aligned}$$

should contain not only the parameters of transport in the bulk film, namely, t_m , D_{eff} and A_0 (where t_m is the transference number of counterions in the bulk film) but also additional eight parameters characterising the charging and injection at the film interfaces.

A salient feature of the impedance $Z(\omega)$ is as follows. Generally, the impedance is not an additive sum of the solution resistance R_s , instantaneous resistance of bulk film $R_f = RTL/\alpha F^2 D_{eff}$, and the impedances of both interfaces:

$$Z(0, \omega) = \left[\frac{F|I_{im}^0|}{RT} + i\omega C(0) \right]^{-1}$$

and

$$Z(L, \omega) = \left[\frac{F|z_m I_m^0|}{RT} + i\omega C(L) \right]^{-1},$$

and the diffusion impedance of the bulk film. The impedance component Z_f in expression (17) includes cross-effects that characterise both the direct effect of the current carrier concentration gradients that appear in the bulk on the charging of the diffuse layers and the reverse effect of the charging of these layers on transport in the bulk film. The necessity of these effects apparently follows from relations (13), according to which the rate of charge carrier injection into the film is determined by not only the potential jump at the k th interface but also the concentration shifts $\delta C_m(k, t) = \delta n_m(k, t)$ at the boundaries of the electrically neutral bulk film adjacent to the diffuse layers. Only for the frequencies at which the reactive components of the interface impedances are small compared to the active components of the interface impedances

$$\frac{F|I_{im}^0|}{RT} \gg \omega C(0) \text{ and } \frac{F|z_m I_m^0|}{RT} \gg \omega C(L),$$

expression (17) is transformed into the following relationships

$$Z(\omega) = R_f + R_s + \frac{RT}{F|I_{im}^0|} + \frac{RT}{F|z_m I_m^0|} + \frac{(t_{im}^2 + t_m^2)RT}{F^2 A (i\omega D_{eff})^{1/2}} \left\{ \frac{A_0}{C_R^0 (1 - \theta_R^0)} + \frac{1}{z_m^2 C_m} \right\}, \quad (18)$$

$$Z(\omega) = R_f + R_s + \frac{RT}{F|I_{im}^0|} + \frac{RT}{F|z_m I_m^0|} + (1 - 3t_m t_{im}) \left\{ \frac{A_0}{C_R^0 (1 - \theta_R^0)} + \frac{1}{z_m^2 C_m} \right\} \frac{LRT}{F^2 A (3D_{eff})}, \quad (19)$$

for the limiting cases of high ($\omega L^2/D_{eff} \gg 1$) and low ($\omega L^2/D_{eff} \ll 1$) frequencies, respectively. Expressions for the Warburg impedance components follow from Eqns (18) and (19) and have the form

$$\text{Re}Z_w(\omega) - \text{Re}Z_w(\infty) = -\text{Im}Z_w(\omega) = \frac{RT(t_{im}^2 + t_m^2)}{C_{eff} F^2 (2\omega D_{eff})^{1/2}}$$

at $\omega L^2/D_{eff} \gg 1$, where

$$\text{Re}Z_w(\infty) = R_f + R_s + \frac{RT}{F|I_{im}^0|} + \frac{RT}{F|z_m I_m^0|};$$

$$C_{eff} = \left[\frac{A_0}{C_R^0 (1 - \theta_R^0)} + \frac{1}{C_m^0} \right]^{-1},$$

and for the low-frequency limiting imaginary component of the impedance

$$-\text{Im}Z_w(\omega) = \frac{1}{\omega F^2 C_{eff} L} \text{ at } \omega L^2/D_{eff} \ll 1.$$

They are most widely used in processing the data on the impedance of modified electrodes. In the Gabrielli model,¹² the components of the interface impedances ($RT/F|I_{im}^0|$ and $RT/F|z_m I_m^0|$) from relations (18) and (19) are in essence formally replaced by the impedance

$$Z(0, \omega) = \left\{ \frac{F|I_{im}^0|}{RT} + i\omega C(0) \right\}^{-1}$$

and

$$Z(L, \omega) = \left\{ \frac{F|I_{im}^0|}{RT} + i\omega C(L) \right\}^{-1},$$

respectively. From consideration of Refs 16 and 17 given above it is clear that this replacement as well as representation of the

impedance by expressions (18) and (19) may appear to be quite incorrect. It should be noted again that in the framework of the model described all eight parameters (see above, except for the rate constants for injection σ_e^0 and ρ_e^0) characterising the charging of the film interfaces can be expressed through the bulk film properties, electrode potential and electrolyte concentration. This was demonstrated above taking the injection rate as an example. As to calculations of other parameters, relations¹⁶ between them and the electrode potential and electrolyte concentration exemplify the realisation of this possibility for a system consisting of two metallic electrodes and a binary electrolyte solution. Extension of these results to the modified electrode will be reported elsewhere. Here we can only mention that carrying out such an analysis (or similar analysis in the framework of other models) will indicate that only the parameters of charge transport in bulk polymer films should be taken into account.

IV. Experimental results on the impedance of modified electrodes

Among the best studied and at the same time simplest systems are inorganic redox polymer films, in particular, films based on various metal hexacyanoferrates. They belong to zeolite-type inorganic compounds with rigid crystal lattice and alkali metal cations can migrate into and out of the film structure. Since the lattice structure of such films has been well studied and the stoichiometry of corresponding compounds established reliably, they can be treated as convenient systems for experimental evaluation of the available concepts of charge transfer in electroactive polymer films.

The kinetics of electrode processes in Prussian blue (PB) films was studied by the EIS method.^{50–54} The EIS spectra of the PB films deposited on a platinum substrate exhibited no high-frequency semicircle and the major portion of the spectrum corresponded to the Warburg diffusion impedance.^{53, 54} Analysis of the EIS spectra obtained in the framework of the homogeneous film model showed⁵³ that the model correctly describes diffusion-controlled charge transport in the film. It was established^{53, 54} that a decrease in the film thickness leads to shortening of the Warburg region $Z_d(\omega^{-1/2})$, however, as should be expected from theoretical predictions [see Eqn (18)], this is not accompanied by significant changes in the slope. The diffusion coefficients D_{eff} , calculated for the first redox process, namely, recharging of outer-sphere ions $\text{Fe}^{3+}/\text{Fe}^{2+}$, were found to depend on the nature of the cation of the bathing electrolyte and decreases in the order $\text{K}^+ > \text{NH}_4^+ > \text{Cs}^+$. It was also found that for both redox processes the plots of the diffusion coefficients vs. the initial potential of the PB film exhibit maxima near the formal potentials. This is consistent with the published data.⁵¹

At the highest frequencies, the impedance spectra of the PB films synthesised on an oxide ($\text{SnO}_2 + \text{In}_2\text{O}_3$) conducting substrate in 1 M KCl solutions exhibited semicircles characteristic of retarded interfacial charge transfer.^{50–52} At lower frequencies, the Warburg impedance region was followed by a poorly pronounced initial part of the capacitive behaviour of the film. The resistance, R_{et} , of 'thick' PB films (film thickness $> 1 \mu\text{m}$) reached a value of 3.3Ω at the formal potential of the first redox process and was treated as the resistance of the electrode–film interface. This conclusion is consistent with the published data,^{53, 54} from which it follows that replacement of the oxide substrate by a platinum substrate should lead to disappearance of the semicircle in the spectrum. The coefficients of charge carrier diffusion in the film were calculated from analysis of the impedance response at medium frequencies⁴² assuming that the PB film consists of two layers with different transport characteristics, namely, a compact inner layer and a more porous outer layer. It is believed^{51, 52} that the diffusion coefficients calculated for these layers (4.6×10^{-10} and $1.1 \times 10^{-10} \text{ cm}^2 \text{ s}^{-1}$, respectively) correspond to slow motion of counterions.

The EIS spectra of cobalt hexacyanoferrate (CoHCF) films on a platinum electrode exhibit a Warburg portion at high frequencies and the capacitive behaviour of the film at low frequencies.^{55,56} Deviations from the major linear part of the Warburg plot at the highest frequencies were explained⁵⁶ by the bilayer character of the system comprising a relatively thin dense layer and a thicker porous layer.

The diffusion coefficients D_{eff} derived for the compact and porous layers from the slopes of the linear portions are respectively 2.4×10^{-12} and $1.1 \times 10^{-11} \text{ cm}^2 \text{ s}^{-1}$ at $E = 0.4 \text{ V}$ and 8.4×10^{-11} and $3.7 \times 10^{-10} \text{ cm}^2 \text{ s}^{-1}$ at $E = 0.8 \text{ V}$. The higher diffusion coefficients at 0.8 V can be a consequence of different nature of the redox processes occurring at 0.8 and at 0.4 V. The diffusion coefficients of the CoHCF films are in reasonable agreement with the published data for PB films.

The effect of the substrate material on the high-frequency semicircle in the EIS spectra was also established in studies of indium hexacyanoferrate (InHCF) films in potassium nitrate solutions.^{57–59} Replacement of platinum substrate by glassy carbon one as well as an increase in roughness of the platinum surface led to considerable increase in the charge transfer resistance R_{ct} (up to a factor of 7); however, the interfacial capacitance C_{dl} decreased to almost the same extent and the product, $R_{\text{ct}}C_{\text{dl}}$, remained nearly constant. Changes in the substrate roughness had no effect on the measured effective diffusion coefficient D_{eff} ; hence, the bulk film structure is independent of the substrate material. Based on these facts, it was concluded that the process is controlled by charge transfer across the interface between the InHCF films and the support electrode.^{58,59}

Another interpretation of the observed impedance spectra was reported⁵¹ in a CV and EIS study of charge transfer on composite electrodes (geometric surface area of 0.2 cm^2) fabricated from a mixture of powdered copper hexacyanoferrate (CuHCF) and impregnated graphite. The EIS spectra of these electrodes exhibited a distorted semicircle which was considered as consisting of two components. The first of them, contributing largely to the high-frequency spectral region, was attributed to electron transfer in the bulk film. The electron diffusion coefficient was estimated from parameters of this component at $D_e = 0.1 \text{ cm}^2 \text{ s}^{-1}$. The high D_e value was treated as an indication of the semiconductor conductivity mechanism involving the valence band instead of conventionally assumed hopping mechanism of charge transfer.⁶⁰ The second semicircle was ascribed to slow injection of counterions (K^+ ions) into the metal hexacyanoferrate crystallites. However, then the authors of Ref. 60 made a conclusion about the hopping mechanism of charge transfer in the metal hexacyanoferrate crystallites and calculated $D_{\text{eff}} = 1.5 \times 10^{-9} \text{ cm}^2 \text{ s}^{-1}$ from the observed portion of the Warburg impedance. Large difference between the D_e and D_{eff} values indicates a slow diffusion of counterions in the metal hexacyanoferrate crystallites.

The charge transfer resistances R_{ct} , determined from the high-frequency semicircle in the impedance spectrum of poly-[NiMe₂Salen] films in 0.1 M solutions of tetraethylammonium tetrafluoroborate in acetonitrile, were ascribed to the film–electrolyte solution interface.⁵² The R_{ct} values were almost independent of the potential in the region of electrical activity of the film (0.8–1.1 V). Analysis of the impedance spectra at medium and low frequencies permitted the determination of the low-frequency capacitance C_{lf} and the effective diffusion coefficient D_{eff} . The D_{eff} values calculated from the slopes of the Warburg portions of the spectrum using the relationships for the homogeneous film model ($\approx 3 \times 10^{-7} \text{ cm}^2 \text{ s}^{-1}$) are about two orders of magnitude higher than the D_{eff} value found from the CV current peaks using the Randles–Sevcik equation.⁶¹ It was assumed that this discrepancy is mainly due to the neglect of the short-range forces between film fragments in the calculations using the Randles–Sevcik equation. The observed large half-width of CV peaks points that this effect, which corresponds to large positive values of the attraction constant α_0 [see the system of equations (2)], should also be taken into account.

Among conducting polymers with conjugated bonds, polypyrrole, polythiophene and substituted polythiophene films exhibit a relatively simple electrochemical behaviour. When using non-aqueous solvents, these systems are free from problems that are due to protonation effects and certain redox processes, which is characteristic of, *e.g.*, polyaniline-based polymers.

In most cases the impedance of such systems can to a first approximation be correctly described by the circuit shown in Fig. 2a. A similar spectral pattern or certain characteristic parts of the spectrum were found for polypyrrole and its derivatives^{6,62–74} and for polythiophene-based polymers.^{13,75–93} For instance, the high-frequency semicircle (usually, it is distorted and more correctly, suppressed) and an extended (with respect to frequencies) capacitive response were observed for polypyrrole films on various substrates in solutions of LiClO_4 in propylene carbonate^{69–73} and in aqueous KCl solutions.^{6,74} Similar parts in the impedance spectra were observed for polythiophene derivatives, namely, poly(3-methylthiophene) (PMT),^{75–79,85,86} poly(3-octylthiophene) (POT),^{80,84,87} poly(3,4-ethylenedioxythiophene)^{90–93} and some other compounds.^{88,89} It was also reported that the impedance spectra of the reduced or weakly oxidised forms of polythiophenes exhibit not only the high-frequency semicircle regions and low-frequency capacitive responses at medium frequencies but also parts corresponding to the Warburg impedance with slopes approaching unity.^{82,83,87} The high-frequency semicircle was most pronounced for little doped polypyrrole.^{70,74} The presence of the high-frequency semicircle and noticeable capacitive response was also reported⁷¹ for polypyrrole, poly(3,6-dioxyheptylpyrrole) and poly(3-methylthiophene) films in 1 M LiClO_4 solutions in propylene carbonate [for poly(3-methylthiophene) and for solid electrolytes based on poly(ethylene oxide), (PEO)₂₀ LiClO_4].

Thus, the impedance spectra of polypyrrole- and polythiophene-based polymer films exhibit characteristic portions with well-separated frequency regions corresponding to the kinetics of different stages of charge transfer. This points to common nature of electrode processes in these polymers. Now we will dwell on the results obtained for particular systems in which the impedance parameters were analysed systematically.

From the impedance measurements of polypyrrole films at specified constant frequencies ($f > 10 \text{ Hz}$) it was found⁶² that the plots of the film capacitance, C_p , and conductivity, $1/R_p$, vs potential have maxima at the formal potential [$E = (E_{p,k} + E_{p,a})/2$]. Analysis of the frequency dependences of these parameters suggested⁶² that polypyrrole behaves as a porous material whose resistance is mainly due to the resistance of the electrolyte filling its pores. High film capacitances (a few mF cm^{-2}) were attributed to the double layer capacitance of the developed inner surface of the polymer. It should be noted that in most studies^{65–68} on polypyrrole it was concluded that in the conducting state the rate of charge transfer in the polypyrrole film is controlled by the diffusion of ClO_4^- anions.

Typical impedance spectra exhibiting three noticeable regions (capacitive, Warburg and high-frequency semicircle) were observed for polypyrrole films in various aqueous electrolyte solutions.⁷⁰ Using these data, the electron diffusion coefficient for polypyrrole films was calculated, $D_e \approx 10^{-3} \text{ cm}^2 \text{ s}^{-1}$. It was found⁶² that the ion diffusion coefficient D_m for the film ($L = 15 \mu\text{m}$) strongly depends on the nature of the anion in the electrolyte, namely, $D_m = 2.5 \times 10^{-6}$ (Cl^-), 6.2×10^{-7} (ClO_4^-), 8.2×10^{-8} (SO_4^{2-}) and $\sim 1 \times 10^{-9} \text{ cm}^2 \text{ s}^{-1}$ (tosylate ion) and weakly depends on the nature of the cation in the electrolyte (H^+ , Na^+ , Me_4N^+). Particular attention was given^{63,64} to analysis of the capacitive regions of the impedance spectra of polypyrrole films. An attempt was made to separate the contributions of the capacitive and Faradaic currents to the overall impedance response. The capacitive component was attributed to the charging of the double layer at the film interface and the Faradaic component was attributed to the incorporation of the dopant anions, ClO_4^- , into compact film fragments.

The impedance spectra of polythiophene films were analysed as functions of the potential and film thickness for asymmetric configuration of the metal–polymer–solution system characteristic of modified electrode and for symmetric configuration (metal–polymer–metal) using air-dry film.¹³ The high-frequency semicircle in the spectrum obtained for the asymmetric configuration and the derived parameters of the RC -circuit ($R_{ct} \approx 30 \Omega \text{ cm}^2$ and $C_{dl} \approx 1\text{--}5 \mu\text{F cm}^{-2}$) were ascribed to the film interface. However, strictly speaking, no experimental facts for identification of this interface (substrate or solution) are available. The calculated¹³ diffusion coefficient D_- attributed to the motion of ClO_4^- anions in the film were of the order of $(0.05\text{--}1.2) \times 10^{-12} \text{ cm}^2 \text{ s}^{-1}$. The D_- value increased almost linearly with an increase in the polythiophene film thickness from 0.1 to 1.6 μm , which suggested an inhomogeneous film structure (in particular, formation of a more porous structure with an increase in the film thickness). The diffusion coefficients D_- were calculated with inclusion of the relations for the Warburg constant that follow from the classical electrochemistry. As was shown in a number of studies, these relations require redefinition of parameters which have a more complex sense in the case of modified electrode. Probably, so low D_- values are due to the calculation procedure employed, being not reliable.

The system platinum electrode–PMT film in a 0.2 M LiClO_4 solution in MeCN was studied by the electrochemical impedance method.⁷⁵ It was established that the impedance spectra of the films of the reduced form of PMT exhibit a semicircle which is gradually transformed into the capacitive response of the film as the frequency decreases. On going to the oxidised form of PMT the diameter of the semicircle noticeably decreases; the charge transfer resistance R_{ct} derived from the diameter of the semicircle was about $15\text{--}20 \Omega \text{ cm}^2$. This R_{ct} value was attributed to the bulk polymer resistance assuming the major contributions of the conductivity of the electrolyte in pores of the polymer for the oxidised form of the PMT film and the electron conductivity for the reduced form of the PMT film. However, this assumption was unsubstantiated.⁷⁵ The diffuse part of the spectrum, which is usually characterised by a unity slope of the $Z_{Re}(Z_{Im})$ plot, was almost not observed. At the same time, data analysis allowed the authors to find the diffusion impedance component and to determine the coefficient of charge carrier diffusion in the film (D varied from 1.5×10^{-14} to $1 \times 10^{-12} \text{ cm}^2 \text{ s}^{-1}$), which was attributed to diffusion of the dopant ions in the film. The lowest D values were obtained for thin (about 20 nm) polymer films. Since the coefficient D characterises diffusion of ions both in the compact polymer and in pores, the fact⁷⁵ that D values are independent of film thickness indicates that the average size of dense domains (aggregates) and the average pore size behave analogously. It should be noted that very low values of diffusion coefficients⁷⁵ are inconsistent with the assumptions of high film porosity and corresponding capacitive response. Besides, at such D values one would observe a large contribution of the diffusion resistance of the film; however, the impedance spectra in the frequency range $10^4\text{--}10^{-3} \text{ Hz}$ exhibited no Warburg response with a characteristic linear dependence with a slope approaching unity (see above).

The impedance of PMT films was also measured in 0.1 M $\text{NBu}_4^+\text{PF}_6^-$ solution in propylene carbonate⁷⁷ and in 0.05–0.5 M LiClO_4 solutions in acetonitrile.⁸⁶ Strongly suppressed, poorly pronounced high-frequency semicircles were observed in both cases. The mid-frequency parts of the spectra exhibited some indications of the Warburg impedance and transformed into abruptly rising curves associated with the capacitive response of the films. The charge transfer resistance determined from the diameter of the semicircle ($30\text{--}60 \Omega \text{ cm}^2$) was attributed to the film–electrolyte solution interface.⁷⁷ The estimates of the coefficients of charge carrier diffusion obtained from direct measurements of the electron and ionic components of the conductivity of the PMT film are $D_e = 5.6 \times 10^{-3}$ and $D_i = 1.6 \times 10^{-9} \text{ cm}^2 \text{ s}^{-1}$. Thus, from the results obtained it follows that the mobilities of

electrons and counterions (PF_6^-) in the polymer phase differ by a factor of 10^6 and the overall charge transfer is controlled by the diffusion of counterions in bulk polymer. The dependence⁶⁹ of the impedance parameters on the PMT film thickness was explained with allowance for the porous structure of the polymer films. It should be noted that, in spite of considering a porous film, the authors⁷⁷ reported the possibility of interpreting the same results in the framework of the homogeneous film model. However, parameters obtained in such a fashion have different physical meaning.

It was found⁸⁶ that the high-frequency semicircle in the spectrum becomes more pronounced as the LiClO_4 concentration decreases by an order of magnitude; the diameter of the semicircle increases by about a factor of four. The authors⁸⁶ concluded that the appearance of the semicircle in the EIS spectra is due to predominant contribution of the impedance of the film–electrolyte solution interface in this frequency range. Slow charge transfer at this interface seems to be due to partial desolvation of dopant anions (ClO_4^-) during incorporation of these ions into the polymer matrix. This conclusion was confirmed by the results obtained in a study⁹⁴ on the effect of solvent viscosity and the size of the solvent molecules on the reversibility of the oxidation of poly(3,4-ethylenedioxythiophene) films. Seemingly, yet another argument in favour of this assignment is provided by a decrease in the resistance R_{ct} with an increase in the film thickness; here one can assume that the outer surface of the film becomes looser (see above). A decrease in R_{ct} with an increase in the electrode potential was explained⁸⁶ by additional solvation of the polymer molecules upon swelling of the film, which leads to a decrease in the energy barrier to incorporation of the dopant anions into the film. The effective diffusion coefficients, D_{eff} , of PMT films calculated using the homogeneous film model were almost independent of the potential in the range 0.6–1.2 V [$D_{\text{eff}} = (1.3\text{--}2.3) \times 10^{-7} \text{ cm}^2 \text{ s}^{-1}$].

Impedance measurements of PMT films deposited on platinum in aqueous electrolyte solutions containing different anions were reported.⁷⁸ It was concluded that the charge transfer resistance at the film–solution interface contributes largely to the measured impedance. The overall patterns of the impedance spectra of PMT films were also reported;^{80, 81} however, here the authors made only qualitative conclusions about the appearance of incomplete high-frequency semicircle and low-frequency pseudocapacitive response.

Significantly different impedance spectra of the neutral and oxidised forms of POT were obtained with the Pt/POT-electrode immersed in a 0.1 M solution of LiBF_4 in propylene carbonate.^{82–84} The spectra of the neutral form of POT (at potentials $E = 0.0\text{--}0.7 \text{ V}$) exhibited a semicircle corresponding to a rather high resistance R_{ct} (about 30 k Ω). The impedance spectrum of the neutral form of POT was explained⁸² by the effects of the double layer with $C_{dl} = 2 \mu\text{F cm}^{-2}$, which was attributed to the polymer–electrolyte solution interface. For the doped (oxidised) form of POT (at $E = 0.8\text{--}1.2 \text{ V}$) the semicircle becomes more pronounced and its diameter considerably decreases as the degree of film oxidation increases, namely, R_{ct} decreases to 980–790 Ω at a potential of 1.2 V. As the potential changes in the range 0.8–1.2 V, the capacitance C_{dl} increased by nearly a factor of 1.5 (from 2.8 to 4 $\mu\text{F cm}^{-2}$) and the low-frequency capacitance C_{lf} changed from 0.76 to 4.1 mF cm^{-2} . The coefficients of charge carrier diffusion, determined at different oxidation states of the POT film lie in the range $(1\text{--}8) \times 10^{-8} \text{ cm}^2 \text{ s}^{-1}$. Similar measurements for poly(3-octylthiophene) films were carried out in solutions of lithium perchlorate in acetonitrile.^{86, 87} The pattern of the impedance spectra is consistent with the data obtained for solutions of LiBF_4 in propylene carbonate. Three characteristic spectral features were revealed, *viz.*, the high-frequency semicircle, the transient spectral region and an abrupt increase in the imaginary impedance component, $-Z_{Im}$, with a decrease in frequency. As the degree of film oxidation increases, the diameter of the semicircle and the transient region at medium frequencies

decreases appreciably (for the neutral form of the polymer, the transient region exhibits the properties of the Warburg impedance). The diffusion impedance components are particularly pronounced when analysing the data in the $-Z_{\text{Im}}, Z_{\text{Re}}-f^{-0.5}$ coordinates. This analysis reveals parallel linear regions indicating diffusion-controlled charge transfer in the film. The diffusion coefficients, which apparently should be associated with the diffusion of counterions (ClO_4^-), depend on the potential and are as follows:

E/V	0.8	0.9	1.0	1.1	1.2
$10^7 D/\text{cm}^2 \text{ s}^{-1}$	0.29	0.68	1.5	6.3	17

Similar values of the diffusion coefficient of BF_4^- ions ($D_{\text{eff}} = 8 \times 10^{-9} \text{ cm}^2 \text{ s}^{-1}$ for the potential of the anodic maximum in CV) were reported for POT films.⁸²

In contrast to the spectra considered above, in most cases the impedance spectra of polyaniline films and films based on polyaniline derivatives, *e.g.*, poly(*o*-phenylenediamine) (PPD) and poly(*o*-aminophenol) (PAP), have a more complex shape. This manifests itself in the absence of well-defined spectral regions which could be associated with particular processes. In other words, the impedance spectra of these systems cannot be described by simple theoretical relations.

The impedance of polyaniline films was studied in hydrochloric acid.⁹⁵ The dependences of the capacitance and conductivity on the potential measured at a constant frequency of 10 Hz exhibit maxima in the region of electrical activity of the film. The authors⁹⁶ reported a thorough analysis of the published data⁹⁵ and concluded that the properties of the polyaniline film can be explained with allowance for the porous film structure.

Based on the IR spectroscopy and quartz microbalance data for PPD and PAP films, it was established^{89,90} that the electrode process in acid aqueous solutions involves hydrogen ions as charge-compensating ions. In contrast to the processes in polyaniline, here anions are involved in the electrode process to a much lesser extent, although some researchers intensively elaborate anion-related concepts.

The EIS spectra of PPD films exhibit a region corresponding to the Warburg impedance and a poorly pronounced low-frequency capacitive response.⁹⁷ Analysis of the impedance spectra and estimation of parameters of the processes were carried out in the framework of the homogeneous film model. It was established that the low-frequency capacitance is proportional to the film thickness and the maximum capacitance is reached at the formal potential of the polymer. A minimum of the Warburg constant and the maximum width of the Warburg impedance region were also observed near the formal potential.

The effective diffusion coefficients are of the order of $(1-10) \times 10^{-8} \text{ cm}^2 \text{ s}^{-1}$ depending on the film potential.⁹⁷ It was concluded that charge transfer is controlled by electron 'diffusion' and the 'electron diffusion coefficient' D was estimated at $D_e = 2 \times 10^{-9} \text{ cm}^2 \text{ s}^{-1}$. At the same time it was reported that the model used is irrelevant to specific features of the processes occurring in the polymer, in particular, to protonation of the redox centers in the film.

A solution study⁹⁸ of the impedance spectra of PPD film on glassy carbon in a broad range of pH values allowed the dependence of the film parameters on the concentration of hydrogen ions to be analysed in detail. It was found that at low pH values the impedance spectra were slightly different from the published spectra^{97,99} and a high-frequency semicircle appeared in the spectra at $\text{pH} > 4$. The key parameters, *viz.*, interfacial charge transfer resistance R_{ct} , low-frequency capacitance C_{lf} and the effective diffusion coefficient D_{eff} were determined⁹⁸ using relations for the homogeneous film impedance. It was established that the capacitance C_{lf} and diffusion coefficient D_{eff} depend on potential and reach maximal values near the formal potential.

An increase in D_{eff} with a decrease in pH value was treated as an indication of the fact that electron transfer is accompanied by intermolecular proton transfer and the shape of this dependence

was explained by an increase in the rate constant for homogeneous electron transfer upon protonation of the polymer.

The electrochemical properties of PPD films in solutions of different anionic compositions at different pH values were also studied.⁹⁹ The impedance spectra of the PPD films exhibited a 'non-classical' shape, which was probably due to similar values of the characteristic relaxation frequencies corresponding to diffusion and pseudocapacitive charging of the film.

To describe these EIS spectra, the equivalent circuit (see Fig. 2a) was modified⁹⁹ by introducing an additional capacitance and a CPE element responsible for occurrence of certain reactions with solution components and for structural features of the film (namely, film porosity). Finally, processing of the spectra gave dependences of the effective diffusion coefficient D_{eff} on the potential E for PPD films. The D_{eff} values calculated using any of the three models employed by the authors vary by several orders of magnitude as the electrode potential increases by 400 mV. These changes in D_{eff} values were explained by strong interaction between electroactive centres in the polymer and counterions.

Analysis of the EIS spectra of PPD films was continued in the next study⁴⁶ reported by the same authors. To describe the EIS spectra, they elaborated a new model with inclusion of diffusion and migration of three charge carriers (proton, electron and anion) in bulk film. Expressions for the impedance were derived with allowance for the effects of two interfaces (electrode–film and film–solution). The equivalent circuit proposed for this model is shown in Fig. 5.

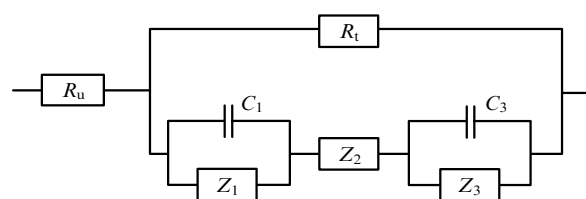


Figure 5. Equivalent circuit of PPD films.⁴⁶

Z_1 and Z_3 are the impedances of the interfaces; Z_2 is the bulk film impedance; C_1 and C_3 are the capacitances of the interfaces; R_t is the shunt resistance responsible for charge leakage; and R_u is the solution resistance.

Among quantitative results obtained,⁴⁶ the diffusion coefficients and the double layer capacitances deserve particular attention. Despite the fact that the diffusion coefficients vary by several orders of magnitude as the potential changes (this is similar to study⁹⁹), no comments were made. The interfacial capacitances ($C_1 = 80-200$ and $C_3 = 300-450 \mu\text{F cm}^{-2}$) exceed conventional values of the double layer capacitances. A possible explanation for this anomaly for the metal–film interface (C_1) is provided by roughness of the electrode surface, *i.e.*, larger actual surface area compared to the geometric surface area. However, the effect of adsorptive capacitance on C_1 and C_3 seems to be a more probable explanation.

Analysis of the results obtained in this study revealed some difficulties faced by the authors in constructing their own, 'improved' models of charge transfer in order to describe complex, 'non-classical' impedance spectra with poorly separated frequency regions corresponding to a certain process. As a rule, mathematical formalism employed is rather complicated and includes parameters that are often difficult to compare with real characteristics of the system under study. Besides, a large number of such parameters complicates processing of experimental data, which forces the authors to essentially simplify their models in order to decrease the number of independent variables. Sometimes, this leads to paradoxical consequences as in, *e.g.*, the study considered above. Having elaborated a rather complex model of

charge transfer involving three different current carriers, in processing experimental data the authors had to reduce the number of particles to two, thus returning, in essence, to the well-known formalism.

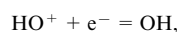
Dispersion of the low-frequency capacitance, which is characteristic of the impedance spectra of PPD films was investigated.^{100, 101} The authors concluded that this phenomenon is due to inhomogeneity of the polymer surface, whereas the surface structure of the conducting substrate and the binding of counterions in the film have no effect on the dispersion of the low-frequency capacitance. This is inconsistent with theoretical consequences reported in other studies,^{72, 73} according to which one should observe a noticeable effect of the binding of counterions on the low-frequency capacitance.

Poly(*o*-aminophenol) is one of the nearest analogues of PPD. As in the case of PPD films, studies of PAP films were accompanied by debates concerning the nature of counterions involved in the electrode process. Although a significant role of protons in charge transfer in these films is undoubtful,^{102–104} the authors of some studies (see, *e.g.*, Ref. 105) consider the involvement of anions of the bathing electrolyte as counterions. Nevertheless, the scheme^{102, 103} involving hydrogen ions as counterions should be considered as the most probable scheme of the redox processes occurring in such films.

The apparent diffusion coefficients of $(3.6 \pm 0.4) \times 10^{-10}$ and $(5.5 \pm 0.3) \times 10^{-10} \text{ cm}^2 \text{ s}^{-1}$ for the anodic and cathodic processes, respectively, are two orders of magnitude lower than the values obtained by the same authors for PPD.¹⁰²

PAP films were studied by the EIS method.¹⁰⁶ The EIS spectra were processed using the homogeneous film model.¹² The spectra obtained exhibited the high-frequency semicircle and a characteristic region corresponding to the low-frequency capacitance of the polymer. The following parameters of the semicircle were determined: the electrolyte resistance R_u ($2.8 \pm 0.5 \Omega$) and the charge transfer resistance θ attributed to the bulk film. Then the standard rate constant for charge transfer $k_{s,h} = (2.3 \pm 0.4) \times 10^{-6} \text{ cm s}^{-1}$ and the double layer capacitance $C_{dl} = (8 \pm 2) \times 10^{-6} \text{ F cm}^2$ were calculated. By analysing the pseudocapacitive spectral region the low-frequency capacitance, C_{lf} , of the polymer and the effective diffusion coefficient D_{eff} were determined. The latter parameter was almost independent of the potential and equal to $1.3 \times 10^{-11} \text{ cm}^2 \text{ s}^{-1}$, which, similarly to Ref. 102, is two orders of magnitude lower than the values obtained by the same method for PPD.^{97, 98} In spite of apparent simplicity and reliability of this 'classical' approach to processing of the EIS spectra, it casts some doubt when comparing the results obtained in different studies. For instance, the same authors studied¹⁰⁷ the dependence of charge transfer parameters in PAP films on the film thickness and ionic strength of the bathing electrolyte solution; the diffusion coefficients obtained under identical experimental conditions differed from the published data¹⁰⁶ by an order of magnitude. Even higher diffusion coefficients ($10^{-8} \text{ cm}^2 \text{ s}^{-1}$) were obtained¹⁰⁸ for PPD using the equations of the Mathias and Haas model.¹¹ In spite of different compositions of the bathing electrolytes used^{98–100} such a large discrepancy between the diffusion coefficients is hard to explain.

Unlike the Inzelt model, the charge transfer model developed in order to describe the EIS spectra of PAP¹⁰⁹ represents an attempt to allow for the effect of protonation on the EIS spectra. This model was based on the Gabrielli model¹² with inclusion of slow protonation in order to explain a strong effect of the pH values on the electrochemical properties of PAP and related polymers. The authors assumed that the proton concentration in the film is constant in time and independent of the electrode potential. Therefore, the distribution coefficient K_p was introduced, which determines the ratio of the concentrations of hydrogen ions in the film and in solution ($[H^+]_{film} = K_p \times [H^+]_{sol}$). Representing the reactions in the polymer by two consecutive stages (protonation and the redox process itself)



and assuming that the kinetics of the second stage at the electrode–film interface obeys the Butler–Volmer equation, the authors derived the final expression for the film impedance. Using this approach, experimental data were fitted quite correctly, reasonable values of diffusion coefficients were established (2.2×10^{-10} and $0.53 \times 10^{-10} \text{ cm}^2 \text{ s}^{-1}$ for pH values of 1 and 2, respectively) and the acidity constant K_a for the oxidised form of the polymer ($pK_a = 2.93$), consistent with the expected value for deprotonation of the amino group of polyaniline, was determined.¹¹⁰

It should be noted that the assumption of constant concentration of hydrogen ions in the film seems to be somewhat incorrect, because in this model protons are counterions and maintain electrical neutrality of the entire film. Mention should be made, also concerning other studies, that the results of approximation using different models for the same systems under study and similar experimental data often provide good agreement between experiment and theory. However, the physical meaning of the parameters obtained is often ambiguous.

The role of porosity in the charging of conducting polymer films has long been discussed in the context of the 'faradaic' and 'capacitive' components of the overall current.^{103–111} A number of methods for experimental separation of these contributions were proposed. Among them, the most important is spectroelectrochemical study of conducting polymer films in the UV and visible spectral regions.^{111–118} It was assumed that the capacitive current can be determined based on electrochemical measurements carried out along with optical spectral measurements, which contain information on changes in the concentration of the redox species (polarons, *etc.*) in bulk film. However, as was established to date, such a separation is impossible, because the surface and bulk film charging processes occur involving species of the same chemical nature. Therefore, the problem of interpreting the capacitive response is still to be solved.

Recently, spectroelectrochemical studies of conducting polymer films have been widely used to elucidate the nature of quasi-particles generated in films and the mechanism of the redox processes.^{119, 120}

When analysing the experimentally determined low-frequency capacitance C_{lf} of electroactive polymer films in the region of redox activity, in most cases C_{lf} is a parabolic function of the potential E with a maximum at an oxidation state θ of about 0.5. This is associated with the maximum value of the product of the concentrations of the oxidised and reduced fragments in the polymer near the formal potential. The experimentally observed dependence of C_{lf} on potential is in qualitative agreement with the theoretical ratio for the low-frequency capacitance, which follows from the homogeneous film model,

$$C_{lf} = \frac{AF^2L}{RT} \left\{ \frac{1 + \alpha_0 \theta_R^0 (1 - \theta_R^0)}{C_R^0 (1 - \theta_R^0)} + \frac{1}{z_m^2 C_m^0} \right\}^{-1}.$$

The C_{lf} – E curve calculated⁸⁷ for poly(3-octylthiophene) films is in good agreement with the experimental curve assuming a value of 6.8 for the fitting coefficient (interaction parameter α_0). According to the definition of the parameter α_0 , its sign and magnitude indicate a repulsive interaction between redox fragments in the film, with a rather high interaction energy. Similar character of the approximation of the experimental C_{lf} – E curve was established for PPD films.⁹⁷ Possible reasons for significant differences between theoretical and experimental curves include structural-chemical inhomogeneity of films leading to dispersion of the formal redox potentials and film swelling effects; both of them are ignored in the homogeneous film model.⁸⁷ It seems that these factors affecting the low-frequency capacitance cannot be formally 'included' by the fitting parameter of the model, α_0 .

An important feature of the capacitance C_{lf} experimentally observed for certain electroactive polymer films is the frequency dependence of this parameter. Up to now the nature of the frequency dispersion of the capacitance C_{lf} is a debated topic. Considerable attention to this issue was paid by Bisquert *et al.*^{72, 73, 121, 122} who reported detailed analysis^{72, 73} of the dependence of the low-frequency capacitance on the thickness of polypyrrole film and on the potential. The frequency dispersion of capacitance was explained⁷³ by film porosity and the experimental data were treated in the framework of the modified Albery model for charge transmission lines. However, from this analysis it follows that the specific low-frequency capacitance $C = C_{lf}/L = 100\text{--}200\text{ F cm}^{-3}$ is almost independent of film thickness. This points to a linear dependence of C_{lf} on the film thickness and, with allowance for the available data on noticeable changes in the morphology of polypyrrole films with an increase in the film thickness, suggests the volume character of the film charging rather than formation of charged double layers on the large inner surface of the porous film. In this case the dispersion of capacitance was associated⁷³ with effects of diffusion length (pore size and polymer grain size) distribution for charge carriers over the bulk polymer and with the binding of counterions in the film.

The data obtained in the impedance studies^{58, 59} of indium hexacyanoferrate films are of interest in the context of the problem of dispersion of the low-frequency capacitance. It was found that for potassium nitrate solutions the capacitive response fits well by a linear dependence of $-Z_{lm}$ on ω^{-1} , whereas a considerable change in the slope $\partial(-Z_{lm})/\partial(\omega^{-1})$ with frequency was observed for lithium nitrate solutions. These results were explained⁵⁹ by the binding of lithium ions to negatively charged film lattice fragments. The absence of dispersion of the capacitance of the InHCF film in the case of K^+ -containing solutions points that most of potassium ions in these films are in free state. As to the Li^+ -containing solutions, it seems likely that the contributions of the free and bound forms of counterions vary with frequency, thus being responsible for the observed frequency dependence of C_{lf} .

V. Conclusion

Analysis of electrochemical aspects of research on modified electrodes reveals that specific features of charge transfer in these systems due to mixed electron-ionic conductivity have, in principle, become understandable. Experiments showed that a large number of systems exhibit such features as simultaneous appearance of high-frequency semicircles and the presence of diffusion portions (Warburg impedance) in the EIS spectra and the absence of dispersion of the low-frequency capacitance, *i.e.*, behaves consistently with the homogeneous film model. However, quantitative agreement between experiment and theory is a long way in the future. The case in point consists in *a priori* uncertainty of the extent to which the charge transport parameters obtained correspond to real processes (in particular, processes at polymer film interfaces) rather than possible errors in determinations, which are usually performed using the simplified theory of homogeneous film impedance by Mathias and Haas. Therefore, the development of the theory of injection of current carriers into films and obtaining relevant experimental data are topical problems of investigations in the field of charge transport in modified electrodes.

A recent trend towards allowance for the structure of real polymer films and film morphology effects on the electrochemical properties indicates a new step in research on modified electrodes. Researchers have been refining their understanding of such systems. In this connection not only the problems considered above but also construction of correct models with inclusion of the film structure and their experimental evaluation seem to be important. And, as earlier, search for novel systems based on electroactive polymer films and fulfilling practical demands remains a task of paramount importance.

This review has been written with the financial support from the Russian Foundation for Basic Research (Project Nos 04-03-33018 and 05-03-33262).

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^a — *Russ. J. Electrochem. (Engl. Transl.)*^b — *Dokl. Chem. (Engl. Transl.)*^c — *Russ. J. Phys. Chem. (Engl. Transl.)*

Successive ionic layer deposition. The use in nanotechnology

V P Tolstoy

Contents

I. Introduction	161
II. Conditions for successive ionic layer deposition reactions	162
III. Ionic layer deposition reactions without changes in the oxidation states of ions	163
IV. Successive ionic layer deposition with a change in the oxidation states of adsorbed ions	166
V. Conjugated ionic layer deposition reactions including oxidation or reduction of ions and adsorption	167
VI. Successive ionic layer deposition involving ions and molecules	167
VII. Successive ionic layer deposition involving ions and nanoparticles	168
VIII. Applications of nanolayers synthesised by successive ionic layer deposition	168

Abstract. The problems related to the synthesis of nanolayers of various classes of substances (inorganic, organic and hybrid, *i.e.*, inorganic/organic) by successive ionic, ionic–molecular and ionic–colloidal layer deposition are discussed. The experimental data are systematised in terms of the type of reaction occurring on the surface during the synthesis. The use of successive ionic layer deposition in nanotechnology for the preparation of practically valuable nanolayers is considered. These nanolayers include the layers in SnO₂-based conductometric gas sensors, passivating protective coatings on the metal surface, semiconductor cells for solar energy conversion, photo-, electrochromic and magnetic materials, pervaporation membranes, electrocatalysts, light diodes, and so on. The bibliography includes 201 references.

I. Introduction

The development of nanotechnology brings about new challenges for the preparative chemistry, in particular, the precision synthesis of nano- and multinano-layers and 2D and 3D-nanostructures based on inorganic, organic and hybrid (inorganic/organic) substances.

Among the procedures of such synthesis, ‘chemical assembly methods’,^{1,2} *i.e.*, layer-by-layer syntheses, occupy an important place. They are based on successive adsorption of low-dimensional precursors on the substrate surface with obligatory removal of an excess of non-consumed reagent. As a consequence, a layer of the substance being synthesised with a thickness of several nanometres or fractions of a nanometre (a nanolayer) is formed on the surface. Upon multiple repetition of the adsorption reactions, the layer thickness increases in proportion with the number of treatment cycles.

After the first publications by V B Aleskovskii and S I Kol'tsov,^{3,4} as well as T Suntola,⁵ the use of gaseous reagents for the thin-film synthesis began. This was believed to create

conditions for the complete irreversibility of the reactions. However, the design of these structures is faced with the problem of low volatility of the precursors at the relatively low temperatures used for this purpose (as a rule, lower than 400 °C).

In recent years, solutions of salts containing ions that react on the sorbent surface to give poorly soluble compounds have been used more and more often as reagents in the preparation of nanolayers.

Most of reactions of inorganic compounds are carried out in solutions. In particular, metal complexes are synthesised in solution and then isolated by crystallisation, extraction or another method. Solutions are also used for the preparation of thin films of inorganic compounds by chemical metallisation, alkaline oxidation, phosphatation or chromatation, which have found wide use in mechanical engineering for the protection of the surface of metal articles.

The key feature of these methods is the use of so-called mixing regime in which the final product is formed from a mixture of reactants as the equilibrium shifts towards the least soluble compound.

The first syntheses by the ‘layer-by-layer’ procedure using colloidal solutions were carried out by Iler.⁶ This procedure was further developed by using true solutions. The syntheses of ZnS and MnO₂ layers involving the cations and anions occurring in solutions were independently described in the patents by Nicolau⁷ and Tolstoy *et al.*⁸ The reaction conditions were found such that successive adsorption of cations and anions, which react to give the layer compound, takes place on the substrate surface in each stage of the synthesis.

This method of the synthesis has been called⁹ Successive Ionic Layer Deposition (SILD).[†] An obligatory condition for the layer synthesis by this method is removal of excess reagents and products, for example, by washing with a solvent after each stage of adsorption. If the excess of reagents is not removed, the synthesis of the layer will take place under ‘mixing’ conditions and it will be impossible to control precisely the thickness of the growing layer. This distinguishing feature of SILD is illustrated by Fig. 1, which shows the variation of the reagent concentration at the substrate–solution interface during the synthesis.

V P Tolstoy Department of Chemistry, St Petersburg State University, Universitetskii pr. 26, Petrodvorets, 198504 St Petersburg, Russian Federation. Fax (7-812) 428 69 39, tel. (7-812) 428 41 04, e-mail: vptol@yandex.ru

Received 10 March 2005

Uspekhi Khimii 75 (2) 183–199 (2006); translated by Z P Bobkova

[†]Other names are Successive Ionic Layer Adsorption and Reaction (SILAR) or Layer-by-Layer (LbL) synthesis.

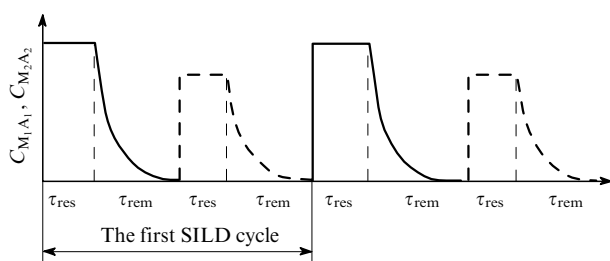


Figure 1. Variation of the reagent concentrations $C_{M_1A_1}$ and $C_{M_2A_2}$ in the layer at the solution–substrate interface during SILD synthesis (2 cycles).

τ_{res} is the residence time in solution of each reagent, τ_{rem} is the time of removal of excess reagent and reaction products by washing the substrate with the solvent.

The interest in these studies is increasing. Thus in the early 1990s several papers a year were published on this subject, in 2000 more than 200 papers appeared, while the number of publications in 2003 was ~ 400 . Reviews^{9,10} and a collective monograph¹¹ devoted to the synthesis of polyelectrolyte layers were published.

This study describes systematically the results of investigations on the nanolayer synthesis carried out during the last 10 years and considers the most promising fields of its application in nanotechnology for the solution of practically valuable problems.

II. Conditions for successive ionic layer deposition reactions

The SILD reactions on the substrate surface are carried out using two types of special automated equipment. Devices of the first type are designed for the synthesis of layers on the surface of block substrates. They consist of beakers with reagents, an electro-mechanical drive with a cartridge for samples and a PC-based control unit. The synthesis is performed by successive immersion of the specimen into solutions of reagents. It is assumed that in the beaker containing a solution of the cationic reagent, for example $Pb(NO_3)_2$ (the simplest case), adsorption of the Pb^{2+} cations on the substrate surface takes place and then excess reagent and reaction products are removed. During treatment with an anion-containing solution, for example Na_2S , in the other beaker, adsorption of the S^{2-} or HS^- anions takes place in a similar way. A SILD cycle gives rise to a single nanolayer of the compound being synthesised (in this case, PbS). When the cycle is repeated many times, the layer thickness is increased.

Layers on the surface of disperse substrates are prepared using a flow-type setup. In this case, the substance to which the nanolayer is applied is fastened in a chemical reactor and reagent solutions and washing liquids are added in succession. The order of treatment is specified by the control unit by opening and closing the appropriate electromagnetic valves.

As shown by experience, tens, hundreds or more cycles of layer deposition may give thin-layer structures according to a pre-specified pattern.

After the SILD, a layer with a thickness of about several nanometres or fractions of a nanometre, *i.e.*, a nanolayer, is formed on the surface. This definition of the ‘nanolayer’ does not imply any information concerning its morphology. Indeed, the reactions on the surface can yield either the continuous layer of new structural units (monolayer) or a discontinuous layer. In some cases, due to incomplete coverage of the surface by a reagent or incomplete removal of the reagent during washing, one can

expect an ‘islet’ mechanism of layer growth where the layer thickness in the growth area would exceed the monolayer thickness (but this would be still a ‘nanolayer’).

Even the first experiments have shown that for most compositions, washing after the adsorption results in the removal of not only excess reagents and reaction products but also a part of the (or entire) adsorbed layer. Thus, determination of the conditions of a SILD synthesis is a complicated task, as more than 10 parameters are to be controlled (including the pH values and concentrations of several solutions of reagents, pH of wash liquids, residence times, and so on). The monographs^{12,13} devoted to studies of ion exchange on the surface cover the results of numerous papers. However, they do not clarify the point concerning the choice of optimal conditions of synthesis, because the studies were aimed at elucidating the conditions of adsorption of cations (or anions) by ion exchange resins and their subsequent desorption needed for regeneration of the ion exchanger. However, the conditions for irreversible adsorption for most ion exchangers have not been described systematically and, in some cases, they are presented only as oblique results. As a rule, these studies are devoted to adsorption on a sorbent or ion exchange resin, whereas the SILD method requires information on irreversible adsorption conditions in each cycle.

Nevertheless, the optimal conditions for the SILD synthesis of nanolayers of most classes of inorganic solid compounds, in particular, metal sulfides,^{14–49} selenides,^{50–52} oxides,^{53–59} hydroxides,⁶⁰ peroxides^{61–68} and fluorides,^{69,70} have now been elucidated. An important phase in the development of this subject would be systematisation of the accumulated experimental data and classification of the SILD reactions and the approaches used.

In our opinion, SILD procedures can be divided into groups according to the main types of reactions of cations with anions in solutions.⁷¹ The major group comprises the surface reactions of an adsorbed cation (or anion) with an anion (or cation) situated in solution. The oxidation state of ions does not change. If the reaction gives a poorly soluble compound, a nanolayer is formed on the surface. The reaction of adsorbed Zn^{2+} aqua complexes with the HS^- anions to give a strong $Zn-S$ bond is an example. Water molecules are ‘squeezed out’ of the coordination sphere of zinc cations. Drying affords a layer of anhydrous ZnS .

Yet another group comprises redox reactions. Two types of such reactions are distinguished. The first type includes reactions where the adsorbed cation is oxidised ($Sn^{2+} \rightarrow Sn^{4+}$) (see Ref. 55) or reduced ($Ag^+ \rightarrow Ag^0$) (see Ref. 72), or the adsorbed anion is reduced ($Cr_2O_7^{2-} \rightarrow Cr^{3+}$) (see Ref. 73), and so on. In this case, the dissolved molecules or ions of the oxidising or reducing agent involved in the process are not incorporated in the resulting layer.

The second type comprises redox reactions where the oxidising or reducing agent and probably the product of its chemical transformation are incorporated in the layer, giving rise to a multi-component surface nanolayer (for example, $Sn^{2+} + MoO_4^{2-} \rightarrow Sn_xMoO_y$).⁵⁹

There exists a group of ‘conjugated’ SILD processes in which the redox reaction of one of the types indicated above taking place on the surface is accompanied by adsorption of other cations or anions to give a poorly soluble compound. For example, treatment of an adsorbed Ce^{3+} layer with a solution containing H_2O_2 and OH^- results in the $Ce^{3+} \rightarrow Ce^{4+}$ oxidation, accompanied by adsorption of H_2O_2 and OH^- to give a $Ce(OH)_2OOH$ nanolayer.

Apart from the reactions of cations and anions, numerous processes involving reagents as molecules or colloidal nanoparticles can also be referred to as SILD reactions. The set of these reactions is schematically shown in Fig. 2; the methods of synthesis with these reagents are defined as ionic–molecular and ionic–colloidal layer deposition, respectively.

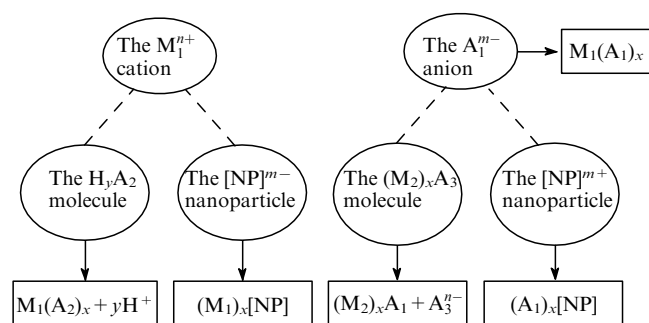


Figure 2. Main types of SILD reactions with solutions containing ions, colloidal particles and molecules in the liquid and gas phase as reagents.

III. Ionic layer deposition reactions without changes in the oxidation states of ions

1. Nanolayers of inorganic compounds

a. Synthesis of ZnS and CdS layers

The ZnS and CdS layers attract keen attention of researchers due to the attempts to create efficient electroluminescent and cathodoluminescent panels, windows for solid-state solar energy converters, photoconductors, *etc.*; therefore, the largest number of publications was devoted to this topic.^{14–43}

A pioneering systematic study of the preparation of ZnS and CdS layers using solutions of metal chlorides and sulfates and a solution of Na₂S has been carried out by Nicolau.^{14,15} The reagent concentrations were 0.005–5.0 mol litre^{−1}; the residence time in solutions and in water was 20 s; the substrates used were glass with indium and tin oxide (ITO) layers, Si, Ge, GaAs, InP, CaF₂, Al₂O₃ and LiNbO₃ single crystals, polycrystalline Ti, Mo, and Ta. The growth rate of the nanolayer depended on the solution concentration; the highest rates for ZnS and CdS, equal to 0.31 and 0.14 nm, respectively, were attained at ZnCl₂ and CdCl₂ concentrations of 5 mol litre^{−1} and a Na₂S concentration of 2.8 mol litre^{−1}. All other factors being the same, a higher growth rate was observed with chloride rather than sulfate solution. The effect of pH on the adsorption of the cations and anions on the surface of zinc and cadmium sulfides was judged from the data on the ζ -potential. These studies allowed one to determine more precisely the region of specific adsorption of ions and to construct adequate models of the processes taking place on the surface. The ZnS and CdS layers prepared under the optimal conditions were uniform and polycrystalline and had a mirror surface. The ZnS layers possessed a cubic structure and CdS layers were hexagonal, their predominant orientation being dependent on the substrate used.

In addition to layers of individual ZnS and CdS, solid solutions Cd_xZn_{1−x}S were prepared.²³ Aqueous solutions (0.1 M) of Cd(NO₃)₂, ZnSO₄ and Na₂S were used as reagents and silicon and germanium plates were used as substrates. Solid solutions were obtained using a mixture of zinc and cadmium salts. The mole fraction of cadmium was varied from 0.0001 to 1.0. The thickness of the synthesised layers was estimated based on their interference colour. For CdS, the thickness was 0.32, while for ZnS, 0.29 nm per cycle. The ZnS layers synthesised on the silicon surface had a wurtzite type hexagonal lattice after the first 20 cycles and a sphalerite type cubic structure after 40 cycles. The subsequent cycles resulted in an increase in the crystallite size and gave rise to mosaic blocks whose (111) plane was oriented parallel to the substrate. The growth of CdS layers at the Ge (111) face started with the formation of a polycrystalline cubic phase, but as the layer thickness increased, some of the crystallites oriented themselves with the (111) plane. Solid solutions were formed if the mole fraction of cadmium was 0.0001–0.003, the most perfect ones were produced for a value of 0.0002. If the mole fraction of

cadmium exceeded 0.003, layers with a CdS cubic structure were formed.

The ZnS/CdS multilayers on a glass surface coated with ITO or GaAs were prepared³⁹ by alternating treatment of the substrate with solutions of ZnCl₂ and CdCl₂ according to the SILD procedure. The thickness of each layer in the multilayer was 1–6 nm (and larger) and the overall thickness was 100–120 nm. The interfaces in the multilayer were not sharp and contained the Cd_xZn_{1−x}S solid solution. The layer-by-layer identification was carried out by scanning electron microscopy (starting with 20 nm).

It has been shown²⁷ that ZnS layers on a poly(vinyl chloride) and polycarbonate surface can be synthesised under conditions similar to those used in the synthesis on the surface of inorganic solids. The difference lied in the special preparation of the polycarbonate surface. The poly(vinyl chloride) specimens were washed only with ethanol prior to the synthesis, while the polycarbonate specimens were treated with a 10% acidic solution of KMnO₄. The MnO₂ layer thus formed was etched with concentrated HCl to give surface carbonyl groups, which then participated in the sorption of reagents in SILD synthesis. The structure of these layers was polycrystalline in the case of poly(vinyl chloride) and amorphous in the case of polycarbonate. Apart from the zinc and sulfur atoms, the layers contained about 20% of oxygen [apparently, as a constituent of ZnO or Zn(OH)₂]. On the basis of these results, the researchers concluded that SILD can be used to obtain ZnS layers with good adhesion on a polymer surface.

The oxygen content in the ZnS layers synthesised on a glass surface with an ITO layer was determined by EXAFS.²⁸ Depending on the conditions of synthesis, this was 10%–30%. In non-heated samples, oxygen was incorporated in Zn(OH)₂, while in those heated at 500 °C, in ZnO. The crystal structure in the latter case was fully identical to the structure of the layers synthesised in the gas phase by molecular layer deposition at the same temperature.

The synthesis of ZnS layers was also performed on the polyether surface.³⁰ Prior to the synthesis, the polymer samples were kept for 12 h in a 0.1 M solution of SnCl₂ for the creation of the surface layer ensuring high adhesion. Then they were washed and dried in air. One SILD cycle gave, depending on the conditions, a 0.16–0.22-nm thick sulfide layer. The layers were amorphous, but at thicknesses of more than 250 nm, crystallite peaks were noted in the diffraction pattern.

b. Synthesis of Ag₇SbS₆ layers

The ways of synthesis of nanolayers containing two metals and an anion-forming element (S^{2−}, F[−], OH[−], *etc.*) have been considered.^{19,20} The authors were the first to show that not only simple anions like S^{2−} but also complex thio salts such as SbS₄^{3−} can be used for SILD. The synthesis was carried out using solutions of S^{2−} and AgNO₃ or Pb(NO₃)₂.

The growth kinetics of Ag–Sb–S-containing nanolayers on a fused quartz surface was studied by spectrophotometry. From the dependence of absorbance on the concentration of the silver salt solution, it was found that an increase in the concentration above 0.01 mol litre^{−1} does not induce a substantial change in the absorbance. This indicates that the compound is formed in the layer of ions adsorbed on the substrate surface rather than in the solution. In 0.01 M solutions of AgNO₃ and Na₃SbS₄, the absorbance increased linearly upon an increase in the number of SILD cycles. This was indicative of a stepwise layer synthesis. The X-ray photoelectron spectrum of the layer showed electron binding energies of 368.0, 529.3 and 161.4 eV, which were assigned to the Ag⁺, Sb⁵⁺ and S^{2−} ions, respectively. According to X-ray spectral microanalysis, the ratio of these elements in the layer prepared on silica gel over ten SILD cycles was Ag:Sb:S = 8.2:1.0:7.2. With allowance for the experimental error, this ratio corresponds most closely to Ag₇SbS₆. According to powder X-ray diffraction (CuK α radiation), the layer was X-ray

Table 1. Synthesis of nanolayers of some metal chalcogenides and Cu(I) iodide and thiocyanate.

Layer	Substrate	Reagents	pH	$\tau_{\text{res}}/\text{s}$	$\tau_{\text{rem}}/\text{s}$	Note	Ref.
Ag ₂ S	SnO ₂ layer on glass	0.05 M AgNO ₃ , 0.4 M solution of thiourea	— ~6	10–12	—	$\Delta d_1 = 14$ nm	17
CuS	ITO-coated glass or CdS	(0.00625–0.05) M Cu(OAc) ₂ , (0.003–0.025) M Na ₂ S	5.3–5.7 11.0–12.0	20	75–120	on a substrate with the CdS sublayer a CuS layer (polycrystalline)	45
	glass,	0.1 M CuSO ₄ ,	~10	—	—	on glass, a CuS layer (amorphous),	46
	Si(111)	0.1 M solution of thiourea	~6	—	—	on Si, a CuS layer (polycrystalline)	
HgS	quartz glass	0.01 M Hg(NO ₃) ₂ , 0.01 M Na ₂ S	— —	30	30		22
PbS	Ge(111)	(0.01–1.0) M Pb(NO ₃) ₂ , 0.1 M Na ₂ S	— —	40	10	single crystalline layer with 0.1 μm blocks	37
	Si ₃ Na-silicate glass	0.2 M PbAc ₂ with addition of TEA	7.7	20	70	$\Delta d_1 = 0.08$ –0.12 nm. Polycrystalline	36,
		0.4 M thioacetamide	4.6	—	—	layers with a cubic structure	38
PbSe	Si ₃ Na-silicate glass	0.2 M PbAc ₂ with addition of TEA	7.7	20	70	$\Delta d_1 = 0.18$ nm. Polycrystalline	51
		sodium selenosulfite	—	—	—	layers with a cubic structure	
CdSe	glass	0.2 M solution of CdSO ₄ and tartaric acid, 0.1 M Na ₂ SeSO ₃	3.0 ~10.5	30	50	$\Delta d_1 = 8$ nm. Amorphous layer	44
In ₂ S ₃	quartz glass	0.01 M In(NO ₃) ₃ , aqueous H ₂ S	—	30	30		18
	glass	0.05 M InCl ₃ Na ₂ S	4.0 8.0	15–20	10	layers with cubic structure	44
Sb ₂ S ₃	quartz glass, silica gel	SbCl ₃ in acetic acid, aqueous Na ₂ S	—	—	—	$\Delta d_1 = 0.49$ nm	21
Sb ₂ Se ₃	glass	0.2 M solution of the potassium salt of antimony tartrate, 0.1 M Na ₂ SeSO ₃	—	—	—	layers with orthorhombic structure	50
As ₂ S ₃	glass,	0.1 M As ₂ O ₃ in HCl with EDTA,	1.0	15	10	$t = 80$ °C. Polycrystalline layer on Si	48
	Si(111)	0.1 M Na ₂ S ₂ O ₃	6.0	—	—		
Bi ₂ S ₃	quartz glass	0.01 M Bi(NO ₃) ₃ , solution of Na ₂ S	— ~8.5	30	30		73
Bi ₂ Se ₃	glass with a SnO ₂ layer	0.01 M Bi(NO ₃) ₃ with TEA additive 0.01 M Na ₂ SSeO ₃	8.0 8.5	30	40	polycrystalline layers with hexagonal structure	50
CuI	glass with a SnO ₂ layer	0.1 M Cu(S ₂ O ₃) ²⁻ , 0.0025 M KI	— —	5–20	5	polycrystalline layers with a false galena structure	74
CuSCN	glass with a SnO ₂ layer	0.1 M Cu(S ₂ O ₃) ²⁻ , 0.00625 M KSCN	—	10–20	5	layers with orthorhombic structure	74

Note. Here Δd_1 is the layer thickness per SILD cycle; TEA is triethylamine; EDTA is *N,N,N',N'*-ethylenediaminetetraacetic acid.

amorphous; however, the X-ray diffraction pattern contained a small peak at $2\theta = 30.34^\circ$, typical of Ag₇SbS₆.

The conditions and the results of syntheses of layers of other metal sulfides, selenides, iodides and thiocyanates are summarised in Table 1.

c. Synthesis of LaF₃ · *n* H₂O layers

The conditions of synthesis of LaF₃ · *n* H₂O nanolayers have been elucidated.^{69,70} Aqueous solutions of lanthanum chloride or nitrate and gaseous HF were used as reagents. First, the substrate was immersed into solutions of a lanthanum salt and then into water. Then the specimen was dried in an air flow and placed for 10 min into a flow reactor through which an air–HF gas mixture was passed. A concentrated solution of hydrofluoric acid through which air was passed at a flow rate of 0.2–0.3 dm³ min^{−1} served as the source of hydrogen fluoride. This sequence formed one SILD cycle.

Solutions of NaF or NH₄F acidified with HF to pH ≈ 4.2 were other sources of fluoride ions used in the synthesis. These were used to obtain a sample of hydrofluoride complex in the solution and on the surface. The synthesis conditions were optimised by varying the concentration of metal salts, solution pH, residence times of the specimen in the liquid and gas phases and the number of SILD cycles. The change in the lanthanum salt concentration from 10^{−2} to 10^{−3} mol litre^{−1} barely influenced the increment of the LaF₃ layer thickness (~0.45 nm) per SILD cycle. It was found by electron diffraction that the layer prepared

using gaseous HF is polycrystalline and has a hexagonal LaF₃ structure with the unit cell parameters $a = 0.716$ and $c = 0.732$ Å.

d. Synthesis of BiVO₄ layers

In the synthesis of Bi–V–O-containing layers,^{75,76} 0.01 M aqueous solutions of BiOClO₄ and NaVO₃ were used as the reagents.

These layers were prepared at an equilibrium pH of the solution of BiOClO₄. The pH value of the solution of NaVO₃ varied, being 2.0, 3.0, 6.0 or 8.0. In a solution of NaVO₃ with pH 2, a light-yellow nanolayer with the ratio Bi : V = 1 : 0.79 was formed on the silica gel surface (according to X-ray spectral microanalysis of the specimen formed after ten SILD cycles). In a solution with pH 3.0, the layer was bright-yellow and the Bi : V ratio was 1 : 1. At pH 6.0 or 8.0, the colour was less bright, while the Bi : V ratio in the layer was 1 : 0.3.

These differences were attributed to different compositions of the vanadium(V) oxyhydroxide complexes in solutions at these pH values.⁷⁷

The layers synthesised were amorphous (X-ray analysis) but the X-ray diffraction pattern of the specimen obtained from a solution of NaVO₃ at pH 3 showed a number of peaks typical of BiVO₄. On heating in air (300 °C), the intensity of these peaks increased.

e. Synthesis of metal hydroxyperoxide layers

A number of syntheses based on the formation of poorly soluble metal peroxide or hydroxyperoxide layers on the substrate surface

have been proposed. According to one of these, a layer can be obtained by successive adsorption of metal cations, H_2O_2 molecules and hydroxide ions. The adsorption irreversibility is attained due to lower solubility of hydroxyperoxides of some metals with respect to the solubility of hydroxides. First of all, this refers to the hydroxyperoxides $\text{CuO}_{1+x} \cdot n\text{H}_2\text{O}$,⁶³ $\text{ZnO}_{1+x} \cdot n\text{H}_2\text{O}$,^{61, 68} $\text{NiO}_{1+x} \cdot n\text{H}_2\text{O}$ ⁶² and $\text{La}(\text{OH})_{3-x}(\text{OOH})_x$.⁶⁶ It is clear that after heating in air, metal hydroxyperoxides should be converted into hydroxides or oxides, although for some of them [in particular, for $\text{La}(\text{OH})_{3-x}(\text{OOH})_x$], the formation of relatively stable basic carbonates cannot be ruled out either.

In the synthesis of copper hydroxyperoxide $\text{CuO}_{1+x} \cdot n\text{H}_2\text{O}$, aqueous solutions of $\text{Cu}(\text{NO}_3)_2$, solutions of $\text{Cu}(\text{OAc})_2$ in aqueous ethanol, aqueous and aqueous-ethanolic solutions of H_2O_2 and ammonia were used as the reagents. The substrate was successively treated with ammoniacal copper, wash solution, a weakly alkaline solution of H_2O_2 and again with the wash solution. The optimisation of the synthesis conditions demonstrated the necessity of using solutions of ammoniacal copper with $\text{pH} \approx 8-9$ and concentrations of $0.01-0.1 \text{ mol litre}^{-1}$ and $0.1\%-3.0\%$ of hydrogen peroxide. Under these conditions, an increase in the number of SILD cycles induces a regular increase in the absorbance of the layer in the UV transmission spectrum (*i.e.*, layer thickness). According to ellipsometry data, depending on the synthesis conditions, one SILD cycle gives a 0.3- to 1.5-nm thick layer.

It should be borne in mind that in weakly alkaline media, ammoniacal copper cations are adsorbed on the silica surface, the removal of their excess affording a $\equiv \text{SiOCuOH}$ layer. When the specimen is put into a weakly alkaline solution of H_2O_2 , the $\equiv \text{SiOCuOOH}$ groups, which dissociate to give CuOO^- and H^+ ions, appear on the surface.

The surface acquires again a negative charge and, hence, ammoniacal copper ions can again be adsorbed, thus forming the next copper peroxide layer.

Poorly soluble compounds are also formed when some metal cations react with soluble peroxo complexes. This synthetic protocol was tested experimentally to prepare $\text{La}_x\text{NbO}_y \cdot n\text{H}_2\text{O}$ layers using solutions of $\text{La}(\text{OAc})_3$ and peroxyphosphoric acid.⁶⁴

f. Synthesis of hybrid iso- and heteropoly oxometallates

The difficulty of preparing polyoxometallate layers on various substrate surfaces is due to their relatively low thermal stability; therefore, thin layers cannot be applied by, for example, vapour deposition. The preparation of heteropoly compound (HPC) layers from reagent solutions is also faced with difficulties, as due to the 'cluster' structure of HPC, the energy of their adsorption on most substrates is too low to produce a dense monolayer. In addition, the adsorbed HPC layer has no sites for sorption of the subsequent layer. However, some heteropolyacids (HPA), for example, $\text{H}_3\text{PMo}_{12}\text{O}_{40} \cdot n\text{H}_2\text{O}$, can be reduced rather readily to $[\text{PMo}_{12}\text{O}_{40}]^{n-}$ (in particular, with a solution of SnCl_2).⁷⁸ The resulting species may prove more reactive toward SILD synthesis. It is known⁷⁹ that the least soluble compound is formed in the reaction of the reduced form of phosphomolybdic acid with Zr^{4+} cations.

The use of aqueous solutions of $\text{Zr}(\text{OAc})_4 \cdot n\text{H}_2\text{O}$, $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ and $\text{H}_3\text{PMo}_{12}\text{O}_{40} \cdot n\text{H}_2\text{O}$ as reagents gave a $\text{Zr}_{2.6}(\text{OH})_x\text{PMo}_{8.0}\text{Sn}_{1.9}\text{O}_y \cdot n\text{H}_2\text{O}$ layer on the surface.⁸⁰ It can be considered as a sort of 'hybrid' compound containing structural fragments of the initial HPA and zirconium polyhydroxy cations. Together with Sn^{4+} cations, the latter serve as a sort of bridges binding HPA anions to one another. Thus, a three-dimensional network of chemical bonds is formed on the surface.

2. Polyelectrolyte nanolayers

The first layer-by-layer synthesis of a polymer layer on a solid surface was reported by Nicolau *et al.*^{81, 82} This was done using solutions of pyrrole or aniline in ether, 3-methylthiophene in dichloromethane; and solutions of FeCl_3 in MeOH or MeCN were

used as oxidants. Repeated successive adsorption of organic molecules and their oxidation on the substrate surface gave a layer of the corresponding polymer. In essence, this was a molecular layer deposition reaction.

Aqueous solutions of polyelectrolytes in the cationic or anionic form have been proposed⁸³⁻⁸⁵ as reagents for precision synthesis of layers of organic compounds. Examples of such polyelectrolytes are poly(ethyleneimine) (PEI) with a molecular mass of 20–750 kDa (contains NH_2 groups and forms cations in the solution) and sodium poly(styrenesulfonate) (PSS) with a molecular mass of 70–500 kDa (contains SO_3^- groups and forms anions in solution). When the substrate whose surface has a charge opposite to the charge of the polyelectrolyte is immersed in the solution, the polyelectrolyte is adsorbed (Fig. 3). To produce a multilayer, the substrate is withdrawn from the solution, washed with water, placed into a polyelectrolyte solution (with the opposite charge of the macromolecule functional groups), kept in this solution, and once again withdrawn and washed with water (see Fig. 3). A distinctive feature of the process of synthesis of polyelectrolyte nanolayers compared to the synthesis of nanolayers of inorganic compounds is the necessity to dry the specimen in air after each cycle. This is required to remove water molecules from the layer and to enhance 'adhesion' of the long-chain polyelectrolyte molecules (to the substrate and to one another).

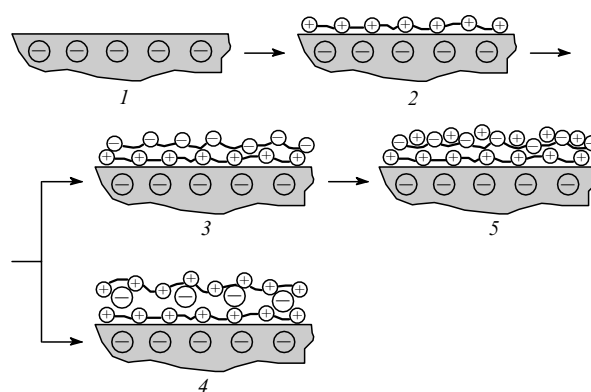


Figure 3. Schemes of SILD reactions involving polyelectrolyte solutions. (1) Initial substrate, (2) specimen with the layer of a cation-containing polyelectrolyte, (3) specimen with the layer of a cation- and anion-containing polyelectrolyte, (4) specimen after the adsorption of nanoparticles and a cationic polyelectrolyte layer, (5) specimen after the adsorption of metal cations.

The described method of synthesis has found a rather broad use.^{86, 87} The following compounds have now been studied as cationic polyelectrolytes: poly(diallyldimethylammonium chloride) (PDDA, 20–200 kDa), poly(allylamine hydrochloride) (PAH, 8–15 kDa), poly(L-lysine) (PLL) and poly(D-lysine) (PDL, 30–70 kDa), tetra(*p*-toluenesulfonate) 5,10,15,20-tetrakis(1-methyl-4-pyridinio)porphyrin (TMPyP), diazo resin (DR), poly(amidoamine) (PAMAM), (4-vinylbenzyl)dodecyltrimethylammonium chloride (VDAC), and 4,4'-bis(5-pyridylpentyl)-biphenyl (4,4'-BPPOBP).

Among anionic polyelectrolytes, one can mention albumin, heparin, PSS (70–500 kDa), hyaluronic acid (HA), poly(L-Glu) (PGA, 50–100 kDa), polyacrylic acid (PAA, 90 kDa), polymethacrylic acid (PMA, 100 kDa), DNA, poly(aniline-*N*-butylsulfonate) (PANBUS, 3500 Da) and poly(vinyl sulfate) (PVS, 170 kDa).

These polyelectrolytes have been used to prepare PDDA/PSS, PVS/PAH, PLL/HA, PSS/PAH, heparin/PAH, PAA/PAH and other layers.

Detailed description of the reactions with polyelectrolyte solutions can be found in a collective monograph.¹¹ Some examples of the use of these nanolayers for solving practical problems are considered below.

3. Multinanolayers of hybrid (organic and inorganic) substances

The most significant studies deal with the synthesis of hybrid layers containing polyelectrolyte macromolecules in the cationic form and HPA anions. The use of polyelectrolytes allows one to overcome the above-noted (see Section II) problems which arise in the synthesis of HPA layers, because polyelectrolytes function as a peculiar transition layer, which glues together the HPA anions. Examples are provided by the layers containing PAH and $[\text{Eu}(\text{P}_2\text{W}_{17}\text{O}_{61})_2]^{17-}$ or $[\text{Eu}(\text{SiW}_{11}\text{O}_{39})_2]^{13-}$ (see Refs 88, 89), PAH and $[\text{Eu}(\text{BW}_{11}\text{O}_{39})_2]^{15-}$ (see Ref. 90), $[\text{Eu}(\text{SiW}_{10}\text{VO}_{39})_2]^{15-}$ and PEI,⁹¹ $[\text{Eu}(\text{SiW}_{11}\text{O}_{39})_2]^{13-}$ and the poly(4-vinylpyridine)–Os(2,2'-bipy) complex,⁹² PEI, $[\text{PMo}_{12}\text{O}_{40}]^{3-}$ and the $[\text{Ru}(\text{bipy})_3]^{2+}$ complex,⁹³ $[\text{W}_{10}\text{O}_{32}]^{4-}$ or $[\text{NaP}_5\text{W}_{30}\text{O}_{110}]^{14-}$ and PEI,⁹⁴ PEI and $[\text{NaP}_5\text{W}_{30}\text{O}_{110}]^{14-}$ (see Ref. 95).

Anionic polyelectrolytes can form poorly soluble compounds and nanolayers with metal cations under the reaction conditions (see Fig. 3). The studies,^{96–98} devoted to the synthesis of Tb^{3+} –PSS, Y^{3+} –PSS and Gd^{3+} , Eu^{3+} or Nd^{3+} and PSS layers, deserve attention.

IV. Successive ionic layer deposition with a change in the oxidation states of adsorbed ions

1. Reactions accompanied by the oxidation or reduction of cations

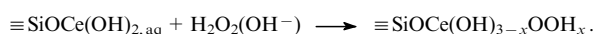
The preparation of layers of poorly soluble metal hydroxides using successive adsorption of metal cations and OH^- anions is faced with some complications. This is due to the fact that after adsorption of cations and anions, it is necessary to treat the substrate with a salt solution containing a metal cation. The hydroxide layer formed may react with the protons formed upon hydrolysis of the salt, this may result in hydroxide dissolution, and the synthesis of a thick layer may become impossible.

A solution of SnF_2 and a weakly alkaline solution of H_2O_2 have been chosen as the reagents in order to attain conditions for irreversible synthesis of SnO_2 nanolayers.⁵⁵ Under the action of hydrogen peroxide, the adsorbed Sn^{2+} cations are oxidised to Sn^{4+} [in an alkaline medium, the Sn^{2+} cations are converted into $\text{Sn}(\text{OH})_4$]. The use of these reagents also appears justified based on the analysis of another publication,⁷⁷ which reports the precipitation conditions for Sn^{2+} and Sn^{4+} hydroxides from 0.001 M solutions. Complete precipitation of $\text{Sn}(\text{OH})_2$ is known to occur at $\text{pH} \approx 6$, and that of $\text{Sn}(\text{OH})_4$, at $\text{pH} \approx 3$, i.e., the $\text{SnO}_2 \cdot \text{H}_2\text{O}$ layer synthesised by treatment of an alkaline solution with an oxidant is not dissolved in the next cycle.

In aqueous solutions at $\text{pH} 2\text{--}3$, adsorption of SnOH^+ ions takes place on the silica surface; after the removal of excess salt, a nanolayer of adsorbed $\text{Sn}(\text{II})$ hydroxide is formed. Then treatment with a weakly alkaline solution of H_2O_2 induces the $\text{Sn}(\text{II}) \rightarrow \text{Sn}(\text{IV})$ transition.

In the second SILD cycle, the $\text{Sn}(\text{IV})$ hydroxide is not dissolved on treatment with SnF_2 , and SnOH^+ ions are adsorbed on the surface. After SILD cycles repeated many times, a layer of the $\text{Sn}(\text{OH})_4$ hydroxide is formed.

Similar redox reactions in the layer of adsorbed cations have been used in the synthesis of iron(III) hydroxide⁶⁰ and hydrated $\text{Ti}(\text{III})$ oxide layers.⁵⁴ A weakly alkaline solution of H_2O_2 is also an oxidant for the adsorbed Ce^{3+} cations. However, unlike SnO_2 , apart from participating in the redox reaction, this reagent tends to form a stable peroxide compound by the reaction

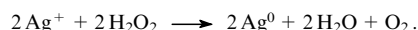


The $\equiv \text{SiOCe}(\text{OH})_{3-x}\text{OOH}_x$ fragment can dissociate to give the $\equiv \text{CeOO}^-$ groups, which function as adsorption sites for the Ce^{3+} ions in the subsequent SILD cycles.

For some cations, for example, Pb^{2+} , an alkaline solution of KMnO_4 is the most efficient oxidant.⁵⁶ On treatment of the substrate with a solution of $\text{Pb}(\text{NO}_3)_2$, the Pb^{2+} or PbOH^+ ions are adsorbed on the surface, while the subsequent treatment with a weakly alkaline solution of KMnO_4 results in $\text{Pb}^{2+} \rightarrow \text{Pb}^{4+}$ oxidation and reduction of Mn^{7+} , probably to Mn^{5+} . The latter reacts with excess solution of KMnO_4 to give MnO_4^{2-} ions. After washing, a $\text{PbO}_2 \cdot n\text{H}_2\text{O}$ layer is formed on the substrate surface. The layer has the structure of orthorhombic α - PbO_2 with the unit cell parameters: $a = 0.4038$, $b = 0.503$, $c = 0.5486$ nm; the c axis is perpendicular to the substrate surface.

The Ag^0 (see Ref. 72) and Cu^0 (see Ref. 99) nanolayers were synthesised by SILD by reduction of the cations adsorbed on the surface. The key problem of this synthesis (compared with the synthesis of, for example, metal sulfides or fluorides) is that the layer consists of only one sort of atoms and it is difficult to select conditions of irreversible layer-by-layer adsorption.

The reduction of Ag^+ in a weakly alkaline solution of H_2O_2 was chosen as a method for the synthesis of Ag^0 nanolayers. A metallic silver layer is formed in the mixing regime according to the following reaction



In the first cycle of SILD, the substrate was successively treated with a solution of $[\text{Ag}(\text{NH}_3)_2]\text{NO}_3$, washed with ammonia ($\text{pH} 9$) and with a weakly alkaline solution of H_2O_2 , and then washed with distilled water. In the subsequent cycles, a solution of AgNO_3 was used for Ag^+ sorption, water was used for washing and the reduction of Ag^+ ions was performed by a weakly alkaline solution of H_2O_2 . After treatment of the substrate with a solution of the silver ion and washing off the excess of the reagent with an ammonia solution, adsorption of ammoniacal silver takes place on the surface. Subsequently, after treatment with a solution of the reducing agent, only partial reduction of Ag^+ ions takes place to give known¹⁰⁰ compounds of the Ag_2^+ or Ag_4^{2+} type. They are characterised by a sharply lower intensity of the absorption bands of free and bound OH groups at 1370 and 1400 nm. Apparently, after treatment with a reducing agent, the Ag_2^+ , Ag_4^{2+} and other clusters form peculiar complexes of the $\equiv \text{Si}-\text{OAg}_2$, $\equiv \text{Si}-\text{OAg}_4^+$ type on the surface. When the substrate is treated with a solution of AgNO_3 , these complexes may function as adsorption sites for the Ag^+ ions, which are then (on treatment with a reducing agent) converted into Ag^0 to give a larger complex. As the number of SILD cycles increases, a layer of metallic silver is formed.

Layers of Cu^0 were prepared using solutions of $\text{Cu}(\text{II})$ salts and a highly alkaline ($\text{pH} 13\text{--}14$) solution of formaldehyde. Water served as the wash liquid. The nanolayers were characterised using scanning electron microscopy and atomic force microscopy (AFM). Unfortunately, the method used to check the completeness of reagent removal after reduction of the cations is not mentioned in the study cited.⁹⁹ Probably, alkali was not removed completely during washing, and treatment with a solution of the copper salt was accompanied by 'precipitation' of copper hydroxide, which was then reduced to the metal on multiple treatment with a solution of a reducing agent.

Metal cations can serve as oxidants for adsorbed cations. In the synthesis of $\text{Ag}^0 \cdot \text{MnO}_2$ layers,¹⁰¹ Mn^{2+} cations function as reducing agents and Ag^+ cations are the oxidants. It is important that, for these cations, a pH region exists in which the reaction products formed on the surface, namely, MnO_2 and Ag^0 , are poorly soluble. These underlay the choice of the reagents for the synthesis of so-called 'hybrid' metal–oxide layers.

For the synthesis of an $\text{Ag}^0\text{--Mn--O}$ -containing nanolayer,¹⁰¹ aqueous solutions of $\text{Mn}(\text{OAc})_2$ and AgNO_3 were used as the reagents. The growth of the layer was observed when 0.01 M aqueous solutions of $\text{Mn}(\text{OAc})_2$ ($\text{pH} 7.5$) and AgNO_3 ($\text{pH} 8.5\text{--}9$)

were used. To increase the pH in the solution of $\text{Mn}(\text{OAc})_2$, a solution of sodium acetate was used; in the case of AgNO_3 , this was attained by an ammonia solution. At the given pH values, the reagents were adsorbed on the surface, and irreversible Mn^{2+} oxidation and Ag^+ reduction took place. The X-ray photoelectron spectrum displayed a peak at 642.2 eV corresponding to Mn^{4+} ions ($2p_{3/2}$) in MnO_2 and a peak at 368.6 eV corresponding to Ag^0 ($3d_{5/2}$). The Ag^0 : MnO_2 ratio in the layer was determined from the peak intensities to be ~ 0.7 . The diffuse reflectance spectra of the layers on the silica gel surface exhibited broad bands at 400–500 nm, *i.e.*, in the absorption region of metallic silver clusters. In a powder X-ray diffraction study, the metallic silver in the layer exhibited a peak at $2\theta = 64.48^\circ$. This confirms its crystalline structure.

2. Reactions involving the oxidation of cations and the reduction of anions

If the SILD makes use of reactions involving the oxidation of cations and the reduction of anions, the oxidant reacts with the adsorbed cationic layer, thus passing to a lower oxidation state and forming a poorly soluble compound with the layer of the oxidised cation.

This synthetic strategy was first tested in the preparation of $\text{MnO}_2 \cdot n\text{H}_2\text{O}$ nanolayers on the silica surface.^{8,53} Solutions of MnCl_2 , MnSO_4 and $\text{Mn}(\text{OAc})_2$ served as the reducing agents and weakly alkaline solutions of KMnO_4 was used as the oxidant. When these compounds react in the mixing regime, a $\text{MnO}_2 \cdot n\text{H}_2\text{O}$ layer is produced on the surface, which is confirmed by X-ray fluorescence and IR spectroscopy. The layer is mechanically strong, its thickness being controlled by the number of SILD cycles.

If cations and anions of different elements are used in the redox reaction on the surface, the layer will be multicomponent, which was observed in the synthesis of layers containing $\text{Co}(\text{III})$ – $\text{Mn}(\text{IV})$ – O ,⁵⁷ $\text{Ce}(\text{IV})$ – $\text{Mn}(\text{III})$ – O ⁵⁸ and $\text{Fe}(\text{III})$ – $\text{Cr}(\text{III})$ – O .¹⁰² The compositions of the prepared layers were described as $\text{Co}_3\text{MnO}_x \cdot n\text{H}_2\text{O}$, $\text{Ce}_4\text{MnO}_x \cdot n\text{H}_2\text{O}$ and $\text{FeCr}_{0.7}\text{O}_x \cdot n\text{H}_2\text{O}$, respectively.

The Ce_xNbO_y nanolayers were synthesised in a similar way.¹⁰³ The Ce^{3+} cations served as the reducing species, while the NbO_8^{3-} anions were the oxidants. The layer composition can be described as $\text{Ce}_{0.7}\text{NbO}_x \cdot n\text{H}_2\text{O}$.

A similar strategy has been used⁵⁹ to prepare nanolayers $\text{Sn}(\text{IV})\text{Mo}(\text{VI},\text{V})_{0.6}\text{O}_y \cdot n\text{H}_2\text{O}$ using aqueous solutions of SnCl_2 and $(\text{NH}_4)_2\text{MoO}_4 \cdot 2\text{H}_2\text{O}$ or $(\text{NH}_4)_2\text{Mo}_7\text{O}_{24} \cdot 2\text{H}_2\text{O}$ as the reagents. Apart from the molybdate anions, heteropolyacid anions can also react with the reducing agent, a SnCl_2 solution. This was shown in a study¹⁰⁴ where $\text{H}_3\text{PW}_{12}\text{O}_{40} \cdot n\text{H}_2\text{O}$ was used to prepare the $\text{Sn}_{16}(\text{OH})_x\text{PW}_{19}\text{O}_y \cdot n\text{H}_2\text{O}$ nanolayer.

V. Conjugated ionic layer deposition reactions including oxidation or reduction of ions and adsorption

Using the SILD method, it is possible to prepare not only one- but also multi-component layers, in particular, multilayers of different composition. A necessary condition for the synthesis of multilayers is the insolubility of the peroxide nanolayer already formed in the reagent solutions used to form the subsequent layers. The $\text{CeO}_{2+x} \cdot z\text{H}_2\text{O}$ and $\text{LaO}_{1.5+x} \cdot z\text{H}_2\text{O}$ multilayers have been obtained.⁶⁶ The synthesis was carried out on a silicon surface in the following way: one SILD cycle gave a $\text{CeO}_{2+x} \cdot z\text{H}_2\text{O}$ nanolayer; this was followed by the cycle giving a $\text{LaO}_{1.5+x} \cdot z\text{H}_2\text{O}$ layer; and then these cycles alternated many times (up to 60). The resulting multilayer was studied by X-ray photoelectron spectroscopy. The results showed the presence of both $\text{La}(\text{III})$ and $\text{Ce}(\text{IV})$. Their relative concentration equal to $\sim 1:1$ was determined based on the band intensities.

In the synthesis of multicomponent layers, metal ions can be introduced into the layer using mixtures of solutions of their salts. Thus for the synthesis of a two-component Ce- and La-containing layer, $\text{La}(\text{NO}_3)_3$ was added in different proportions to a solution of $\text{Ce}(\text{OAc})_3$. The overall solution concentration was $0.01 \text{ mol litre}^{-1}$, while the mole fractions of lanthanum were 10%, 20% and 40%. However, the lanthanum concentrations in the resulting layer (according to X-ray photoelectron spectroscopy) were 9%, 15% and 22%, respectively. The decrease in the lanthanum content in the layer with respect to its concentration in the solution is due to lower sorbability of the $\text{La}_{\text{aq}}^{3+}$ ions compared to that of $\text{Ce}_{\text{aq}}^{3+}$.

Yet another example of using conjugated SILD reactions is provided by the synthesis of nanolayers consisting of the double $\text{Fe}(\text{III})$ – $\text{Ni}(\text{II})$ hydroxide.¹⁰⁵ A freshly prepared solution of Mohr's salt $(\text{NH}_4)_2(\text{FeSO}_4)_2 \cdot 6\text{H}_2\text{O}$ and an ammoniacal solution of NiSO_4 (pH ≈ 8.0 – 8.5) with concentrations of $0.01 \text{ mol litre}^{-1}$ served as the reagents. The sequence of operations for the preparation of a $\text{Fe}(\text{III})$ hydroxide layer (this procedure has been reported⁶⁰) is as follows: Fe^{2+} ions are adsorbed from a solution of Mohr's salt, the excess of the solution is removed, the sorbed ions are oxidised in an H_2O_2 solution, and the excess of hydrogen peroxide is removed by washing with water. For the synthesis of the double hydroxide layer, it has been proposed¹⁰⁵ to combine the oxidation of sorbed $\text{Fe}(\text{II})$ ions with sorption of $\text{Ni}(\text{II})$ ions and to synthesise a double hydroxide layer over a minimum number of surface treatment cycles. In an ammoniacal $\text{Ni}(\text{II})$ solution, the $\text{Fe}(\text{II}) \rightarrow \text{Fe}(\text{III})$ catalytic oxidation with oxygen dissolved in water, the formation of a $\text{Fe}(\text{III})$ hydroxide layer on the surface and the adsorption of $\text{Ni}(\text{II})$ ions on this layer took place. The results of investigations of the layers showed that the $\text{Fe}:\text{Ni}$ concentration ratio in the layer is $1:0.4$, while the layer thickness increases by $\sim 0.7 \text{ nm}$ after every SILD cycle.

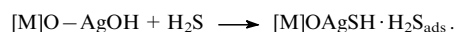
VI. Successive ionic layer deposition involving ions and molecules

The use of ionic reagents in one stage and molecular reagents (in the gas or liquid phase) in another stage of treatment allows one to markedly extend the range of obtained objects. This synthetic strategy can be referred to as ionic–molecular layer deposition. This method was first proposed by Tolstoy and Bogdanova¹⁰⁶ for the synthesis of a BaHPO_4 protective layer on the surface of carbon steel. The process was carried out in the following way: at a temperature of 280°C , the steel surface was treated with P_4O_{10} vapour, the excess of the vapour being removed by evacuation; then the specimen was cooled and placed into a solution of a Ba^{2+} salt. After removal of excess salt by washing with water and drying, the sequence of operations was repeated. This gave a dense BaHPO_4 layer on the surface, which efficiently protects steel from corrosion.

To carry out alternating treatment with a reagent solution and vapour, the specimen has to be dried in between, which restricts the scope of the procedure. The use of this procedure is justified only if the layer cannot be prepared by SILD using reagent solutions. It has been shown⁶⁹ that this situation arises if the layer to be synthesised is dissolved in the solution of either of the reagents. For example, synthesis of the $\text{ScF}_3 \cdot n\text{H}_2\text{O}$ layer is accompanied by layer dissolution during treatment with aqueous NaF to give the $[\text{ScF}_6]^{3-}$ complex ion. Therefore, a procedure including surface treatment with a solution of the Sc^{3+} salt and with gaseous HF was used for the synthesis.

Yet another example of this sort is the synthesis of Ag_2S layers.¹⁶ It was noted that with aqueous solutions of silver nitrate and sodium sulfid used as the reagents, no reproducible layer is produced, because of either the desorption of silver ions during washing of the specimen with water or the dissolution of the synthesised Ag_2S in excess Na_2S to give thio salts. Therefore, to attain the irreversibility of the surface reactions, a solution of ammoniacal silver with pH 8.8–9.2 and gaseous H_2S were used as

the reagents. After adsorption of $\text{Ag}(\text{NH}_3)_2^+$ cations, excess ammoniacal silver was removed from the substrate surface by washing with a solution of NH_4OH (pH 8.5). After that, the specimen was dried in an air flow at 70–80 °C. Apart from the removal of water, destruction of ammonia complexes took place during drying to give $\text{Ag}-\text{OH}$ and $\text{Ag}-\text{O}-\text{Ag}$ bonds on the surface. Treatment with gaseous H_2S followed by removal of its excess yielded a silver sulfide layer



The adsorbed hydrogen sulfide molecules and the S–H bonds on the surface served as the adsorption sites for the Ag^+ ions in the following SILD cycle and ensured a regular increase in the layer thickness.

VII. Successive ionic layer deposition involving ions and nanoparticles

The SILD reactions involving ions and nanoparticles were first accomplished by Iler,⁶ who studied the conditions for synthesis of multilayers of cations, for example, $\text{Al}_2(\text{OH})_5^+$, and nanoparticles from colloidal solutions of SiO_2 or boehmite on a silicate glass surface. Metal cations and negatively charged colloidal SiO_2 particles were successively adsorbed on the glass surface (Fig. 4).

The greatest number of publications is devoted to the synthesis of multilayers with participation of polyelectrolytes in the cationic or anionic form and nanoparticles in colloidal solutions (see Fig. 3). Pioneering studies in this field were published by Kotov *et al.*¹⁰⁷ and Fendler.¹⁰⁸ As an example, note the studies dealing with the syntheses of polyelectrolyte layers and nanoparticles of CdS ,¹⁰⁹ CdSe ,¹¹⁰ CdTe ,¹¹¹ ZnS ,¹¹² PbS ,¹¹³ TiO_2 ,¹¹⁴ ZrO_2 ,¹¹⁵ Ag ,¹¹⁶ Au ,¹¹⁷ SiO_2 ,¹¹⁸ MoO_2 ,¹¹⁹ and Fe_3O_4 ,¹²⁰ which have also been described in a monograph.¹¹

Among the most recent studies, noteworthy is the synthesis of mesoporous layers consisting of TiO_2 nanoparticles ~6 nm in diameter on the surface of a gold crystal.¹²¹ A specific feature of this study is that the researchers proposed to use, as the anion, the phytic acid multifunctional anion, which is adsorbed on the surface of TiO_2 nanoparticles through the PO_4^{3-} groups and simultaneously creates the adsorption sites for the next layer of nanoparticles.

VIII. Applications of nanolayers synthesised by successive ionic layer deposition

A highly important trend in the modern materials science is the design of devices with nanometre-range sizes of functional elements. The synthesis of ‘hybrid’ multilayers consisting of nanolayers of various classes of compounds is also topical, because in this case one can expect new practically valuable properties.

Among the methods used for the synthesis of nano- and multinano-layers, a special place is occupied by layer-by-layer methods, in particular, those using ion-containing solutions as precursors.

The scope of application of SILD reactions for the solution of practical problems is determined by features of the synthesis. In particular, the synthesis can be carried out under mild conditions at room temperature using automated devices with simple hardware; the layer can be applied on the surface of a series of articles of any complex shape, including disperse materials, rather than one article; dilute (10^{-1} – 10^{-3} M) solutions with a broad pH range can be used; the thickness of the resulting layer can be precisely controlled, *etc.* These features make this method promising for the synthesis of new protective passivating coatings on metal surfaces, sensors, optical coatings for the devices used for solar energy conversion, electrochromic, photochromic and magnetic materials, biocompatible coatings on the metal surface, polymeric pervaporation membranes, quantum-sized structures for optoelectronics and so on.

Now we will consider several examples of the use of these nanolayers.

1. Synthesis of biochemical and gas sensors

New opportunities for the design of structures comprising an inorganic substrate, a polyelectrolyte multilayer and a biologically active macromolecule were implemented in the existing biochemical sensors.¹²²

Several ways of immobilisation of biologically active molecules on the surface of a solid support can be distinguished: adsorption, adsorption in a matrix of a polymer layer fixed on the surface, positioning in space between the surface and a partially permeable membrane or in polymer capsules synthesised by SILD and fixed on a support surface. The last-mentioned version has been used to prepare glucose oxidase (GOx) encapsulated into the PSS/PAH layer and to study its sensory properties with respect to the glucose content in solutions. The sensor showed a linear response in the concentration range of 0–2 mmol litre⁻¹ and a non-linear response up to 5 mmol litre⁻¹. Encapsulation results in a pronounced increase in the time of sensor operation.

For deposition of cholesterol oxidase (COx) or cholesterol esterase (CE) layers on the ITO, platinum, mica, quartz or silicon surface, the PSS/PEI multilayers were used as the sublayers.¹²³ This gave the PSS/PEI/COx, PSS/PEI/COx/PEI/CE, and PSS/PEI/COx–CE/PEI structures. Study of the voltammetric characteristics of these structures has shown that they can find application in flow-type electrochemical cells for detecting cholesterol molecules.

A new approach to addressing the problem of glucose determination in physiological solutions has been proposed.¹²⁴

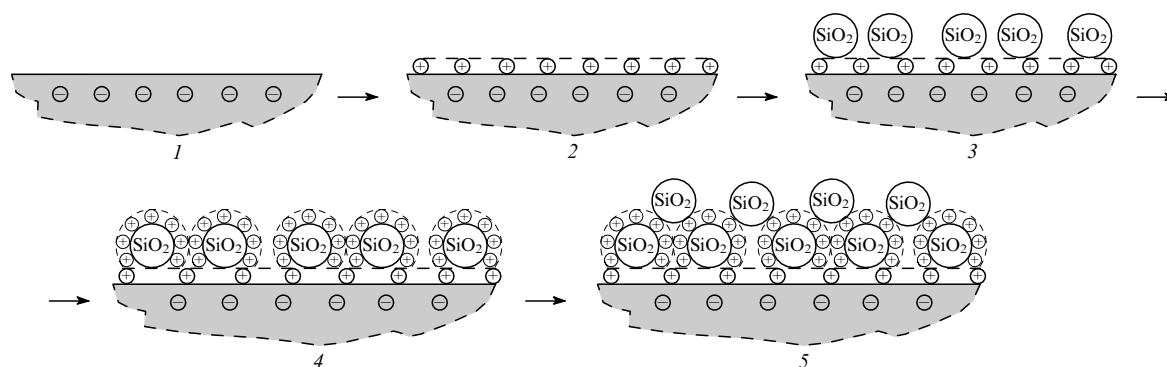


Figure 4. Schemes of SILD reactions involving SiO_2 colloidal particles and an $\text{Al}(\text{III})$ solution.

(1) Initial substrate, (2) after adsorption of $\text{Al}(\text{III})$ cations, (3) after treatment in a colloidal solution containing SiO_2 particles, (4) after adsorption of $\text{Al}(\text{III})$ cations, (5) after treatment in a colloidal solution containing SiO_2 particles.

According to this approach, the sensor is produced on the basis of the silicon cantilever of an atomic-force microscope coated with the pre-synthesised $(\text{PEI/PSS})_3(\text{PEI/GOx})_3$ layer. Study of the response of this sensor in various physiological solutions has shown that it is sensitive to the range of glucose concentrations of 1×10^{-2} – 1×10^{-3} mol litre $^{-1}$, which can be used for diabetes diagnosis.

If a PAH/PAA multilayer is synthesised on the surface of a quartz resonator (20 cycles),¹²⁵ this structure becomes sensitive to the adsorption of smoke particles from air. The adsorption of these particles in the multilayer is reversible: after heating in air or placing into hot water, the sensor restores its initial characteristics.

The ITO/PB/GOx – PAH structure (PB is the Prussian blue) was synthesised on the ITO surface on glass to design a sensor for determining the glucose concentration in solution.¹²⁶ The efficiency of this sensor is due to not only high level of enzyme immobilisation but also to the minimisation of the diffusion problem in nanolayers. The biosensor exhibited high selectivity with respect to glucose in the presence of acetoaminophene, ascorbic and uric acids and proved to be stable for 20 days.

To determine the concentration of oxygen dissolved in water, a sensor based on the $[\text{Ru}(\text{bipy})_3]^{2+}$ and PSS (or PDDA) multilayer has been proposed.¹²⁷ The layer shows a fluorescence maximum at 620 nm ($\lambda_{\text{excit}} = 450$ nm) whose intensity depends on the concentration of the dissolved oxygen (in the 0–12 mg litre $^{-1}$ range).

In addition to the use as biochemical sensors, the layers synthesised by SILD proved to be efficient as parts of conductometric gas sensors based on SnO_2 films. It is known that modification of SnO_2 with transition metal oxides or noble metal clusters results in the change in adsorption and catalytic properties of the surface with respect to oxygen, water and gas molecules to be detected. This is accompanied by the change in the electro-physical properties of the sensor, and, hence, its response to a change in the concentration of the mixture under analysis. A series of studies devoted to this topic were carried out by Korotchenkov *et al.*^{128–130} Both the SnO_2 layers synthesised by SILD on the quartz surface and SnO_2 films obtained on a glass-ceramic surface by spray pyrolysis and modified by oxide layers were used as investigation subjects. The SILD synthesis of SnO_2 layers was carried out by the procedure reported by Tolstoy⁵⁵ using solutions of SnF_2 and H_2O_2 . After 40 SILD cycles, a nanostructured amorphous SnO_2 layer appeared on the substrate surface; after heating at 200–400 °C, the layer consisted of 6–7-nm particles. Testing of this layer as the conductive layer in sensors for ozone, CO and H_2 demonstrated its high sensitivity with respect to ozone. The sensor shows a fast (about 2–3 s) response to the change in the concentration of this gas.

The effect of the layer synthesised on the surface of a SnO_2 film obtained by spray pyrolysis on the properties of the conductometric sensor has been studied.¹²⁹ The experiments were carried out for Cu, Co, Mn and Fe metal–oxygen layers and Ag and P metal layers. Prior to testing, all specimens were heated at 300 °C. At this temperature, the initial peroxide or hydroxide layer synthesised by SILD decomposed to give the layer of the metal oxide. It was found that the sensitivity with respect to CO and ozone increases most sharply for the sensor containing Fe–O layers. The synthesis of the Fe–O-containing layers on a SnO_2 film surface results in enhanced ‘gas response’ of the sensor, whereas the synthesis of Cu–O layers sharply decreases the response in an ozone atmosphere. The Mn–O layers are sensitive to CO.

The synthesis of Pd and Ag layers on the SnO_2 surface increases the ‘gas response’ of the sensor in a reducing gas atmosphere more than 5–10-fold and sharply suppresses the sensitivity towards ozone. For example, after two SILD cycles, the ‘gas response’ decreases more than 20–40-fold for SnO_2 –Pd samples and more than 100-fold for SnO_2 –Ag.

Thus, it follows from the foregoing that the sensitivity and the selectivity of SnO_2 -based sensors can be varied over a broad range by synthesising metal and metal oxide nanolayers on the surface.

2. Passivating protective coatings on the steel, zinc and silver surfaces

Nanolayers of inorganic compounds are widely used in the synthesis of passivating protective coatings on the metal surface. However, for some metals the corrosion resistance of this layer is limited due to its low thickness and porosity. Attempts to increase the corrosion stability by creating so-called ‘conversion’ passivating layers formed upon metal dissolution in a highly alkaline or acidic medium followed by deposition of a porous protective oxide layer on its surface have not provide the desired outcome.

Meanwhile, by using SILD, it is possible to synthesise protective layers under mild conditions using weakly alkaline or neutral solutions and to ‘after-grow’ the natural oxide layer on the metal. These experiments were carried out by Bogdanova and co-workers.^{131–134} The layers were synthesised using the SILD method by multiple treatment of the metal pre-passivated in a solution of an oxidant (as a rule, $\text{H}_2\text{Cr}_2\text{O}_7$) with salt solutions containing ions that react to form a poorly soluble compound. In particular, the following processes were conducted successively on a zinc surface. The specimen was placed into a solution of $\text{H}_2\text{Cr}_2\text{O}_7$; as a result, a polymolecular layer of hydrated chromic acid was adsorbed on the surface. Then the specimen was withdrawn and dried in air at 120–180 °C, and the excess reagent was removed by water. The specimen was placed into a solution of a metal salt [for example, $\text{Zn}(\text{OAc})_2$], dried and washed. This gave a surface layer of poorly soluble zinc chromate, which increased the corrosion resistance of zinc.

Apart from the above method, redox reactions have also been used to form a Cr(III) hydroxide layer.¹³³

The effect of nanolayers on the corrosion resistance of metals has also been demonstrated for silver.¹³¹ Corrosion tests were carried out by a drop method in a 0.18 M solution of Na_2S or by keeping the specimen in saturated vapour of a 0.1 M solution of Na_2S until a dark spot of Ag_2S appeared. The results of testing of Cr(III)–Cr(VI)-containing nanolayers showed that the corrosion resistance increases from 2–3 to 8–9 min as the number of SILD cycles increases from 1 to 6. Typically, the period of stability after six SILD cycles is 2–3 times longer than after other types of treatment.

3. Nanomaterials with magnetic properties

A nanomaterial synthesised using colloidal particles of Prussian blue, poly(ethyleneimine) and sodium poly(styrenesulfonate) can be a molecular ferromagnet.¹³⁵ The size of colloidal particles was 40 to 100 nm, the number of SILD cycles varied from 6 to 45. Fluorite, quartz, silicon and an ITO layer on glass were used as substrates. The synthesised layers were characterised by cyclic voltammetry, UV and IR spectroscopy, AFM and EPR. The researchers concluded that the concentration of, and the residence time in, the Prussian blue solution influence the content of colloidal particles in the synthesised layer; its magnetic properties at temperatures of 4–15 K were studied.

Multilayers of the PAH/PSS polyelectrolyte containing magnetite particles 20–30 nm in diameter were synthesised on the surface of melamine-formaldehyde (MF) grains 2.7 μm in diameter and human erythrocytes.¹³⁶ After dissolution of the MF matrix in an acidic medium, the polyelectrolyte capsule has nearly preserved its shape and still retained the magnetite particles. For capsules containing erythrocytes, the possibility of changing the orientation in space upon the change in the magnetic field was demonstrated. In view of these results, the researchers cited suggested that new nanomaterials with a unique set of physico-chemical properties could be designed on the basis of polyelectrolytes.

Kim *et al.*¹³⁷ designed a new material exhibiting magnetic and electrically conductive properties. On a silicon surface, the [(PSS/

PPy)₃PSS/ferrite]₂ structure was synthesised (PPy is polypyrrole). The ferrite Co_{0.67}Zn_{0.33}Fe₂O₄ with 9 nm particles was taken as the nanomaterial with magnetic properties. The layers had a conductivity of 18 S cm⁻¹ and exhibited a magnetic hysteresis.

Two procedures for the synthesis of Fe₃O₄ particles in PAH/PSS microcapsules 5.6 µm in diameter have been considered.¹³⁸ One is based on impregnation of the inner space of the microcapsule with a colloidal solution containing Fe₃O₄ particles 8 nm in diameter stabilised by citrate anions (pH 4.5). The other procedure involves the synthesis of nanoparticles inside the capsule. To this end, the capsules were kept in aqueous NaOH to create inside a solution with pH 10, which was treated with a solution containing 0.66 mol litre⁻¹ of FeSO₄ and 0.62 mol litre⁻¹ of Fe₂(SO₄)₃. This gave magnetite colloidal particles with an average size of 10 nm located inside the capsule.

A multilayer containing 10-nm Fe₃O₄ particles and PDDA macromolecules was prepared on the surface of SiO₂ nanoparticles.¹³⁹ It was shown by electron microscopy that one deposition cycle yields a 31 to 43-nm thick layer with a C : Fe ratio of ~ 2.3.

4. Luminophores, structures with a photochromic effect and photocatalysts

Europium-containing polyoxometallate layers exhibit photoluminescent properties. After UV excitation ($\lambda_{\text{excit}} = 276$ nm) of the PAH and [Eu(P₂W₁₇O₆₁)₂]¹⁷⁻ or [Eu(SiW₁₁O₃₉)₂]¹³⁻ layer, luminescence maxima are observed at 594 and 616–622 nm.^{88, 89} The intensity of the luminescence bands is directly proportional to the number of SILD cycles for layers synthesised in 1–12 cycles. The excitation of a PAH and [Eu(BW₁₁O₃₉)₂]¹⁵⁻ layer by the UV radiation of a xenon lamp gives rise to photoluminescence peaks at 591 and 613 nm,⁹⁰ while for [Eu(SiW₁₀VO₃₉)₂]¹⁵⁻ and PEI layers excited by the radiation with $\lambda = 310$ nm, the peaks are at 598 and 623 nm.⁹¹ The maximum of the photoluminescence band ($\lambda_{\text{excit}} = 276$ nm) from a [Eu(SiW₁₁O₃₉)₂]¹³⁻ and poly(4-vinylpyridine) layer containing Os(2,2'-bipy), which was obtained over 1–9 SILD cycles, was at 617 nm.⁹²

A layer containing PEI, [PMo₁₂O₄₀]³⁻ and the [Ru(bipy)₃]²⁺ complex has been synthesised.⁹³ Study of its photoluminescence showed that UV excitation with a xenon lamp results in an emission spectrum with a peak at 592 nm.

One of the polyanions can be represented by a molecule that gives a fluorescence spectrum. For example, it was shown¹⁴⁰ that a multilayer can be prepared from PVBC or PDDA polycations and fluorescein sodium salt anions. After nine SILD cycles, the PVBC/fluorescein layer exhibited an emission spectrum with peaks at 515 and 557 nm.

A luminescence spectrum was also observed for a multilayer consisting of CdTe_xS_{1-x} nanoparticles 4 nm in diameter and PAH formed after four SILD cycles on the surface of polystyrene (PS) particles with a diameter of 0.6 µm. The emission maximum in the spectrum of this specimen was at 600 nm.¹⁴¹ On the basis of these results, the researchers concluded that this method is suitable for preparing new coatings for photon crystals.

Layers of PAH and PSS polyelectrolytes with fluorescein isothiocyanate (FITC) on the surface of PS particles with a diameter of 640 nm have been proposed for the design of new class of particles with specified fluorescence and biofunctional properties.¹⁴² Fluorescein isothiocyanate has been used previously as a label in immunochemical and biomedical assays. For the PS/(PAH–FITC/PSS)_n specimen and $\lambda_{\text{excit}} = 492$ nm, the fluorescence peak was observed at 526 nm. It was shown that with allowance for the subsequent physical adsorption of proteins (immunoglobulin G), one can carry out biospecific recognition tests.

New multilayers of the hybrid compound [W₁₀O₃₂]⁴⁻ or [NaP₅W₃₀O₁₁₀]¹⁴⁻ and PEI exhibiting a photochromic effect have been reported.⁹⁴ Quartz and silicon served as substrates. The concentration of reagent solutions was 10⁻² mol litre⁻¹ and the residence time in each solution was 20 min. The number of bilayers applied varied from 1 to 12. After UV irradiation of the

layers from a mercury lamp, light-blue colour was noted to appear; this was due to the W⁵⁺ ions resulting from the redox reaction of W⁶⁺ with the NH₂ groups of PEI. The colour disappears after a 5-min exposure in air, apparently, due to the oxidation of W⁵⁺ with the atmospheric oxygen.

The colour of the [NaP₅W₃₀O₁₁₀]¹⁴⁻ and PEI layer can arise not only upon the UV irradiation but also on heating *in vacuo* to 120–180 °C.⁹⁵ In this case, a similar W⁶⁺ reduction takes place.

On the silica surface, a PEI/PSS layer and a multilayer composed of PDAC and colloidal particles Zn_{1-x}Cu_xSe stabilised by mercaptopropionic acid were obtained.¹⁴³ Excitation of the layer ($\lambda_{\text{excit}} = 322$ nm) induced an intensive blue luminescence with a peak at 450 nm, the highest intensity being observed for specimens with 2% Cu²⁺.

Photocatalysts for the oxidation of the iodide anion and decomposition of methyl orange based on TiO₂ nanoparticles and PAH with PAA have been developed.¹⁴⁴ Fused quartz, glass and silicon plates served as the substrates. The TiO₂ nanoparticles had a size of 4 nm and an anatase crystal structure. Photocatalytic reactions were induced by UV radiation of a xenon lamp (3 h). The specimens with different thickness of the TiO₂/PAH/PAA layer specified by the number of SILD cycles exhibited different activities. The final concentration of ions and molecules involved in the photocatalytic reaction in solution was lower for samples with thicker layers. Hence, no diffusion retardation for the reactants is present in the synthesised multilayer.

It has been shown¹⁴⁵ that polyelectrolyte multilayers on a glass surface may underlie the creation of a five-step photochemical structure having features of a natural photochemical structure analogous to plant leaves. The visible light is absorbed by so-called 'antennas', which represent PAH layers with coumarin (Coum) or fluorescein (Fl) additives and the porphyrin complex of divalent palladium (PdTSP⁴⁻) separated by inert Zr(HPO₄)₂ or HTiNbO₅ layers. Polyviologen molecules in poly(vinyltoluene) (PVT–MV) served as electron acceptors. The highest quantum yield was found for the Coum–PAH/PdTSP⁴⁻/Fl–PAH/HTiNbO₅/PVT–MV structure.

5. Electronic and optoelectronic devices and electrocatalysts

The synthesis of structures consisting of polyelectrolytes and semiconductor nanoparticles opens up the way for the development of a new class of electroluminescent devices, in particular, multicolour light-emitting diodes.^{146–152} These diodes can consist of a polymer with *p*-type of conduction, *viz.*, poly(*p*-phenylenevinylene) (PPV) and an *n*-type semiconductor (CdSe).

A brief review on the scope of the synthetic methods in question for the development of nanolayer-based diodes has been reported.¹⁵³ The following structures were considered: ITO/PPV/(HDT/CdSe)_n/Al layer (HDT is 1,6-hexanedithiol), ITO/PPV/(HDT/CdSe)₃/Al layer, ITO/(PDDA/TiO₂-nano)₁₀/PDDA/(GO)₃₀/PDDA/Au layer (GO is oxidised graphite), (*p*- or *n*-)Si–(Si-nano)PPy/Au layer. The CdSe nanoparticles in these structures had the size of 2–4 nm, TiO₂; 2.3 nm; Si, 5 nm.

Zener diodes have been produced.¹⁵⁴ To this end, a PPy layer and then (after several cycles), a PAH/CdSe layer were applied onto a gold substrate pre-treated with 2-mercaptoethylamine hydrochloride. The particle size of this compound was 2.0 nm. An aluminium layer sputtered onto the surface of a planar structure served as the second electrode. The synthesised nanolayers were studied by UV/Vis emission and absorption spectroscopy, AFM, X-Ray photoelectron spectroscopy and electrochemical methods.

Light-emitting diodes incorporating polyelectrolyte layers synthesised using SILD reactions have also been reported.^{84, 155, 156}

The possibilities of the design of materials for optoelectronics have been considered^{157–159} in relation to the layer-by-layer synthesis of a multilayer containing electron-conductive CdTe nanoparticles and hole-conductive polymers (for example, polyaniline and polypyrrole).

A new method for immobilisation of 5-nm CdS nanoparticles stabilised on the surface with 3-mercaptopropyltrimethoxysilane has been developed.¹⁶⁰ The method is based on nanoparticle adsorption on the substrate surface and hydrolysis of the Si—OMe groups of nanoparticles to give SiOH groups, which serve as the immobilisation sites in the next cycle of adsorption. The sequence of layer deposition cycles on the surface yields a multilayer of CdS nanoparticles non-uniformly coated by a SiO₂ layer. The photochemical reaction of CdS with atmospheric oxygen yields CdSO₄, which is water-soluble. The nanoparticle diameter decreases and they become enclosed in a SiO₂ nanocapsule.

In addition to semiconductor nanoparticles, an organic molecule giving an electroluminescence spectrum can be built-in into the multilayer of cationic and anionic polyelectrolytes. A light emitting diode was manufactured based on the PAH polycation, PAA polyanion and the Evans blue dye.¹⁶¹ The multilayer consisting of five bilayers was applied onto ITO-supported glass, heated *in vacuo* for 3 h at 120 °C, and coated with an aluminium layer by sputtering. Study of the electroluminescence intensity showed that the structure synthesised in this way has 2–3 times better parameters than the structure based on an Evans blue layer obtained by solvent evaporation on a rotating substrate.

Recent years have seen the enhanced interest in the synthesis of conductive polymer layers transparent in the visible region, in particular, PEDOT/PSS [PEDOT is poly(3,4-ethylenedioxythiophene)]. These layers are used in electroluminescent cells as buffers between the layer of a transparent conductive ITO and a layer of organic molecules with hole conduction. These polymers were obtained by SILD.¹⁶² To reduce the roughness on the layer surface, ultrasonic pre-treatment of the solution of PEDOT/PSS was carried out to destroy large colloidal particles. The resulting layers had a hole diffusion constant of $5 \times 10^{-10} \text{ cm}^2 \text{ s}^{-1}$, which is better than that for the layers synthesised by the mixing procedure.

The electrooptical properties of the layers obtained by SILD from high- and low-molecular-mass polyelectrolytes, PAH and PSS, have been studied.¹⁶³ It was found that stable layers are formed at pH 4.

A series of works on the synthesis and study of the nanowire exhibiting a diode effect was performed by Mallouk, Kovtyukhova, *et al.*^{164–166} First, a silver layer was applied by the electrochemical method as one of the contacts into the 70–200 nm pores of the Al₂O₃ film obtained by anodic treatment of Al or into a polycarbonate membrane. Then TiO₂/PSS, ZnO/PSS or ZnO/PAH layers were formed in nine SILD cycles, and the second contact, *viz.*, a gold or platinum layer, was synthesised on the surface by an electrochemical procedure. The oxide or polycarbonate matrix was dissolved. The ‘nanowire’ thus formed showed voltammetric characteristics corresponding to the rectifying effect.

The structure metal–insulator–gold nanoparticles–insulator–metal, functioning as a one-electron tunnelling device, has been produced.¹⁶⁷ The size of gold nanoparticles was 2.5 nm and the insulator was represented by a multilayer containing $\alpha\text{-Zr}(\text{HPO}_4)_2 \cdot \text{H}_2\text{O}$ and PAH nanoparticles. The ‘upper’ conductive layer which ensured the contact consisted of polypyrrole applied by polymerisation.

The properties of the Ag₂S,¹⁷ (CdS)_{*x*}(Bi₂S₃)_{1–*x*},⁴⁹ Bi₂Se₃⁵⁰ and Bi₂Se₃–Sb₂Se₃⁵² nanolayers synthesised by SILD have been studied within the solar cells. The photoelectrochemical characteristics were obtained for the cells comprising an electrode that included a fluorinated tin oxide layer coated with a sulfide or selenide layer synthesised on its surface, a carbon electrode and a polysulfide electrolyte layer (Na₂S + NaOH + S). For these cells, electrophysical characteristics in the light and in the dark, spectral and temporal response and other parameters were studied.

Photoelectrochemical characteristics were also measured for a cell consisting of an electrode represented by a thin layer of fluorinated SnO₂ on a glass surface and a TiO₂ layer applied

thereon (from a TiF₄ solution).¹⁶⁸ To create internal porosity in this layer, prior to its deposition, a PAH/PAA layer was synthesised on the substrate in ten SILD cycles, and the resulting structure was heated in air at 650 °C to remove organic substances. A 0.3 M solution of LiI and a 0.03 M solution of I₂ in acetonitrile served as the electrolyte in this cell. Platinum was the counter electrode. The nanostructured TiO₂ layers showed a fourfold higher degree of light to electrical energy conversion than analogous continuous layers.

For the same purpose, SILD syntheses of polymer-based layers have been carried out.¹⁶⁹ Glass plates coated with an ITO layer were the substrates, and fullerene molecules positively or negatively charged by PPV and PSS polyelectrolytes and PAH served as the reagents. After 20–74 SILD cycles, the substrates were dried *in vacuo* at 270 °C and coated with a 200-nm thick Al layer. The voltammetric characteristics of the resulting structures were measured. A photoresponse whose magnitude depended on the ‘architecture’ of the resulting multilayer was found.

An important field of application of the SILD method is the development of new thin-layer structures exhibiting electrochromic effects. This was observed in relation to nanolayers of organic, inorganic and hybrid compounds. A polymer layer was obtained¹⁷⁰ on the ITO surface after successive treatments of the substrate in solutions of PANBUS, which is the anionic form of a polyelectrolyte, and VDAC, which is a polycation in solutions. The electrochemical cell contained ITO-coated glass with the PANBUS–VDAC bilayer applied by SILD as one electrode, an ITO layer on glass as the second electrode and the CF₃SO₃Li solid electrolyte in a photopolymerised polymer. Upon application of a potential from –3.0 to +3.0, the cell colour changed from yellow to dark-green. At 1–10 bilayers, the response time of the cell was ~10 s. If the number of bilayers exceeded 10, the response time sharply increased to be up to 24 s. Thus, the ‘depth’ of the colour of the active layer can be varied with high accuracy by specifying its thickness.

Electrochromic properties were found for layers of the hybrid compound consisting of tungstic acid and 4,4'-BPPOBP.¹⁷¹

A large number of publications report the synthesis of multilayers on the surface of electrodes and the study of their electrocatalytic activities. For example, it was found that the PDDA and cobalt tetrasulphophthalocyanine multilayer synthesised on a glass carbon surface¹⁷² functions as an electrocatalyst in the oxidation of hydrazine; the multilayer comprising [P₂W₁₇O₆₁]^{7–} and the complex obtained by the reaction of poly(4-vinylpyridine) with osmium bis(2,2'-bipy) chloride (*n*QPVP–Os)¹⁷³ reduces H₂O₂, NO₂[–] and BrO₃[–]; multilayers of PDDA and glucose oxidase involved in the redox reactions of enzymes were also studied. The properties of the layer of phosphomolybdic acid and PAMAM were studied on the surface of a gold electrode;¹⁷⁴ this layer was an efficient electrocatalyst in nitrite reduction and arsenite oxidation; an H₅SiMo₁₁VO₄₀ and *n*QPVP–Os layer¹⁷⁵ was studied in the electrocatalytic reduction of BrO₃[–] and HNO₂; and the layer of tris(2,2'-bipyridyl)ruthenium and sodium decatungstate on the ITO surface¹⁷⁶ was found to function as an electrocatalyst in the reduction of iodate ions and oxidation of oxalate ions. New electrodes exhibiting unique redox properties were produced on the basis of multilayers containing PSS polyelectrolyte and Co(II) ions with a supramolecular ligand [for example, 1,4-bis(2,2':6',2''-terpyridin-4'-yl)benzene¹⁷⁷].

6. Biomaterials and polymer membranes

Using the layer-by-layer procedure and polyelectrolytes, it is possible to incorporate biologically active molecules into the layer being synthesised, to carry out immobilisation on various surfaces and encapsulation. A multilayer of this type has been prepared¹⁷⁸ on the surface of quartz in aqueous solutions of TMPyP and DNA using 2–20 cycles. The DNA/hexadecylamine multilayers were prepared¹⁷⁹ on the fluorite, quartz and silicon surfaces; the DNA/PDDA layer was formed on the glassy carbon and quartz surfaces;¹⁸⁰ DNA/PLL, on the quartz, silicon and mica

surfaces.¹⁸¹ The PEI and DNA multilayer was produced on the surface of polylactic acid.¹⁸²

This method provides the possibility of partial solution of the biocompatibility problem of different materials by the synthesis of multilayers on their surfaces. For example, the hydrophobic surface of the major material of contact lenses permeable for oxygen molecules can be made hydrophilic and compatible with eye tissues by coating it with a polyelectrolyte multilayer (6–20 cycles).¹⁸³

For solving the biocompatibility problem for stainless steel and blood, it has been proposed¹⁸⁴ to use multilayers synthesised by multiple alternating treatment of steel surface in PEI and albumin solutions (in a citrate–phosphate buffer with pH 7.4). The morphology of these layers was studied by AFM. Investigations showed that 11 cycles of treatment of steel surface give a layer stable for 40 days which sharply increases the haemocompatibility. This synthesis was recommended for preparing biocompatible layers on the surfaces of other inorganic substrates.

Other researchers¹⁸⁵ increased the biocompatibility of stainless steel with blood by coating the steel surface with a PEI and heparin multilayer, which remained stable for 21 day after 13 cycles of SILD synthesis. The synthesis of such layers is possible on the surfaces of substrates having complicated shapes, in particular, on the inner surface of blood vessels.

The application of a polyelectrolyte layer on the surface with a complicated shape is used for encapsulation of various particles. The publications of Donat *et al.*,¹⁸⁶ Caruso *et al.*¹⁸⁷ and Radchenko *et al.*¹⁸⁸ should be considered among the first one along this line. First, a layer of macromolecules (in this case, a dextrin layer) is adsorbed on the surface of a matrix microparticle, for example, MF; subsequently, a PSS/PAH multilayer is deposited on its surface in four cycles. After dissolution of MF in 0.1 M HCl, dextrin becomes situated inside the PSS/PAH capsule (Fig. 5).

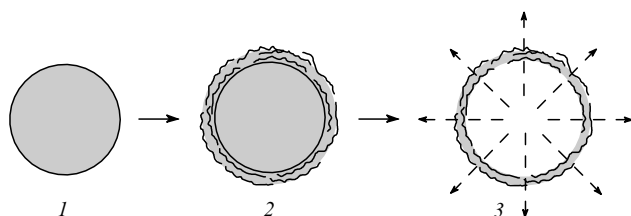


Figure 5. Scheme of SILD synthesis of a capsule on the surface of a solid particle.

(1) Initial particle; (2) after deposition of a multilayer consisting of cation- and anion-containing polyelectrolytes; (3) after dissolution of the initial particle.

The permeability of the PSS/PAH capsules for various compounds reversibly depends on pH.¹⁸⁹ When pH is low, defects and voids up to 100 nm in diameter appear on the walls due to the surface charge. This increases the permeability. In neutral and weakly alkaline media, the permeability disappears.

Apart from colloidal particles, biological blood cells or bacterial spores can be encapsulated into a polymer multilayer. In particular, the PDDA/PSS multilayers formed after two or four cycles¹⁹⁰ increased the adhesion of cells to the silicon surface (AFM study).

The multilayers of PEI/alginate or alginate/poly(L-lysine) polyelectrolytes on the surface of polylactic acid enhance its cytocompatibility with respect to chondrocyte cells, in particular, they are favourable for cell fastening on the surface, growth and activity.¹⁹¹

New systems for drug delivery in the form of microcapsules based on alginate/protamine multilayers have been proposed.¹⁹² The encapsulation procedure of a biologically active compound (α -chymotrypsin) was based on its electrostatic interaction with alginate molecules inside the capsule. A ~ 6.5 μm capsule accom-

modated up to 10^9 molecules, which is almost 1000 times larger than this value for the PSS/PHH capsule. For encapsulation of poorly soluble compounds, it has been proposed⁹⁷ to incorporate them into the multilayer of the capsule wall and then dissolve the matrix core; hence, the compound gets inside the capsule.

The possibility of increasing the time of action of drugs through encapsulation by polyelectrolyte layers has been considered.¹⁹³ Furosemide microcrystals with a size of 5 μm covered with 45- to 125-nm thick gelatin/PSS and gelatin/PDDA nanolayers served as the investigation subjects. The application of a layer formed in 2–6 SILD cycles on the single crystal surface increases the time of action of drugs 50–300-fold. The effect of multilayers on the solubility of biologically active compounds was elucidated taking dissolution of the initial and modified naproxen crystals as an example.¹⁹⁴ The alginate/gelatin, dextran/gelatin, PAA/chitosan and dextran/chitosan layers were used.

Polyelectrolyte multilayers can serve as efficient membranes for the separation of liquid and gas mixtures. The important characteristics of such membranes are the selectivity and high permeability with respect to one of the components. The SILD method provides a unique opportunity for the design of high performance membranes for pervaporation of low-molecular-mass compounds. On the one hand, it allows one to form continuous polyelectrolyte layers, and on the other hand, it is possible to specify precisely the layer thickness and modify the composition (by various additives) thus changing the permeability. The properties of membranes based on multilayers of chitosan, PEI and PDDA polycations and PAA, alginic acid and PSS polyanions have been studied.^{195,196} The density of ionogenic chemical groups was found to be an important parameter of a PEI membrane that increases the selectivity in the separation of a mixture of low-molecular-mass alcohols. Water removal from ethanol and isopropyl alcohol with a separation factor of 10 000 for a PEI/PAA membrane was observed for the multilayer obtained over six SILD cycles. The number of these groups is also important for increasing the membrane stability and enhancing the interaction at the substrate–membrane interface. Examples of separation of water and alcohols have been reported.^{197–199}

A membrane based on polyelectrolyte multilayers is also used for the separation of salt mixtures. The ion transport through ultrathin poly(vinylammonium)/poly(vinylsulfate) membranes, obtained by SILD using aqueous solutions of two polyelectrolytes, has been studied.²⁰⁰ The spectroscopic study of the permeability showed that the transport of CuCl_2 , LaCl_3 , BaCl_2 and $\text{K}_4[\text{Fe}(\text{CN})_6]$ is accompanied by simultaneous ‘intercalation’ of cations or anionic metal complexes into the membrane. In the case of Cu^{2+} , La^{3+} or $[\text{Fe}(\text{CN})_6]^{4-}$ ions, intermolecular bonds are formed inside the membrane, thus decreasing its permeability with respect to other salts, for example, NaCl and KCl. Conversely, the Ba^{2+} ions induce a decrease in the number of bonds; hence, the membrane permeability with respect to NaCl and KCl increases.

On the basis of poly(ethylene glycol methacrylate) and linear poly(2-hydroxyethyl methacrylate) layer on the porous Al_2O_3 substrate, membranes for the separation of O_2 – N_2 (with a selectivity of ~ 2) and CO_2 – CH_4 (with a selectivity of ~ 20) gas mixtures were developed.²⁰¹ The porous structure of the substrate was not changed and the layer thickness was ~ 50 nm.

Thus, different types of the SILD reactions are widely used to prepare nanostructures of inorganic and hybrid compounds on the substrate surfaces. Further development of studies along this line would apparently be related to variation of the layer composition by using diverse substrates and to the synthesis of new multilayers. This would extend the scope of practical application of nanolayers in nanotechnology.

This work was carried out with partial financial support of the Programme ‘Universities of Russia’, the Russian Foundation for Basic Research (Project No. 05-03-33207a) and the Civilian Research and Development Foundation (USA).

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Mechanochemistry and mechanical activation of solids

V V Boldyrev

Contents

I. Introduction	177
II. Studies of the influence of high pressure on the matter	178
III. The influence of pressure and shear on the physicochemical properties of solids and chemical reactions with them	179
IV. Mechanical activation and mechanochemical reactions in mills	179
V. The use of mechanochemistry and mechanical activation for the solution of applied problems	184

Abstract. The effects of the hydrostatic and shear-inducing pressure on the physicochemical properties of solids are analysed. The mechanochemical reactions and mechanical activation are illustrated with various types of chemical transformations ranging from polymorph transitions to solid-state reactions. The prospects for the use of mechanochemistry for the solution of applied problems are discussed. The bibliography includes 299 references.

I. Introduction

The term ‘mechanochemistry’ was first introduced by W Ostwald in the ‘Textbook of General Chemistry’,[†] where he considered, in particular, various methods for the simulation of chemical processes. This term refers to chemical reactions involving reagents in any state of aggregation, although most frequently it is applied to solid-state processes and reactions either initiated by a mechanical means or involving reagents preactivated by a mechanochemical treatment.

The history of emergence and maturation of mechanochemical investigations has been reviewed elsewhere.^{1,2} M Carry-Lea, an American chemist, is commonly recognised³ as a pioneer of mechanochemistry owing to his works on the decomposition of silver halides,^{4,5} where he established specific features of the mechanochemical processes and clearly differentiated them from thermally activated ones. There are equally good reasons to consider M Faraday, who observed an acceleration of the dehydration of crystalline hydrates upon the mechanical treatment, as another father of mechanochemistry.

The first work in this field performed in Russia is likely the study of solid-state reactions with powders upon the mechanical activation by F M Flavitskii.⁶ Later, these investigations were continued in the Leningrad State University within the scope of development of a method for the qualitative analysis of ores and minerals,⁷ and further in the Tomsk State University.^{8–10} In the Soviet Union, in the 1940s, the nature of the shock sensitivity of explosives was systematically investigated.^{11,12} In approximately the same period, the importance of polymers in economics greatly

increased and thus mechanochemistry attracted specialists working in the field of macromolecular chemistry.^{13–16}

There were four major research centres actively involved into mechanochemical investigations.^{2,17}

1. The Institute of Physical Chemistry and the Institute of Chemical Physics of the Academy of Sciences in Moscow, where important theoretical studies on the nature and mechanisms of the mechanochemical processes in various systems have been accomplished.^{14,16,18–20}

2. The A F Ioffe Physico-Technical Institute in Leningrad, where the mechanisms of chemical reactions of polymers under the mechanical treatment have been elucidated by the research team of S N Zhurkov.^{21,22} More recently, a series of works on thermodynamics of the mechanochemical processes have been performed in St Petersburg by A I Rusanov and co-workers.^{23,24}

3. The Siberian scientific school of mechanochemistry of inorganic compounds. The first works in this field were performed in the mid 1950s in the Tomsk State University,^{8–10} but then the ‘centre’ of research activities moved to Novosibirsk, where studies on both the theory of the mechanochemical processes in inorganic systems and the use of mechanochemistry for the solution of applied problems related to the processing of minerals, inorganic synthesis, materials science, catalysis, *etc.* were deployed in the Institute of Chemical Kinetics and Combustion, the Institute of Geology and Geophysics, the Institute of Physico-Chemical Foundations of Mineral Processing, and the Institute of Inorganic Chemistry of the Siberian Branch of the Russian Academy of Sciences.^{25–37}

4. The Scientific Production Association ‘Dezintegrator’ and the Tallinn Polytechnic Institute in Estonia, where I A Hint and co-workers mainly elucidated the industrial applications of the rod disintegrator mills of their own design.^{38–40}

In addition, investigations in the field of mechanochemistry were conducted on a systematic basis in scientific and technological centres in Kiev,⁴¹ Ivanovo,^{42,43} Sverdlovsk,⁴⁴ Ufa,⁴⁵ Minsk,⁴⁶ and other cities of the former Soviet Union.

Nowadays, the interest of researchers to mechanochemistry does not subside but, in contrast, the community of scientists dealing with mechanochemistry and the mechanical activation expands and the number of publications in these fields rapidly increases.^{47,48} New dedicated mechanochemical centres appears in France, Italy, Germany, USA, China, South Korea, Japan, India, Canada, *etc.*

V V Boldyrev Institute of Solid State Chemistry and Mechanochemistry, Siberian Branch of the Russian Academy of Sciences, ul. Kutateladze 18, 630128 Novosibirsk, Russian Federation. Fax (7-383) 332 15 50, e-mail: boldyrev@solid.nsk.su

Received 28 March 2005

Uspekhi Khimii 75 (3) 203–216 (2006); translated by Ya V Zubavichus

[†]W Ostwald *Lehrbuch der Allgemeinen Chemie. Stöchiometrie* Bd. 2 (Leipzig: Engelmann, 1891).

II. Studies on the influence of high pressure on the matter

A mechanical action on a solid can typically be represented as a combination of pressure and shear. Therefore, it is important to establish the role of each of the two factors in the modification of the physicochemical properties of substances subjected to a mechanical treatment. In this regard, studies on the effects of isostatic pressure, *i.e.*, the behaviour of a sample under equal loads from all directions, became important. This field was pioneered by works by G Tammann⁴⁹ and P V Bridgman,⁵⁰ which still retain their significance although they were done in the first half of the 20th century.

So far, the effects of pressure on solid-state reactions have been less explored than the temperature effects. The major reason for this is difficulties related to the experimental instrumentation and monitoring of processes taking place at elevated pressures. Nevertheless, three major aspects of the influence of high pressure on the course of chemical reactions in the solid state can be distinguished.⁵¹

The first aspect includes the influence on the intergrain interactions in mixtures of reacting solids. As has been pointed out by W Komatsu,⁵² it is important to correctly account for the total number and the overall area of the intergrain contacts, since it is they rather than the mere ratio of surface areas of reacting particles that govern the rate of a solid-state reaction, at least in its early steps.

This has been shown by W Poch⁵³ by the example of the synthesis of nickel ferrite and zinc and magnesium aluminates from the respective oxides at a pressure ranging from atmospheric to 60 kbar. The experimentally observed significant acceleration of the reactions under elevated pressures can be explained by an increase in the contact area between the reacting particles, which promotes the diffusion across the interface. The optimum pressure as regards the reaction rates is 40 kbar. A further increase in pressure decelerates the reactions, since under these conditions, the vacancy-mediated diffusion in the bulk of particles becomes the rate-limiting step and it is impeded by high pressures. In some cases, changes in the reaction rates and conversion levels are indicative of the involvement of an intermediate gas phase.⁵⁴

The second aspect of the pressure effects includes the changes within the particles of solid reagents themselves.⁵⁵ The changes can be subdivided into ones occurring with the real structure (primarily, concentrations of various defects), a modification of the interatomic distances and bond angles, and the changes inside the atoms or ions. The direction of the pressure-induced changes in the concentration of point defects is determined by whether the formation of a specific defect gives rise to a lattice dilation or shrinkage. Consequently, the concentration of the ion vacancies should always decrease and that of the interstitial ions increase with an increase in pressure, all other factors being the same. This explains the different possible net effects of pressure on the diffusion in solids and, consequently, on the solid-state chemical reactions, for which the diffusion through the layer of a solid product is the rate-limiting step.

An increase in pressure also modifies the properties dependent on the interatomic distances and bond angles.⁵⁶ In particular, this gives rise to a narrowing of the band gap so that a dielectric starts to behave as a semiconductor and even sometimes as a metal. Thus the effect predicted by K T Herzfeld⁵⁷ and N F Mott⁵⁸ in the beginning of the previous century has been successfully confirmed experimentally.

H G Drickamer and C Frank proposed⁵⁵ a classification of all transformations in solids under the isostatic compression into four groups. The first group includes the transformations accompanied by a rearrangement of atoms, molecules or ions in a crystal without substantial changes in the electronic subsystem. The conversion of the face-centred cubic lattices of alkali metal halides into primitive cubic lattices under the mechanical load can be taken as an example of this type of transformations. The second

group includes similar transitions that are accompanied by changes in the electronic subsystem. As a consequence, such transitions result in an alteration of the electrical or magnetic properties of the substance. The transition of ferromagnetic α -iron into paramagnetic γ -form can be mentioned as an example. The third group includes the structural and bulk transformations, which are characterised by the existence of a specific transition point and are accompanied by a change in the type of the electronic structure. The $\sigma \rightarrow d$ hybridisation of bonding in rubidium and potassium crystals and the transition from the f- to the d-character of bonding in crystals of cerium and other rare-earth metals upon compression fall into this group. Finally, the fourth group comprises the transformations accompanied by continuous changes in the bonding character, such as those observed in iron acetyl acetonate (the transition $\text{Fe}^{3+} \rightarrow \text{Fe}^{2+}$) as well as in some complex compounds with donor-acceptor bonds and molecular crystals upon compression.

Presently, this classification does not cover all the available experimental data and thus it cannot be considered comprehensive. Still, it can be taken as a basis for the analysis of the isostatic pressure effects on solids. Apparently, the consideration of the isostatic compression effects on molecular crystals as well as the analysis of pressure-induced changes in molecules and intermolecular interactions realised through the van der Waals and H-bonds may help to substantially extend this classification.⁵⁹

The range of studies devoted to the influence of high pressure on physicochemical properties of solids is constantly expanding. Over the recent years, the emphasis in such investigations has shifted exactly to molecular crystals.^{60–79} Probably, this relates to broad capabilities offered by this approach in the elucidation of the intermolecular interactions in biological systems and in the characterisation and modification of molecular crystals applied as functional materials (*e.g.*, a pressure-induced transition of an organic ferromagnet into an antiferromagnet).

The experimental results on the behaviour of molecular and ion-molecular crystals under the isostatic pressure have been reported. In particular, it has been established that the isostatic compression of a crystal of deuterated oxalic acid gives rise to a shortening of two hydrogen bonds and an elongation of the third one.⁵⁹ The pressure-induced structural changes in crystals with hydrogen bonds have been explored in detail by Katrusiak.^{60–64} It was demonstrated that the compressibility of an H-bond under the isostatic compression depends on its type, local environment and the type of molecular packing in the crystal.

The compressibility of hydrogen bonds in molecular crystals has been also investigated by other authors.^{65–71} In particular, it has been shown that the two $\text{NH}\cdots\text{O}$ hydrogen bonds present in the crystal structure of $\text{Co}(\text{NH}_3)_5\text{NO}_2\text{Cl}_2$ are characterised by different compressibilities: the longer bond proves more compressible. As a result of the compression, the nitro ligand is rotated, which results in a change in the bond lengths between the cobalt atom and the ligands. The $\text{NH}\cdots\text{Cl}$ bonds present in the structure behave differently: the *cis*- NH_3Cl bonds continuously shorten with an increase in pressure, whereas one of the two H-bonds in the *trans*-position elongates.^{76, 77}

The deformation of the H-bonds in crystals of the monoclinic paracetamol modification subjected to the isostatic compression is accompanied by a change in the molecular conformation: the angle between the planes of the acetamide group and the benzene ring is diminished. In contrast, similar compression of molecular layers in the orthorhombic paracetamol modification is isotropic. The results obtained made it possible to rationalise the mechanism of the polymorph transition of the monoclinic paracetamol modification to the orthorhombic one.^{65–68, 78, 79} Glycine polymorphs also produce different responses to pressure. The α -modification shows no phase transitions up to pressures of 4 GPa and the pattern of changes in the unit cell parameters is generally similar to that observed upon a temperature decrease.^{65, 66, 69–72} Meanwhile, the β -modification undergoes a phase transition already at 0.76 GPa,⁷⁹ whereas the γ -form converts in the pressure

range of 2.7–2.8 GPa into a new previously unknown modification referred by the authors to as δ -glycine.^{74, 75}

The investigations into the influence of pressure on biochemical objects is getting increasingly important. In particular, valuable information on the carbonyl–carbonyl interactions giving new insights into the nature of the β -folds and α -helices in proteins has been gained⁸⁰ and the structural changes in nucleic acids have been elucidated.⁸¹ Studies on the permeability of cell membranes as a function of pressure occupy a special place. Pressure can affect both the structure of the membrane itself and the conformations of its constituent molecules.⁸²

Changes in the intermolecular distances and mutual orientations of molecules at elevated pressures can result not only in the intermolecular changes but also in the intramolecular changes. This was evident already to Bridgman, who observed polymerisation of benzene at a pressure increased to 23–30 GPa.⁵⁰ Also, it has been found⁶¹ that the OH...O bonds joining molecules into chains, layers and helices in the crystal structures of cyclohexane-1,3-dione and dimedone are differently shortened upon compression. A more detailed review concerning the changes in molecular crystals subjected to the isostatic compression can be found elsewhere.⁸²

Studies on the influence of the isostatic pressure on reactions with inorganic compounds are rather numerous. Below, we consider only selected examples of systems, in which an increase in pressure either changes the chemical properties of components or initiates chemical reactions.

Semenenko *et al.*^{83, 84} investigated the formation of ternary intermetallics in pseudobinary systems Hf₂Fe–Hf₂Cu, Hf₂Ni–Hf₂Mn and Hf₂Ni–Hf₂Cu and their interactions with hydrogen. A model for the location of inserted hydrogen atoms within the cavities of the intermetallic matrices was proposed^{83, 84} as well as a dependence of the valence state of hydrogen atoms on their concentration therein.

An interesting inversion of the electronic levels with different symmetries has been observed, which can occur not only under the direct action of the external pressure but also in the course of a pressure-induced chemical reaction, as in the case of the alkali metal intercalation into graphite⁸³ or the formation of intermetallics containing an alkali metal as a component.

Goryainov *et al.*^{85–88} measured the Raman and IR spectra of natrolite at a pressure of 4 GPa. The experimental results were compared with the theoretical calculations of the crystal structure. According to the results obtained, natrolite behaves differently upon compression in water, which can penetrate into its cavities (in particular, the phase transitions occur at 0.75 GPa and 1.25 GPa), and glycerol, which cannot penetrate into the cavities (the compression in glycerol does not result in any phase transitions).

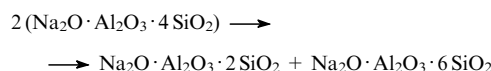
Therefore, the experimental data discussed above clearly indicate that studies of the behaviour of solids under pressure are necessary not only because they give important insights into the mechanisms of the mechanochemical processes but also because they represent a powerful method for the elucidation of structural and intermolecular interactions.

III. The influence of pressure and shear on the physicochemical properties of solids and chemical reactions with them

In addition to the studies of solids under the isostatic pressure discussed above, experiments providing conditions simultaneously for the compression and shear deformation yield valuable information. To the best of our knowledge, this type of studies were pioneered by Bridgman, who designed a dedicated apparatus, which provided control over the values of pressure and shear, deformation rate and sample temperature.^{89, 90}

Modified Bridgman anvil cells were utilised by R Roy *et al.*^{91–93} for the elucidation of various solid-state processes

ranging from polymorph transitions to decomposition reactions. They showed that the shear component strongly affects the process rates sometimes accelerating the reactions by a factor of a few hundred and thus increases the conversion levels, although it does not shift the equilibrium between the reactants and reaction products. For instance, the degree of decomposition of jadeite into nepheline and albite



does not exceed 10% under the action of the hydrostatic pressure at 350 °C, whereas it increases up to 60% under the simultaneous action of pressure and shear at the same temperature.

A similar apparatus was employed for the synthesis of alloys with anomalous concentrations of components and intermetallics.^{94, 95} A A Zharov *et al.*^{20, 96} demonstrated in a series of experiments that organic syntheses are possible under shear deformation and high pressure in a special reactor similar to the Bridgman anvil cells.

Studies of mechanochemical solid-state syntheses of organic compounds in anvil cells are worth a special discussion. However, the mechanisms of such processes as well as the mechanisms of solid-state reactions between organic compounds are significantly less explored as compared to inorganic synthesis.

More recently, studies of mechanochemically activated interactions between low-molecular-weight solid organic compounds appeared. As a result of these research efforts, new reactions of polymerisation of various classes of organic compounds and opening of benzene and pyridine rings were discovered and the dramatic acceleration of the polymerisation with respect to analogous reactions in the liquid phase was achieved.

Dadali *et al.*⁹⁷ demonstrated that the mechanically activated solid-state reactions between two reactants, one of which is an electron donor, while another is an electron acceptor, yield free radicals.

IV. Mechanical activation and mechanochemical reactions in mills

The mechanical activation in a mill is the most common operation in mechanochemistry. Probably, this is mainly due to two factors, *viz.*, the simplicity of the experiment and the interest of technologists, since mills are the most common devices realising the mechanical treatment of solids. Nevertheless, both mechanics and physics of the processes occurring in this type of devices remain a subject of numerous investigations.^{98–116} The vast majority of these studies are devoted to the optimisation of the grinding step for maximising the active surface area of the solid at the minimum energy consumption. The number of studies, in which mills are used exclusively for the mechanical activation, is significantly smaller.

Such studies are based on two main principles: the pulse time structure of the process (the regular alternation of two processes, *viz.*, the development of a stress field and its relaxation^{29, 98–100}) and the spatially local character of the mechanical treatment on solids (indeed, the stress field develops not in the whole volume of a solid particle but only in the areas of its contact with other particles or with the working medium).^{101–103} As a rule, this type of studies are aimed at the determination of the size of the area, where the stress field is developed under the mechanical treatment, as well as the lifetime and the actual form (*e.g.*, a pressure burst) of the field.^{104, 105} Additionally, possible relaxation channels of the stress field (*e.g.*, a temperature rise or formation of various metastable forms and new interfaces, *etc.*) and related secondary processes are explored.¹⁰⁶ Not pretending to the comprehensive survey of works in this filed, we shall just make mentions of several important contributions, *viz.*, by Maurice and Courtney,^{106–108} Gaffet *et al.*,¹⁰⁹ Tkačova *et al.*,¹¹⁰ Delogu *et al.*¹¹¹ performed abroad and by Urakaev *et al.*^{112–116} accomplished in Russia.

Studies in this field are far from being complete and probably they even should be intensified due to the potential applications of the mechanochemical processes in industry. As an example, we cite the results regarding temperatures developed in the contact areas estimated by different authors for the systems similar in terms of their chemical compositions and conditions of the mechanical treatment. The scatter in the reported values is as large as from 38 to 600–700 °C.¹⁰⁹

1. Mechanical activation of single-phase systems

If a compound subjected to the mechanical treatment is strictly single-phase, then the relaxation of the stress field can proceed by several independent pathways and be accompanied by various secondary processes, such as the heat liberation, emergence of new interfaces, accumulation of defects in crystals, formation of metastable polymorphs, amorphisation of solids and chemical transformations.

The exact share taken by each of the channels depends on the conditions of the mechanical load (*e.g.*, the energy input and the loading rate), physical properties of the solid, treatment temperature, *etc.* In some cases, the preferable relaxation channel can be altered at the course of the process. For instance, an increase in the propagation rate of a main crack during decomposition of oxy-acid salts switches the decomposition mechanism in its tip: the thermal decomposition is replaced with the mechanochemical one.^{117, 118} A gradual decrease in the size of particles subjected to the mechanical treatment results in a transition from grinding to plastic deformation.^{119, 120}

The factors affecting the formation of a stress field are depicted in Scheme 1, together with the main pathways of its relaxation.¹²¹ The left side of the Scheme relates to the grinding process, which is covered in detail in the literature, and thus it will not be considered here. The processes listed in the right half of the Scheme are typically classified as the mechanical activation.

Normally, grinding is used to create the maximum active surface of a powder at the minimum energy consumption, whereas the aim of the activation is to accumulate energy in the form of

defects or other structural modifications of a solid, which makes it possible to decrease the activation energy or improve steric conditions for its subsequent chemical transformations.

There are two distinct cases of the mechanical activation. In the first case, the duration of the mechanical treatment involving the formation of a stress field and its relaxation is longer than the chemical reaction time (these processes are commonly referred to as mechanochemical). In the second case, *vice versa*, the duration of the mechanical treatment involving the formation of a stress field is shorter than the chemical reaction time or these processes take place separately. The latter case is associated with the mechanical activation.

There are different forms of the energy storage upon the mechanical activation. Usually, they can be described as the formation of defects in crystals subjected to the activation.^{121, 122} Thermodynamics of the energy accumulation upon the mechanical load has been considered elsewhere.^{23, 24} Most frequently, the mechanical treatment gives rise to the plastic deformation and subsequently to the formation of linear defects, such as dislocations, ion and atom vacancies and interstitial ions. Recently, computer simulations of such processes have been surveyed by Gainutdinov *et al.*¹²³ In addition, this results in changes in the bond angles, emergence of broken bonds and further in the formation of free radicals (in covalent crystals) or amorphisation (in molecular crystals).

Since the defect formation in metal salts, oxides and carbides has been extensively discussed in numerous reviews and monographs (see Refs 122, 124–127), below we consider only those cases of the mechanical treatment, which are non-typical, in our opinion. These include, for instance, the activation of spinels, *i.e.*, ferrite-type complex oxides. Upon the mechanical treatment, the densely packed oxygen sublattice in spinels remains unchanged. The most important changes occur in the cation sublattice, which are manifested in the redistribution of bi- and trivalent cations over the tetrahedral and octahedral cavities.^{101–103, 128–131} This redistribution gives rise to a substantial change in the physical and chemical properties of spinels. An annealing of spinels at 500–600 °C results in the return of the cations to their typical positions so that the normal properties of spinels are restored. Similar results were obtained upon the activation of chalcogenides.¹³²

The mechanical activation enables relatively easy modification of both physical (*e.g.*, changes in the Neel temperature) and chemical (*e.g.*, changes in the leaching order of cations) properties of ferrosinels.^{133–137}

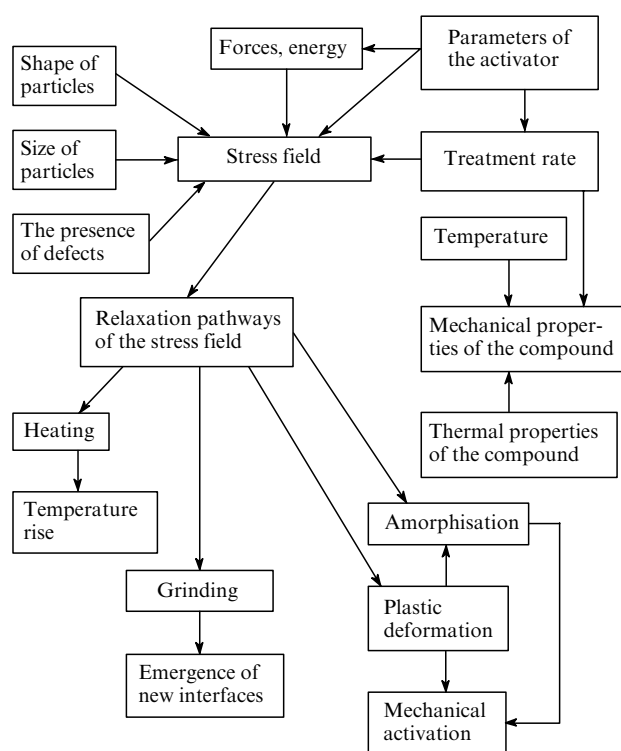
The discovery of the quasi-crystalline state, in which compounds manifest unusual physical and chemical properties, in 1984 (Ref. 138) gave a strong incentive to the search for the alternative methods for the production of quasi-crystals, in addition to the traditional method of quenching of alloys. Among other methods, the mechanochemical one was also evaluated. In 1989, Ivanov, Konstanchuk and Bokhonov^{139–141} obtained for the first time quasi-crystals by the mechanochemical treatment of intermetallics $Mg_{32}(Zn,Al)_{49}$, $Mg_{32}(Cu,Al)_{49}$ with the Frank–Casper structure.

They established that the formation of the icosahedral phase starts already in the early steps of the mechanical treatment. According to the high-resolution electron microscopy results, the nucleation and growth of the icosahedral phase are initiated by the production of rotational twinning defects, whereas the parent and the transformed phases are topotactically related to each other.¹⁴²

The same authors found^{143, 144} that the mechanochemically prepared icosahedral phase $Ti_{45}Zr_{38}Ni_{17}$ manifests a high hydrogenating activity. Similar studies were started abroad approximately at the same time.¹⁴⁵

In general, we note that the period of preliminary experimental information gathering in the field of mechanochemistry and mechanical activation of simple metal, oxide and salt systems comes to its conclusion. Likely, novel results may be anticipated in

Scheme 1



mechanochemistry of complex oxygen-containing (*e.g.*, spinels or silicic acid derivatives) and coordination compounds, where unusual (at least from the viewpoint of the compounds already elucidated) pathways of the energy accumulation due to the changes in the non-equilibrium concentrations of linear and point defects, emergence of shear structures or other pathways related, for example, to the isomerisation processes, changes in the bond angles or rotational defects can be realised.

Nevertheless, we believe that it would be more important for the moment to rationalise the whole array of the experimental information collected up to present. Very often, the results obtained are interpreted in the very standard way, something like: 'The mechanical activation gives rise to the accumulation of defects in reacting crystals thus increasing their reactivities', which is rather meaningless and worthless. Actually, no strict conclusions on the particular type of defects produced upon the activation can be derived based solely on the line broadening in powder diffraction patterns or the calorimetrically estimated enthalpies. Indeed, various defects differently affect chemical processes¹⁴⁶ and therefore a deeper analysis of the activation consequences is necessary, which is ignored by the majority of researchers.

As for the mechanical activation of molecular crystals, the number of studies devoted to the emergence and relaxation of stress fields in these systems is very limited. Although mechanochemistry of polymers is studied in sufficient detail, very little is known about the behaviour of molecular crystals under the conditions of the mechanical treatment.^{147–153} It is known^{149, 150} that structural disordering is frequently observed, which is manifested in the broadening of diffraction lines. In some cases, the H-bonds that join the molecules in the pristine crystal structure into dimers or more complex aggregates break down. Sometimes, zwitter-ionic groups are formed¹⁵⁰ or free radicals appear, if the mechanical treatment results in the scission of strong covalent bonds.^{97, 151–153}

2. Mechanical activation of multi-component mixtures

In addition to studies of the influence of the mechanical activation on single-component systems discussed above, similar studies of multi-component mixtures have been getting increasingly important over the recent years. Three major classes can be distinguished among such systems, *viz.*, solid–gas, solid–liquid and solid–solid mixtures.

a. Mechanical activation of solid–gas systems

As has been established already in the early studies (for instance, see Refs 126 and 154), the mechanical treatment affects both the sorption of gases upon their interaction with various solids and subsequent chemical reactions of adsorbed gases with solids.

The enhancement of adsorption of gases on solid surfaces upon the mechanical treatment is accompanied in some cases by the penetration of gas molecules into the mechanically deformed lattice. The sorption time *vs.* duration of the mechanical treatment function is characterised for many gases by the existence of an optimum value due to the competition of the mechanically activated adsorption and desorption processes as the active surface centres are getting gradually filled with gas molecules.

The adsorbed gas molecules can react with molecules of other compounds co-adsorbed on the same surface. As an example of such a reaction, the co-oxidation of hydrogen and carbon monoxide on quartz surfaces subjected to the mechanical activation can be mentioned. P Yu Butyagin was one of the first to start the elucidation of gas–solid reactions both under the conditions of mechanical preactivation and exactly during the activation.^{14, 18, 19} It was found^{155–157} that the mechanical treatment of metallic and oxide catalysts enhances their activity, which is traditionally associated with the accumulation of various defects in the catalysts, including point and extended defects (typically, dislocations) and changes in the ratio of areas of different crystal faces (*i.e.*, changes in the crystal habitus).

It is important to stress that not only the reaction rate but also the mechanism of the catalytic reaction changes due to the mechanical activation. This fact makes it possible to increase the selectivity of catalysts with the mechanical activation. Among recent works, studies by R A Buyanov *et al.*^{34, 35} devoted to the mechanocatalysis, *i.e.*, catalytic reactions under the simultaneous action of the mechanical treatment, deserve special attention. They accomplished a number of interesting and important catalytic transformations (*e.g.*, pyrolysis of butane over magnesium oxide or hydrogenation of butadiene over metal hydrides). Additionally, they elaborated a promising technique for the conduction of mechanochemical reactions under high pressures (10 MPa) of hydrogen, oxygen or ammonia.

The adsorbed gas molecules can not only react with the solid on its surface but also diffuse into the bulk of the solid in the course of the reaction. The influence of the mechanical activation on reactions in gas–solid systems was studied most thoroughly for oxidation, nitridation, hydrogenation and carboxylation of metals and various metal oxides. The influence of the mechanical activation on reactions of gases with polymers has been elucidated in substantially less detail, whereas the influence on molecular crystals remains virtually unexplored.

The influence of the mechanical activation on reactions of gases with metals yielding volatile products have been carefully investigated by the example of the formation of nickel carbonyl.^{126, 154} Owing to the mechanochemical treatment of nickel foil, the synthesis of nickel carbonyl can be realised under atmospheric pressure, although typically it is performed in an autoclave. During the activation process, the active centres are generated on the nickel surface, which are characterised by a weak (if any) dependence of the reaction rate on temperature. This suggestion explains the anomalies of the dependence of the reaction rate on temperature (*i.e.*, the negative temperature coefficient) and pressure.¹²⁶

The silicon chlorination is another example of the same type of processes. Both mechanical preactivation and the activation of silicon directly during the chlorination substantially accelerate the reaction and increase the yield of the product, methylchlorosilane.^{155, 156}

If the product of a mechanically activated reaction is solid, then the chemisorption of gaseous reactant on the active sites is followed by the generation and growth of the product nuclei and further by the formation of the product layer.

Since no thermal activation is involved, the occurrence of specific thermodynamically forbidden reactions under the conditions of mechanical activation was suggested, in particular, the oxidation of gold by carbon dioxide.¹⁵⁷

After the formation of a product layer, the process continues either in the kinetic or diffusion mode, depending on the ratio of molecular volumes of the solid reactant and product.

The mechanochemical hydrogenation of metals is one of the most common processes utilising the mechanical activation. The rapid attention of researchers to the hydrogenation of mechanically activated metals is likely caused by its potential in the technology of hydrogen storage. The first investigations in this direction were conducted in the Soviet Union in the mid-1980s.^{158–161} It was discovered that the mechanical activation of magnesium noticeably accelerates its hydrogenation. The conversion level can be dramatically increased by the addition of a catalytic amount of nickel, iron or chromium to the basic metal being activated.¹⁶⁰ Later, these studies were extended by foreign researchers^{162–172} to the influence of the mechanical activation on the rates and conversion levels of the hydrogenation of both traditional hydrogen absorbers (*e.g.*, FeTi, LaNi₅ or MgYNi₄) and the novel ones.^{158–161} As has been recently established,^{143, 144} the icosahedral structures produced mechanochemically or using the mechanochemical activation of some intermetallics act as highly efficient hydrogen absorbers.

More detailed information on the application of the mechanical activation for the metal hydrogenation can be found elsewhere.¹⁷³

In the case of the mechanochemically activated oxidation of metals with oxygen or halogens, the metal surface is constantly renewed due to the grinding with the product being fully or partly removed mechanically. The oxidation rate first increases until the minimum particle size is achieved and then starts to decrease.¹⁷⁴

The metal nitridation reaction proceeds through the intermediate formation of a solid solution of nitrogen in metal followed by the precipitation of the nitride phase above a specific critical nitrogen concentration in the solid solution. The further activation gives rise to the overstoichiometric accumulation of nitrogen.¹⁷⁵ The mechanically-assisted nitridation of titanium is only efficient if the nitridation is carried out directly during the activation, whereas the preactivation gives only insignificant gain in the reaction rate.¹⁷⁶

The nitridation of stainless steel in the atmosphere of ammonia is more efficient than in nitrogen. The activation however is accompanied by the conversion of γ -iron into α -modification.¹⁷⁷

The mechanical treatment of silicon in the atmosphere of ammonia at 100 °C yields α -Si₃N₄; the complete conversion requires 48 h. At room temperature, the complete conversion is reached only after ~168 h.¹⁷⁸

Kalinkin *et al.*¹⁷⁹ demonstrated that the mechanical activation of diopside CaMgSi₂O₆ is accompanied by the carbon dioxide adsorption on the surface of the sample.

b. Mechanochemistry of solid – liquid reactions

The investigations into the mechanical activation of solid – liquid reactions are dominantly stimulated by the progress in two industries broadly exploiting these processes. In hydrometallurgy, such processes offer a route to increase the efficiency and selectivity of leaching of valuable components from ores and minerals.^{26, 37} In pharmaceuticals, the mechanical activation is employed for the solubilisation of poorly soluble medicines.^{149, 152, 180}

As has been established already in the early works devoted to the mechanical activation, it is the accumulation of various defects in the reacting solid rather than mere increase in the specific surface area upon grinding that is responsible for the increase in reactivity. Extended defects, *i.e.*, dislocations, play a crucial role in the process of dissolution so that the dissolution rate correlates with the dislocation density.^{181, 182}

When a mixture of two components forming a galvanic pair rather than a single-component solid is dissolved, the mechanical activation of the components can change their electrode potentials and thus affect the dissolution rate.^{183 – 186}

It should be however taken into account that under specific values of viscosity of the slurry and the intensity of the mechanical load, the conditions suitable for hydrothermal processes can evolve in the system upon mechanically assisted dissolution.^{29, 187}

The dissolution of molecular crystals has certain distinctive features as regards the effects of the mechanical activation. Typically, the mechanical activation of such crystals induces either polymorph transitions or amorphisation. The exact mechanism of the process remains unclear: whether it proceeds through the intermediate step of the accumulation of extended defects or through the step of contact melting followed by the recrystallisation.

In some cases, the mechanical activation results in the decomposition of dimers initially present in the crystal structure. The amorphisation of molecular crystals or transition into metastable modifications increases the rates of dissolution and the solubilities (in the case of the micellar mechanism of the dissolution).

The influence of the mechanical activation on the processes of dissolution of solids has been elucidated not only for water but for other solvents as well. In particular, the mechanical activation increases the rate and the conversion level in the interaction of propyl iodide or bromide with aluminium,^{188, 189} initiates the

styrene polymerisation^{190, 191} and pyrazine oxoalkylation.¹⁹² However, very little information is available concerning the mechanisms of the activation for all these processes, despite their significance in chemistry.

c. Mechanochemistry of solid – solid reactions

Mechanochemically initiated solid-state processes have recently become a subject of intense investigations. Probably, this is due to the potential applications of such reactions in technology, in particular, for the development of the so-called dry processes, which are more environmentally friendly and cost efficient than the currently adopted technologies.¹⁹³

Any chemical interaction between solids proceeds neither in the entire volume of the reacting compounds nor on their entire surface but rather exclusively in the contact areas between the particles.¹⁹⁴ Thus the total number of such contacts between reacting particles plays the decisive role at the initial steps of a solid-state reaction. This means that it is always desirable to grind and mix components in such a way as to prevent the aggregation of particles of the same component (this dramatically decelerates the reaction). The mechanical alloying is often classified as a variant of the mechanochemical reactions. As a rule, the mechanical alloying is used for the preparation of solid solutions and metastable intermetallics provided that the traditional methods for their synthesis are either difficult or inconvenient for other reasons.^{195 – 208} Furthermore, a mechanochemical synthesis yields the respective product as a highly dispersed phase, which can be useful for the subsequent technological steps.¹⁹⁵

In order to illustrate such an approach, we mention the systems Mg – Ti or Al – Nb, in which the boiling point of the first component lies below the melting point of the second component.

By means of mechanochemistry, it proves sometimes possible to shift the boundaries of the formation of substitution solid solutions beyond the thermodynamical limits established for the equilibrium state. In particular, the ultimate solubility of aluminium in nickel, according to the respective equilibrium diagram, is 13.5 at.% at 1000 °C; it decreases by a factor of 3.5 at 500 °C and becomes fractions of a percent at room temperature. Notwithstanding, the mechanochemical method enabled preparation of solid solutions of aluminium in nickel with the aluminium content as high as 28 at.% (Ref. 198).

Solid solutions can be synthesised not only by the mechanical treatment of the respective mixtures but also by the mechanical activation of the intermetallic compounds that are characterised by low enthalpies of formation. In particular, solid solutions NiV and CoV manifesting anomalous magnetic properties have been prepared in this way.^{199, 200} Mechanochemical approach has been applied to prepare several solid solutions with positive enthalpies of mixing, such as solid solution of copper in iron.^{208, 209}

The similarity between the atomic sizes and general structures of the components are the main factors governing the possibility of the formation of solid solution under the mechanical alloying.^{197, 203 – 205} As has been established for the systems Ni – In, Cu – Sn and Cu – In, the formation of solid solutions proceeds as follows. First, after the complete intermixing of the alloy components, the respective intermetallics compounds, *viz.*, Ni₁₀In₂₇, Ni₂In₃, Cu₆Sn₅ and Cu₉In are produced. Then, their structures are distorted due to the second order microdeformations giving rise the deformational packing defects.^{204, 205}

Investigations into the mechanochemical transformations in the systems Fe – X (X = C, Si, Sn or Ge) can be illustrated by the results of E P Yelsukov *et al.*^{206 – 211} According to their model, the formation of binary compounds in these systems proceeds in several steps. First, nanostructures with a domain size of ~10 nm are generated due to the diffusion of X along the intergrain boundaries of iron. Then, the intermetallic compounds and the amorphous phase emerge. Further, the atoms X diffuse from the boundaries into the bulk of the iron grains thus giving rise to the intermixed solid solutions.

The sequence of transformations upon the mechanochemical iron carbonisation below 32 °C have been established by X-ray diffraction.²¹¹ If the carbon content $[C] < 20\%$, the product is amorphous; whereas for $[C] > 20\%$, crystalline iron carbides Fe_3C and Fe_7C_3 are formed. The initial steps of the process include grinding of the components, their intermixing and the generation of nanocomposites with a particle size of ~ 10 nm. In parallel, the atoms of the second component X diffuse into α -iron along the intergrain boundaries. In the case of metalloids with the atomic radius comparable to that of iron (*i.e.*, Si, Ge and Sn), the intermetallics (FeSi_2 , FeGe_2 and FeSn_2 , respectively) are directly nucleated in the areas of their local concentration, *i.e.*, along the intergrain boundaries. The further mechanical treatment affords solid solutions. In the case of metalloids with the atomic radius substantially smaller than that of Fe (*i.e.*, C), the emergence of the carbide phase is preceded by the formation of an amorphous phase.

A similar sequence of steps was observed in the solid-state synthesis of intermetallics Fe–Ti,²⁰⁹ Fe–Zr,²¹⁰ Ni–Ge²¹² and Ni–Bi.²¹³

P Yu Butyagin²¹⁴ proposed a classification of all mechanochemically activated solid-state reactions into two groups, depending on the rate-limiting step of the overall process: either the development of contacts (*e.g.*, as in the synthesis of lead niobate, where the reaction proceeds in the near-surface regions) or the mass-transfer into the bulk (as in the synthesis of nickel aluminide).

Very high diffusion coefficients of atoms or ions constituting a solid phase is a distinctive feature of mechanochemical solid-state syntheses. To be distinguished from the ordinary diffusion determined by the concentration gradients, this type of diffusion is denoted with a special term, ‘deformational atomic intermixing’, or ‘ballistic diffusion’. Several hypotheses regarding the mechanism of this process have been suggested. Butyagin proposed¹²² that the interstitial sites of the lattice are responsible for the diffusion, whereas Schwarz argued²¹⁵ that the diffusion proceeds through the dislocations, the number of which increases continuously upon the mechanical treatment. Therefore, the exact mechanism of the deformational atomic intermixing remains a subject of debate.

Sometimes, particular contact conditions are realised so that the direction of the mechanochemical process contradicts the thermodynamical calculations. For instance, the rate of the solid-state interaction of tungsten trioxide with alkali-earth metal carbonates is the maximum in the case of barium carbonate, although this should be opposite, assuming that the rate should correlate with the change in the free energy during the process.²¹⁶ A similar situation is observed for the interaction of potassium persulfate with methyl- and phenyl-substituted imidazoles.²¹⁷ According to both computer simulations^{218,219} and experiments,²²⁰ the mechanical treatment substantially accelerates the diffusion processes in solid phases. In particular, the coefficient of chromium diffusion into iron is $10^{-12} \text{ cm}^2 \text{ s}^{-1}$ and $2 \times 10^{-8} \text{ cm}^2 \text{ s}^{-1}$ at room temperature and at 1400–1600 K, respectively. Meanwhile, it can be increased up to 10^{-5} – $10^{-7} \text{ cm}^2 \text{ s}^{-1}$ with the mechanical activation.

Karagedov *et al.*²²¹ suggested that the accumulation of defects cannot be the only factor driving the marked acceleration of mechanically activated solid-state synthesis of complex oxides from simple oxides since the defects can be cured even before the initiation of the reaction. The most significant result is the adjustment of the size distribution of particles in the reaction mixture in such a way as to provide the densest packing and preventing aggregation.

The mechanochemical synthesis in multi-component systems represents yet another direction in the field of solid-state inorganic synthesis.²⁰⁰

The possibility of participation of fluidic (gaseous or liquid) phases in the processes at their intermediate steps has become increasingly important over the recent years. Indeed, a process,

which is formally considered as a solid-state reaction, can actually represent a certain combination of solid + gas or solid + liquid reactions. In this regard, the control over such processes requires alternative tools as compared to the case of truly solid-state reactions.²²²

The presence of water in solid-state systems either before or after a reaction is of particular interest. E G Avvakumov, E G Devyatkina and N V Kosova^{223,224} elaborated an original method referred to as the mild mechanochemical synthesis. Essentially, two hydroxides, one of which is acidic, while the other is basic, can be used as precursors in the synthesis of a complex oxide instead of simple oxides. The rate of the mechanically activated neutralisation reaction appears higher than the rate of the interaction of non-hydrated oxides.

Studies in the same directions were then continued by M Senna and co-workers²²⁵ The results of these joint research efforts were summarised in a monograph.²²⁶ The authors demonstrated that the mechanical activation converts the bridging metal–oxygen–metal bonds in the acidic component into the bridging bonds between the basic and acidic components, *i.e.*, in the case of the reaction of $\text{Ca}(\text{OH})_2$ with $\text{TiO}_2 \cdot 0.82 \text{ H}_2\text{O}$, the Ti–O–Ti bonds are converted into the Ca–O–Ti bonds.

Water released in the neutralisation process can act as an additional factor for the reaction acceleration. Conditions suitable for hydrothermal processes can evolve in the system. The first assumptions that hydrothermal reactions can be initiated under the mechanical activation of oxides containing water have been made already in the very early works devoted to the mechanochemical synthesis (see, for instance, Ref. 227). However, the comprehensive argumentation in favour of this hypothesis has been given later.^{29,228,229} There is serious experimental evidence of the attainability of hydrothermal synthesis in mechanochemical activators.^{230,231}

The heat delivered in a system as a result of a chemical reaction and the relaxation of a stress field upon the mechanical treatment can actuate the transition from the mechanochemical synthesis regime to the self-propagating high-temperature synthesis.^{232–234} Apart from the cognitive interest, this phenomenon holds some promise for applications. First of all, the self-propagating high-temperature synthesis can be realised in those systems, where the adiabatic temperature is not sufficient for sustaining the combustion. Second, this switch of the modes can eliminate the possible negative combustion impacts on the product, such as sintering and oxidation.^{235,236}

P G McCormick and co-workers²³⁷ discovered that if a system composed of two reactants that react to yield two solid products is diluted with one of the products, then the second target product can be produced in the form of nanoparticles. In particular, cadmium sulfide with the particle size of the order of a few nanometers can be produced by the solid-state reaction of cadmium chloride with sodium sulfide, if the reaction mixture is diluted with sodium chloride. The optical properties of such nanoparticles, the so-called quantum dots, differ substantially from those of crystalline cadmium sulfide.²³⁸ Similar syntheses have been realised for nanoparticles of metals,²³⁹ simple and complex oxides,^{240–245} nitrides²⁴⁶ and salts.^{247,248}

Balaž *et al.*²⁴⁹ reported on a mechanochemical method for the preparation of nanoparticles of cadmium, lead and zinc sulfides by the reaction of the respective metal acetates with sodium sulfide.

Gras *et al.*²⁵⁰ demonstrated that the mechanochemical synthesis of molybdenum silicide from elements yields particles with a size of ~ 90 nm, whereas only larger particles can be produced by the self-propagating high-temperature synthesis due to the sintering of particles in the combustion wave. Boron nitride nanotubes were successfully prepared by Chen *et al.*²⁵¹ by the mechanochemical reaction of boron with ammonia.

Investigations into the mechanochemical solid-state reactions of molecular crystals is a rather new but promising direction. The potential importance of this field relates not solely to the tradi-

tional fields of applications of molecular crystals, such as pharmaceuticals, but also to the newly discovered possibilities of their utilisation as functional materials for molecular electronics, molecular magnets and so on.

Within this field, mechanochemically assisted reactions of organic synthesis play the key role. Studies in this direction were started back in the 1950s.²⁵² Later, the possible implementation of a number of organic syntheses in reactors similar to the Bridgman anvil cells and extruders^{253, 254} was demonstrated by A A Zharov *et al.*^{20, 96} and by N S Enikolopov.¹⁶ More recently, various mills were tested as activators, especially ones providing the high energy input, such as vibrational planetary mills and attritors. It was established that many types of organic reactions (*e.g.*, halogenation, esterification, acetylation, *etc.*^{255–258}) can be realised with these devices. Furthermore, in some cases, the mechanochemical method has proven to be not only simpler and faster than the traditional syntheses but more selective as well.

The number of publications devoted to the use of mechanochemical approach in the synthesis of various organic compounds constantly increases. As selected examples, one can mention the solid-state synthesis of tris(4-imino-2-pentanonato)chromium by the mechanically activated reaction of chromium(III) chloride with (4-imino-2-pentanonato)sodium,²⁵⁹ the synthesis of oxazolidines by the mild mechanical treatment of mixtures of β -aminoalcohols with aldehydes and the synthesis of Schiff bases from mixtures of crystalline aldehydes and amines.^{260, 261} One of the traditional methods for the oxidation of organic compounds is the reaction with lead tetraacetate or manganese triacetate in a liquid phase. Nikishin *et al.*²⁶² implemented this process in the mechanochemical mode by the activation of the reaction mixtures in a vibrational mill.

The phosphorus atoms can be incorporated into the aluminosilicate framework of zeolites by the mechanically activated solid-state interaction of the respective sodium zeolites with aluminium phosphate. This gives rise to the variation in the lattice parameters, which makes it possible to design molecular sieves with improved thermal stability.^{263, 264} In a similar way, various organic molecules can be intercalated into the interlayer space of kaoline by the reaction between them in the presence of alkali metal halides.^{265–268} The mechanochemical method is also useful for other reactions. In particular, Hihara *et al.*²⁶⁹ utilised the mechanical activation for the synthesis of nickel and copper complexes with dimethylglyoxime. The use of solid-state mechanochemical synthesis for the preparation of various boron compounds, including diborane, borane adducts with nitrogen-containing organics, borazine and transition metal tetrahydroborates, have recently been reviewed by Volkov and Myakishev.²⁷⁰

As has already been mentioned, the mechanisms of the solid-state reactions of molecular crystals are less elucidated as compared to the reactions of ionic crystals. In some cases, even the actual solid-state character of the process cannot be proven, since the contact melting or sublimation of components in intermediate steps of the reaction cannot be decisively ruled out. In the case of macromolecular compounds (*e.g.*, cellulose), the interaction can be truly solid-state, whereas the involvement of fluidic phases is highly probable in the intermediate steps of reactions with crystals of low-molecular-weight organics.

Summarising all the experimental evidence discussed above, we note that the extensive experimental data have been gathered thanks to numerous investigations accomplished both in Russia and abroad. Nevertheless, the mechanisms of many processes realised in the mechanochemical reactors remain poorly understood. Partly, this is explained by the complexity of the processes under study. However the main problem, in our opinion, is that the elucidation of the mechanisms is rarely formulated as an aim of the investigation and researchers often limit themselves to the preparation of a material with desired properties or the realisation of a process with the target parameters. However, the deep

understanding of the mechanisms is a prerequisite for the fine control over the processes.

V. The use of mechanochemistry and mechanical activation for the solution of applied problems

Initially, such large-scale industries as hydrometallurgy,^{1, 26, 37, 271} production of construction materials and fertilisers^{39, 40, 272–274} were envisaged as potential fields of application of mechanochemistry. Nevertheless, despite very promising results obtained in laboratories, industrial implementations of the mechanochemical processes remain challenging owing to the lack of high-energy-input devices with sufficient performance. The available equipment (typically, mills) does not provide the energy input that is high enough for the large-scale mechanical activation.

Several attempts have been undertaken to perform industrial validation of the mechanochemical methods in these fields. In particular, mechanochemical processes were implemented in a plant for the hydrometallurgical processing of chalcopyrite into copper and sulfur in Wittenberg, in a facility for the acid-free production of fertilisers from natural phosphates in the Hubsugul deposit in Mongolia and in the production of silicalite in Estonia. Unfortunately, no anticipated benefits from the implementation of these processes were achieved.

On the other hand, mechanochemistry has proven its efficiency in smaller-scale factories aimed at the production of more expensive goods. In non-ferrous metallurgy, the mechanical activation is successfully applied to the opening of tungsten and gold ores.

Nowadays, the mechanochemical methods are in the wide use in the production of catalysts,^{34, 42} functional ceramics,^{275, 276} diverse special-purpose materials,^{277–283} materials for hydrogen storage,¹⁷³ ligatures for metallurgy, *etc.* In pharmaceuticals, the mechanochemical methods are commonly employed for the production of medicines and control of their stability with respect to grinding, mixing, pelletisation and preparation of dosage forms from substances.^{149–152, 284–286}

The mechanical activation is actively employed in the production of pigments and cosmetics.²⁸⁷ The use of this method opens new avenues in preparative chemistry, including both organic and inorganic synthesis.^{259–264}

The mechanical activation is used in processing of organic wastes, including poly(vinyl chloride), bromo- and chloro-containing aromatics.^{288–292} The mechanical treatment of hexachlorobenzene, 1,4-dichlorobenzene, octachloronaphthalene or *o*-nitrochlorobenzene in the presence of alkaline agents, such as calcium oxide or hydride, yields²⁸⁸ recyclable phenols and naphthols. The dechlorination can afford different products, depending on the intensity of the treatment. In particular, *o*-nitrochlorobenzene and 3-chloro-2-nitrophenol are obtained as the main products under mild and drastic conditions, respectively.

The mechanical treatment of clay minerals can be utilised for the extraction of phenol from aqueous solutions^{266, 267} and water purification from radionuclides.^{293, 294} It is of note that these efforts aimed at the application of the modern achievements of mechanochemistry to the intensification of small-scale expensive industrial processes are based on the specific results of dedicated fundamental investigations to the largest extent than ever before.^{295–299}

We believe that industrial implementations of mechanochemical processes should be expected in these directions. However, it would be a mistake to think that the process will be smooth and seamless, and this is due to several reasons.

The apparent simplicity of the method acts simultaneously as an advantage and a disadvantage of the method. Historically, experimentalists armed with ordinary mortars were commonly considered to be prepared for the conduction of mechanochemical investigations. Moreover, a team equipped with a mill instead of mortars was often recognised as one specialised in mechanochemistry.

As a result, the number of successful implementations of mechanochemistry in technology is relatively small despite the huge total number of related studies (as we have mentioned before, the number of publications and patents in this field has increased dramatically over the last decade). It is of no surprise taking into account the fact that the trial-and-error method remains the key methodological tool in the vast majority of the experimental works. In essence, all such studies fall into one simple scheme: a researcher takes a compound or a mixture of compounds, treats it mechanically and looks at the result. It is rather surprising that even this methodology sometimes yielded positive results at all.

Up to the present, mills are most commonly used for the mechanical activation, although these devices are not designed for this purpose, strictly speaking. The purpose of a mill is to treat the material in order to generate the maximum surface area at the minimum energy consumption for the grinding process. In contrast, the purpose of an ideal device for the mechanical activation is to insert the maximum amount of energy into the treated solid to enable the accumulation of the input energy as defects mostly affecting chemical reactivity. This requires high energy inputs to be transferred from the working medium to the treated solid during the mechanical activation, which cannot be achieved with ordinary disintegrators. The ordinary mills have to be redesigned (and sometimes quite significantly) to take this requirement into effect. This, however, can lead to another problem related to the possible contamination of the compound subjected to the mechanical activation with the materials composing the working medium and the reactor body. This problem becomes more and more prominent as the energy input increases.

In order to relieve this problem, hard materials, such as tungsten carbide or silicon nitride coated with teflon or other inert substances can be utilised. The most efficient way is to operate in the self-lining mode, *i.e.*, to use the treated compound itself as a material forming the protective coating of the working medium and the reactor body.

The mechanical activation of mixtures creates even more serious problems. As has already been mentioned above, in order to activate a solid-state process it is necessary, first, to grind the components of the mixture, second, to mix them in such a way as to generate the maximum number of contacts between the particles of reacting components and, third, to create conditions for the mutual diffusion of the atoms or ions involved into the reaction, formation of the intermediate solid solution and withdrawal of the reaction product. Naturally, the currently adopted simultaneous realisation of these three totally different physical operations in the same apparatus does not make much sense. It would be more advisable to separate these operations, which should be taken into account in the design of the activator (the use of three specialised machines could be an alternative). Another possibility is to combine the mechanical activation of a solid-state synthesis with other methods, *e.g.*, with the preliminary mixing of the components by co-precipitation or by the sol-gel technology.

We considered above only several main problems impeding the wide industrial utilisation of the recent advancements in the field of mechanochemistry. Although they are to be solved in different ways, all the ways include one common factor: fundamental investigations in the field of mechanochemistry should be stimulated and developed at the utmost in order to make progress towards applications. As for the character of the most topical investigations, the information gathering step should be already replaced with the systematisation of the available information and construction of models for the mechanical activation and mechanochemical reactions. So far, this has been accomplished only in a few particular cases. The accumulation of experimental facts is still underway but it should not last forever.

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Chemistry of ureido carboxylic and ureylene dicarboxylic acids

A N Kravchenko, I E Chikunov

Contents

I. Introduction	191
II. Synthesis of ureido carboxylic and ureylene dicarboxylic acids	191
III. Chemical transformations of ureido carboxylic acids	197

Abstract. The review presents a comparative analysis of procedures for the synthesis of ureido carboxylic and ureylene dicarboxylic acids. Chemical transformations of these compounds are summarised. New fields of application of ureido carboxylic acids in the synthesis of chiral, diastereomeric and enantiomerically pure *N*-carboxyalkylglycolurils are considered. The bibliography includes 129 references.

I. Introduction

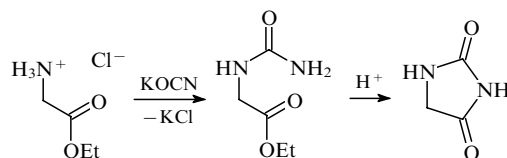
Procedures for the preparation of ureido carboxylic and ureylene dicarboxylic acids (hereinafter, ureido acids and ureido diacids, respectively) and their chemical transformations are being widely discussed in the literature. These compounds deserve attention because of diverse physiological activities.^{1–7} For example, the simplest representative of ureido acids, *viz.*, *N*-carbamoylglycine, exerts sedative, antihypoxic and anticonvulsant effects in mice.² *N*-Carbamoyl- β -alanine binds to the PEPT2 protein in *Pichia pastoris* yeast cells, serves as a peptide transporter in *Xenopus laevis* oocytes and has antidiabetic properties.³ *N*-Carbamoyl- γ -aminobutyric acid shows properties of a weak GABA antagonist (GABA is γ -aminobutyric acid).⁴ *N*⁶-Methyl-*N*⁶-nitroso-(*S*)-citrulline was shown⁵ to be an antitumor agent. *N,N'*-Carbonylbis(methionine) is used for the design of insulin analogues.^{6,7} Besides, ureido (di)acids are promising building blocks in the synthesis of various biologically active heterocyclic compounds.

The aim of the present review is to systematise procedures for the synthesis of ureido (di)acids and their chemical transformations. Reactions of achiral, racemic and optically pure ureido acids with α -dicarbonyl compounds and 4,5-dihydroxyimidazolidin-2-ones in the synthesis of potential biologically active glycoluril derivatives containing *N*-carboxyalkyl groups are considered.

II. Synthesis of ureido carboxylic and ureylene dicarboxylic acids

First syntheses of ureido acids were performed by Harries⁸ in the early twentieth century and were based on the reaction of glycine ethyl ester hydrochloride with potassium cyanate (by analogy with the first synthesis of urea from ammonium isocyanate⁹). The

reaction product, *viz.*, ethyl ester of ureidoacetic acid (*N*-carbamoylglycine), was not isolated in pure form but was subjected to cyclisation giving rise to hydantoin.



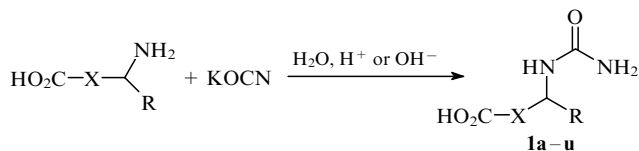
Various procedures have been developed for the synthesis of ureido acids. Let us mention the following three main methods:

- (1) reactions of amino acids with KOCN (the cyanate method);
- (2) reactions of amino acids with urea;
- (3) cleavage of 5-substituted imidazolidine-2,4-diones (hydantoins) and related compounds.

Selected representatives of this class were synthesised according to alternative procedures. Methods for the synthesis of ureylene dicarboxylic acids are reviewed in a special section.

1. Cyanate method for the synthesis of ureido carboxylic acids

Numerous ureido acids were synthesised by the cyanate method. *N*-Carbamoylation reactions were carried out with achiral, racemic and optically active *S*- and *R*-amino acids (Table 1). The reactions of KOCN with amino acids were carried out in aqueous solutions in the absence of catalysts or in the presence of an alkali or an acid at temperatures from 20 to 100 °C; the reaction time varied from 20 min to 48 h. The yields of ureido acids **1a–u** are 40%–67% (see Table 1).



R = H, X = (CH₂)_n; n = 0 (**a**), 1 (**b**), 2 (**c**), 3 (**d**); R = H, X = CH₂NHC(O) (**e**); X is absent: R = Me (**f**), Et (**g**), Prⁿ (**h**), Prⁱ (**i**), Buⁱ (**j**), Bu^s (**k**), CH₂SH (**l**), (CH₂)₂SMe (**m**), CH₂CO₂H (**n**), CH₂C(O)NH₂ (**o**), (CH₂)₂CO₂H (**p**), (CH₂)₂C(O)NH₂ (**q**), CH(OH)Me (**r**), Bn (**s**), CH₂C₆H₄OH-4 (**t**), (CH₂)₃NHC(O)NH₂ (**u**).

The reactions of amino acid esters with alkyl isocyanates also afford ureido acid derivatives. In both cases, the reactions proceed by the mechanism³³ analogous to the mechanism of the synthesis of urea from ammonium cyanate.^{9,28}

A N Kravchenko, I E Chikunov N D Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky prosp. 47, 119991 Moscow, Russian Federation. Fax (7-495) 135 53 28, tel. (7-495) 135 88 17, e-mail: kani@ioc.ac.ru

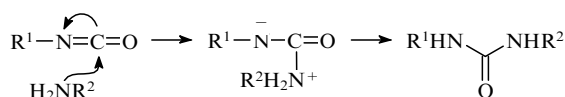
Received 30 March 2005

Uspekhi Khimii 75 (3) 217–233 (2006); translated by T N Safonova

Table 1. Synthesis of ureido acids by the cyanate method.

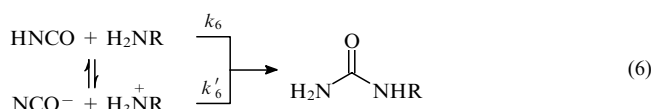
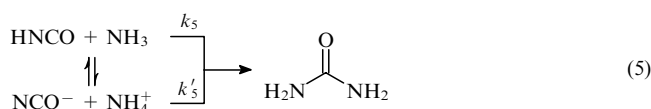
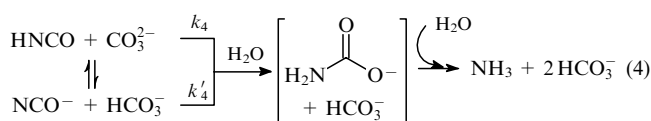
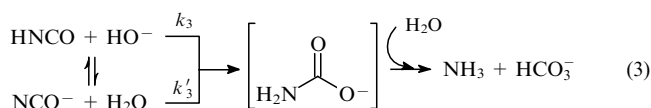
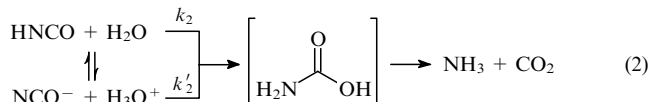
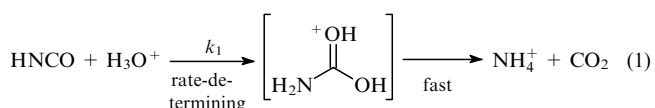
Starting amino acid	Reaction conditions	Ureido acid 1	Ref.
Gly	H ₂ O, 100 °C; HCl	a	10, 11
	H ₂ O, KOH	a	12
	H ₂ O, Δ, 20 min; HCl, pH 3	a	13, 14
β-Ala	H ₂ O, Δ, 20 min; HCl, pH 3	b	13–15
GABA	H ₂ O, 20 °C, 22 h; 6 M AcOH	c	16
	H ₂ O, Δ, 20 min; HCl, pH 2, –20 °C, 7 h	c	14, 17, 18
	H ₂ O, Δ, 4 h; HCl, pH 2	c	19
δ-APA	H ₂ O, Δ, 20 min; HCl, 7 h	d	10, 14, 20
Gly-Gly	H ₂ O, Δ, 30 min; HCl, 20 °C, 7 h	e	10, 14
N-MeAla	H ₂ O, 40 °C	f	21
Ala	H ₂ O, Δ	f	11, 22
	HCl, H ₂ O, Δ, 20 min, pH 3	f	13
	H ₂ O, 50 °C, 15 h, pH 7.5	f	15
Ala·HCl	H ₂ O, 60 °C, 4 h	f	23
α-ABA	H ₂ O, 20 °C, 60 h	g	19
nor-Val	H ₂ O, 20 °C, 48 h, pH 2	h	19, 24
Val	H ₂ O, 50 °C, 15 h, pH 7.5	i	15
	H ₂ O, 60 °C, 4 h	i	11
	H ₂ O, 20 °C, 48 h, pH 2	i	19
Leu	H ₂ O, 20 °C, 72 h, pH 2	j	19
Leu·HCl	H ₂ O, 60 °C, 4 h or 50 °C, 18 h; pH 7.5	j	15
	H ₂ O	k	25
Ile	H ₂ O	k	25
Cys	KOH, H ₂ O ^a	l	26
Met	H ₂ O, Δ, 30 min	m	15
Asp	1 M KOH, H ₂ O ^b	n	27, 28
	H ₂ O, Δ	n	27, 28
Asn	H ₂ O, Δ ^c	o	29, 30
Glu	KOH, H ₂ O	p	12
Gln	H ₂ O, 20 °C, 40 h; HCl, pH 2, 5–7 h	q	31
Thr	H ₂ O, 50 °C, pH 8	r	15
Phe	H ₂ O, Δ, 4 h; pH 2	s	23
Phe·HCl	H ₂ O, 60 °C, 4 h	s	23
	H ₂ O, 50 °C, 15 h, pH 7	s	15
Tyr	H ₂ O, Δ	t	30
Cit	H ₂ O, Δ ^d	u	32

Note Hereinafter, δ-APA is δ-aminopentanoic acid and α-ABA is α-aminobutyric acid, Cit is citrulline; ^a the reaction was carried out also with the use of NaOCN and NaOH; ^b fulminic acid was used instead of KOCN; ^c partial racemisation of amino acid occurs; ^d the reaction was performed with the use of HNCO.



The mechanism and kinetics of the reaction of amino acids with cyanate anions have been considered in detail.¹⁵ In this study, a kinetic model of *N*-carbamoylation in the pH range of 2–13 at ~40–50 °C was suggested. In aqueous solutions, KOCN forms isocyanic acid, which undergoes to hydrolysis or nucleophilic addition of amines, *i.e.*, several competitive processes occur. It is assumed that the reactions of cyanate ions with water (reactions 1–3), ammonia (reaction 5) and alkylamines (reaction 6) involve the electrophilic (proton) or nucleophilic (OH[–]) attack on isocyanic acid to form carbamates or urea derivatives (in the case of *N*-nucleophiles). In addition, the CO₃^{2–} anion efficiently catalyses hydrolysis of HNCO (reaction 4). Each slow step (the rate constants of these steps are denoted by *k*₁–*k*₄) is followed by fast cleavage of carbamates (or carbaminic acid) to give NH₃ and CO₂. It should be noted that ureas are much more stable than

carbamates. Calculations and experimental data showed¹⁵ that all reactions are first order with respect to each reagent.



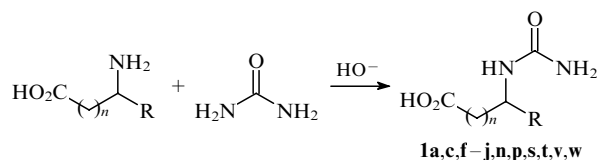
The following optimum conditions of the selective formation of ureido acids were found by studying the reactions of glycine, L-alanine, β-alanine, L-phenylalanine, L-valine, L-leucine, DL-methionine, *N*^ε-trifluoroacetyl-L-lysine and L-threonine: pH 7–8, 50 °C, a 1.5–2-fold excess of cyanate and the reaction time of 10–24 h. Under these conditions, the NH₃ and CO₂ concentrations are low, the formation of carbamates and urea is insignificant, and hydrolysis of ureido acids occurs so slowly that this process can be ignored. Consequently, ureido acids are formed as the major products. The results of kinetic studies were used to synthesise the corresponding ureido acids in preparative yields (40%–80%).

One of the authors of the present review has made an important contribution to the development of the cyanate method (see Refs 13 and 14). The conditions of the reaction of amino acids with KOCN were optimised taking into account the data¹⁵ on the kinetics of *N*-carbamoylation. A distinguishing feature of the procedure is that KOCN is added portionwise to an amino acid solution in water or aqueous isopropyl alcohol at 80–90 °C. Then the reaction mixture is heated to boiling followed by storage of the reaction mixture for 20–30 min, which afforded ureido acids **1a–u** in 60%–94% yields. In the procedures used earlier, KOCN was added in one portion, and, after 48 h, the reaction products were obtained in yields of only 43%–61%.²⁴ In addition, *N*-carbamoylation performed under the conditions used earlier²⁴ was accompanied by competitive hydrolysis of cyanate ions.

In many investigations,^{11–15, 17–27, 29, 31, 32} it was reported that the chiral carbon atom was not affected in transformations of optically active amino acids into ureido acids. However, partial racemisation of (*R*)- and (*S*)-aspartic acids was observed³⁰ in the reaction with potassium cyanate in the presence of an alkali. This fact remained unexplained.

2. Reactions of amino acids with urea

Some ureido acids were synthesised by the reactions of amino acids with urea (Table 2).



$n = 0$: $R = (CH_2)_4NH_2$ (**v**), CH_2Ind (Ind is indol-3-yl) (**w**).

Table 2. Synthesis of ureido acids by the reaction of amino acids with urea.

Ureido acid 1	Reaction conditions	Ref.
a	H ₂ O, NaOH, 110 °C, 2 h; 140 °C	34
	H ₂ O, Ba(OH) ₂	21, 35
c	110–112 °C, 1 h	36
	HCl, H ₂ O, Δ, 15 h	19
f	H ₂ O, Ba(OH) ₂	35
g	HCl, H ₂ O, Δ, 15 h	19
i	H ₂ O, Ba(OH) ₂	35
	H ₂ O, Na ₂ CO ₃	12
j	HCl, H ₂ O, Δ, 15 h	19, 35
n	H ₂ O, Ba(OH) ₂	37
p	H ₂ O, Ba(OH) ₂	35
s	HCl, H ₂ O, Δ, 15 h	19
	H ₂ O, Ba(OH) ₂	35
t	H ₂ O, Ba(OH) ₂	35
v ^a	H ₂ O, Na ₂ CO ₃	12
w ^b	H ₂ O, Ba(OH) ₂	38

^a Lys was used as the starting amino acid; ^b Trp was used as the starting amino acid.

The reactions can be carried out according to two procedures: either by prolonged (up to 15 h) refluxing of an acidified aqueous solution of the reagents or by heating in the presence of an alkali at 110–140 °C (see Table 2). In both cases, it is necessary to purify ureido acids by repeated recrystallisations. The yields of the

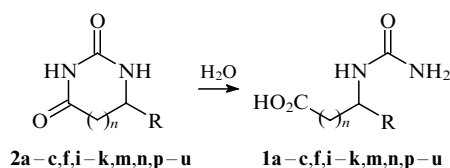
reaction products prepared according to both procedures are comparable with those attained by the cyanate method. However, the advantage of the latter is that the product precipitates from the reaction mixture, so that one recrystallisation from an appropriate solvent is sufficient to obtain pure products in individual form.

The synthesis of ureido acids **1a,j** by the reactions of Gly and Leu, respectively, with nitrourea was also documented.³⁹

On the whole, the procedure for the synthesis of ureido acids involving urea is less popular than the cyanate method.

3. Cleavage of hydantoins and related compounds

Virtually all ureido acids can be synthesised by the cleavage of the corresponding 5-substituted hydantoins or related compounds. Both chemical and biochemical processes are suitable for this purpose (Table 3).



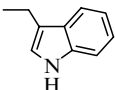
Alkaline hydrolysis is the simplest method for the cleavage of heterocycles **2**. Under these conditions, ureido acids **1a–c** were prepared from the corresponding achiral compounds, viz., hydantoin (**2a**),⁴⁰ dihydrouracil (**2b**)⁴² and [1,3]diazepane-2,4-dione (**2c**),⁴⁴ and compounds **1f,m,n,s–u** were synthesised from chiral substrates, viz., 5-methylhydantoin (**2f**),⁴⁵ 5-[2-(methylthio)ethyl]-hydantoin (**2m**),⁵¹ 2,6-dioxohexahydropyrimidine-4-carboxylic acid (**2n**),²⁵ 5-benzylhydantoin (**2s**), 5-(4-hydroxybenzyl)hydantoin (**2t**)³⁰ and [3-(2,5-dioximidazolidin-4-yl)propyl]urea (**2u**).³² Generally, hydrolysis is performed with aqueous NaOH or Ba(OH)₂ on heating. This approach is suitable only for the synthesis of ureido acids in which the chiral carbon atom retains the configuration of the chiral centre of the starting hydantoin.

Biochemical cleavage of cyclic compounds **2** under the action of microorganisms or enzymes is the most common and preparative method.

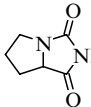
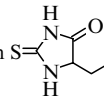
Table 3. Synthesis of ureido acids by decomposition of hydantoins **2**.

Com- pounds 1 and 2	n	R	Chemical method		Biochemical method	
			reaction conditions	ref.	reaction conditions	ref.
a	0	H	H ₂ O, Ba(OH) ₂ , Δ	40	<i>Pseudomonas</i> sp. AJ-11220, Tris–HCl buffer (pH 8.5), 30 °C, 2 h	41
b	1	H	H ₂ O, NaOH, Δ	42	the same	41
					hydantoinase (dihydropyrimidinase EC 3.5.2.2) <i>P. putida</i> DSM 84	43
c	2	H	H ₂ O, NaOH	44	—	—
f	0	Me	0.6 N KOH, 70 °C, 8 h	45	hydantoin-hydrolysing enzyme, ATP, KCl, MgSO ₄ , 0.1 M Tris–HCl, 30 °C, 20 h	46
					anaerobic bacterium <i>P. anaerobius</i> , 50 °C	47
					immobilised cells of <i>Agromyces</i> , <i>Chromobacterium</i> or <i>Cellulomonas</i> , glucose, yeast extract, 30 °C, 20 h	18
					DL-hydantoinase from <i>Bacillus stearothermophilus</i> NS _{1122A} , phosphate buffer (pH 7.0), 60 °C, 30 min	48
					<i>Pseudomonas</i> sp. AJ-11220, Tris–HCl buffer (pH 8.5), 30 °C, 2 h	41
					D-hydantoinase 1, H ₂ O, 50 °C, 22.8 h, pH 8.5	49
i	0	Pr ⁱ	—	—	<i>Pseudomonas</i> sp. AJ-11220, Tris–HCl buffer (pH 8.5), 30 °C, 2 h	41
					D-hydantoinase 2, H ₂ O, 50 °C, 43.7 h, pH 8.5	49
					<i>Hansenula</i> sp. Tris buffer, 32 °C, 24 h	48, 50
					hydantoin-hydrolysing enzyme, ATP, KCl, MgSO ₄ , 0.1 M Tris–HCl, 30 °C, 20 h	46
					<i>Bacillus brevis</i> AJ-12299, 0.1 M Tris–HCl (pH 7), 30 °C, 24 h	46

Table 3 (continued).

Com- pounds 1 and 2	n	R	Chemical method		Biochemical method	
			reaction conditions	ref.	reaction conditions	ref.
j	0	Bu ⁱ	—		DL-hydantoinase from <i>Bacillus stearothermophilus</i> NS _{1122A} , phosphate buffer (pH 7.0), 60 °C, 30 min <i>Pseudomonas</i> sp. AJ-11220, Tris–HCl (pH 8.5) buffer, various solvents, 30 °C, 2 h D-hydantoinase 2, H ₂ O, 50 °C, 18 h, pH 8.5	48 41 49
k	0	Bu ^s	—		hydantoin-hydrolysing enzyme, ATP, KCl, MgSO ₄ , 0.1 M Tris–HCl, 30 °C, 20 h DL-hydantoinase from <i>Bacillus stearothermophilus</i> NS _{1122A} , phosphate buffer (pH 7.0), 60 °C, 30 min D-hydantoinase 2, H ₂ O, 50 °C, 41 h, pH 8.5	46 48 49
m	0	C ₂ H ₄ SMc	NaOH, H ₂ O, 80–120 °C, < 2 h	51	hydantoin-hydrolysing enzyme, ATP, KCl, MgSO ₄ , 0.1 M Tris–HCl, 30 °C, 20 h D-hydantoinase 1, H ₂ O, 50 °C, 12.7 h, pH 8.5	46 49
n	1	CO ₂ H	NaOH, H ₂ O, 25 °C, variable pH	25	—	
n ^a	0	CH ₂ CO ₂ H	—		<i>Pseudomonas</i> sp. AJ-11220, Tris–HCl buffer (pH 8.5), 30 °C, 2 h	41
p	0	(CH ₂) ₂ CO ₂ H	—		the same	41
r	0	CH(OH)Me	—		D-hydantoinase 1, H ₂ O, 50 °C, 21 h, pH 8.5	49
s	0	Bn	KOH, H ₂ O	30	hydantoin-hydrolysing enzyme, ATP, KCl, MgSO ₄ , 0.1 M Tris–HCl, 30 °C, 20 h <i>Pseudomonas</i> sp. AJ-11220, Tris–HCl (pH 8.5) buffer, 30 °C, 2 h; <i>Flavobacterium</i> sp. AJ-3912, Tris–HCl (pH 8.5) buffer, 30 °C, 2 h DL-hydantoinase from <i>Bacillus stearothermophilus</i> NS _{1122A} , phosphate buffer (pH 7.0), 60 °C, 30 min D-hydantoinase 1, H ₂ O, 50 °C, 39.2 h, pH 8.5	46 41 48 49
t	0	CH ₂ C ₆ H ₄ OH-4	KOH, H ₂ O	30	hydantoin-hydrolysing enzyme, ATP, KCl, MgSO ₄ , 0.1 M Tris–HCl, 30 °C, 20 h <i>Pseudomonas</i> sp. AJ-11220, Tris–HCl (pH 8.5), 30 °C, 2 h <i>Flavobacterium</i> sp. AJ-3912, Tris–HCl (pH 8.5), 30 °C, 2 h	46 41 52
u	0	(CH ₂) ₃ NHC(O)NH ₂	NaOH, H ₂ O	32	<i>Agrobacterium radiobacter</i> , 40 °C, 24 h, 6 bar or 1 atm, 40 °C, 24 h	32
w	0		—		<i>Pseudomonas</i> sp. AJ-11220, Tris–HCl buffer (pH 8.5), 30 °C, 2 h	41
x	0	CH ₂ C ₆ H ₃ (OH) ₂ -3,4	—		the same	41
y ^b	—	—	—		<i>Agromyces</i> , <i>Chromobacterium</i> or <i>Cellulomonas</i> , phosphate buffer, 30 °C, 20 h	53
z ^c	—	—	—		<i>Pseudomonas</i> sp. AJ-11220, Tris–HCl (pH 8.5), buffer 30 °C, 2 h D-hydantoinase 1, H ₂ O, 50 °C, 16.6 h, pH 8.5	41 49

Note. Tris is tris(hydroxymethyl)aminomethane; ATP is adenosine triphosphate. ^a Ureido acid **1n** was synthesised from (2,5-dioxoimidazolidin-

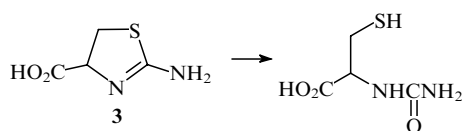
4-yl)acetic acid; ^b ureido acid **1y** was synthesised from  (**2y**); ^c ureido acid **1z** was synthesised from  (**2z**).

Biochemical methods for hydrolytic cleavage of hydantoin (**2a**), dihydrouracil (**2b**), 5-methylhydantoin (**2f**), 5-isopropylhydantoin (**2i**) and 5-isobutylhydantoin (**2j**) under the action of *Pseudomonas* sp. AJ-11220 in a Tris–HCl buffer were documented.⁴¹ Hydantoins **2f** and **2i**, 5-*sec*-butylhydantoin (**2k**), 5-[2-

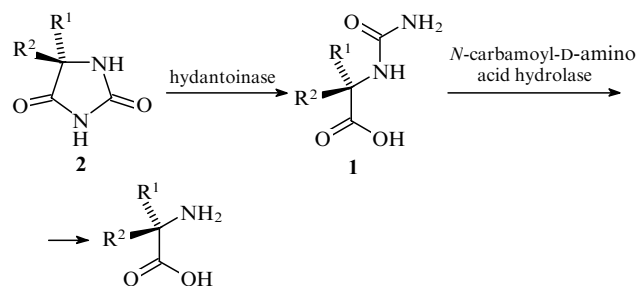
(methylthio)ethyl]hydantoin (**2m**), 5-benzylhydantoin (**2s**) and 5-(4-hydroxybenzyl)hydantoin (**2t**) are transformed into the corresponding *N*-carbamoyl- α -amino acids **1** with different enantiomeric excesses under the action of hydantoin-hydrolysing enzymes in the presence of various inorganic salts (30 °C,

20 h).⁴⁶ Tetrahydropyrrolo[1,2-*c*]imidazole-1,3-dione (**2y**)⁵³ and 5-methylhydantoin (**2f**)¹⁸ are cleaved with immobilised cells of *Agromyces*, *Chromobacterium* or *Cellulomonas* in a yeast extract in 20 h. DL-Hydantoinase from bacterium *Bacillus stearothermophilus* NS_{1122A} in a phosphate buffer (pH 7.0) at 60 °C cleaves hydantoin **2f,j,k**.⁴⁸ Hydantoin **2f-m,s**, (5-mercapto-methyl)thiohydantoin (**2z**) and 5-(1-hydroxyethyl)hydantoin (**2r**) give ureido acids in high chemical and optical yields under the action of D-hydantoinase at 50 °C (pH 8.5).⁴⁹ Dihydrouracil **2b** is cleaved with dihydropyrimidinase (EC 3.5.2.2) from *P. putida* DSM 84;⁴³ 5-methylhydantoin (**2f**), with anaerobic bacterium *P. anaerobius* at 50 °C;⁴⁷ 5-isopropylhydantoin (**2i**), with bacterium *Hansenula sp.*;^{48, 50} 5-(4-hydroxybenzyl)hydantoin (**2t**), with bacteria *Flavobacterium sp.* AJ-3912;² and [3-(2,5-dioximidazolidin-4-yl)propyl]urea (**2u**), with bacterium *Agrobacterium radiobacter*.³²

The ring opening in (+)-2-amino-4,5-dihydrothiazole-4-carboxylic acid (**3**) occurs analogously to hydantoin. This transformation can be performed by either a biochemical method⁵⁴ or alkaline hydrolysis to give *N*-carbamoylcysteine.⁵⁵



Hydantoin derivatives **2** are precursors of substituted α -amino acids and pyruvic acid.^{56–59} Biochemical cleavage of optically active hydantoin occurs through ureido acids and is used for the synthesis of enantiomerically pure amino acids.^{60–65}

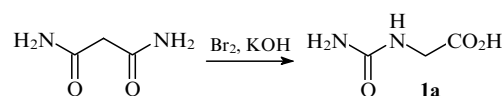


$R^1, R^2 = H, \text{Alk}, \text{Ar}$.

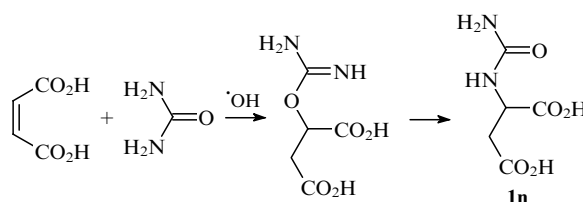
This method can be used for the synthesis of both natural and artificial amino acids having the desired absolute configuration.

4. Other methods for the synthesis of ureido carboxylic and ureido dicarboxylic acids

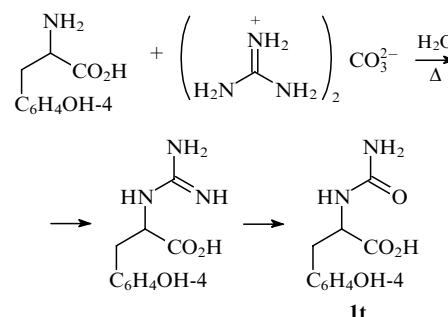
Examples of the synthesis of ureido acids by non-conventional methods are scarce. For instance, *N*-carbamoylglycine (**1a**) was synthesised⁶⁶ by heating of an aqueous solution of malonamide with bromine in an alkaline medium.



N-Carbamoylaspartic acid (**1n**) was prepared by the reaction of maleic acid with an aqueous urea solution at 60 °C or by the flame-induced radical reaction. In the latter case, compound **1n** is formed as a result of the thermal rearrangement of amidinoxy-succinic acid.⁶⁷

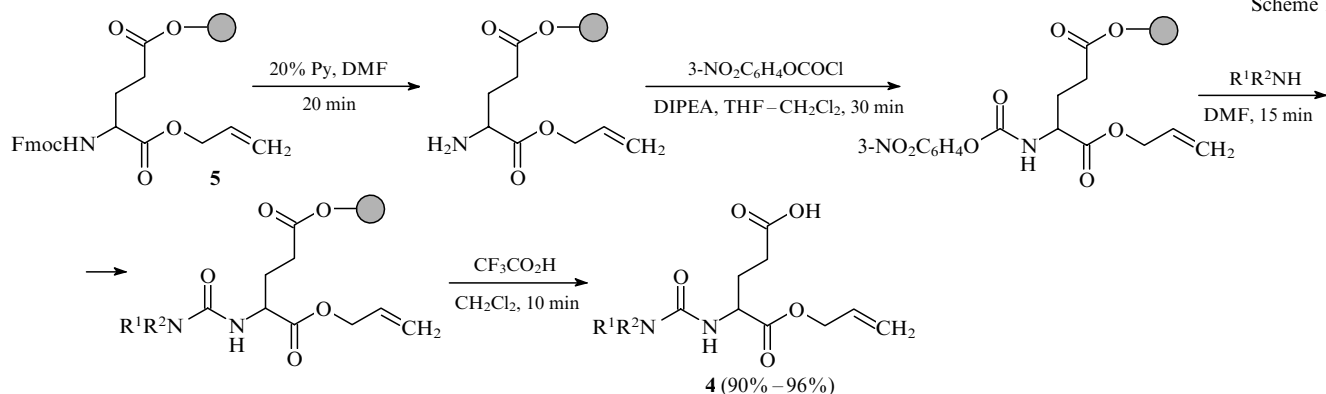


Ureido acid **1t** was synthesised from tyrosine by the reaction with guanidinium carbonate.³⁵ Under the reaction conditions, the guanidine moiety was transformed into the ureido fragment.



Currently, solid-phase syntheses are widely used in amino acid chemistry. In the study,⁶⁸ derivatives of ureido dicarboxylic acid monoallyl ester **4** were prepared. Protected amino acid **5** on a polystyrene support was used as the starting compound. The sequence of transformations is presented in Scheme 1.

Thus, the most convenient method for the synthesis of ureido acids is that developed in the studies.^{13, 14}

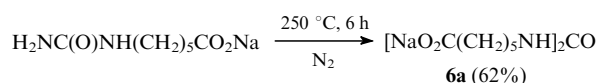


$R^1, R^2 = \text{Alk}, \text{Het}$; Fmoc is 9-fluorenylmethoxycarbonyl, $\bullet$ is a polymeric support, DIPEA is *N,N*-diisopropylethylamine.

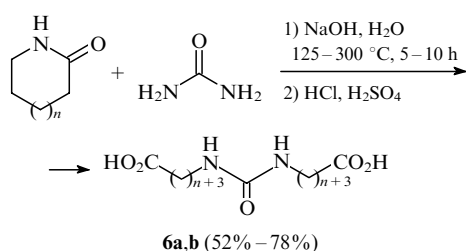
Scheme 1

5. Synthesis of ureylene dicarboxylic acids

The simplest procedure for the synthesis of symmetric ureylene dicarboxylic acids involves thermal decomposition of ureido acid salts at 125–300 °C in a nitrogen atmosphere under elevated pressure. For example, this method was used for the synthesis of disodium 6,6'-ureylenedihehexanoate (**6a**).⁶⁹



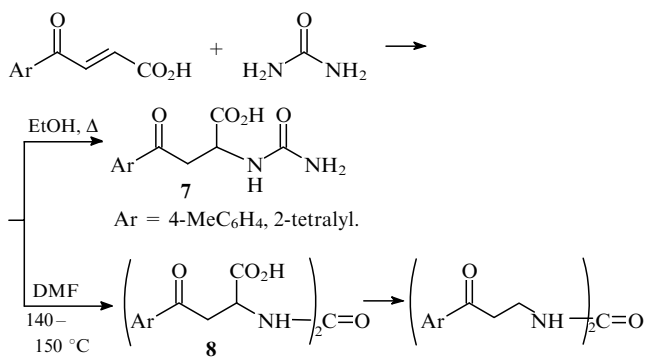
Another procedure for the synthesis of symmetric ureido diacids is based on the reaction of a lactam with urea. For example, compounds **6a,b** were prepared by heating of an alkaline solution of the reagents in an autoclave followed by acidification of the reaction mixture.⁷⁰



$n = 2$ (**a**), 4 (**b**).

An analogous procedure for the synthesis of ureylene dicarboxylic acids $[\text{HO}_2\text{C(CH}_2)_m\text{NH}]_2\text{CO}$ ($m = 3–5$ or 11) with the use of an excess of ω -amino acid instead of lactam was covered by a patent.⁷¹ In this case, the products are purified by anion-exchange chromatography.

The reactions of β -aroylacrylic acids with urea produce different compounds depending on the reaction conditions.

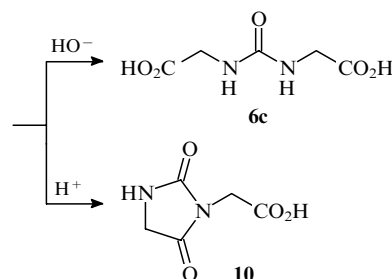
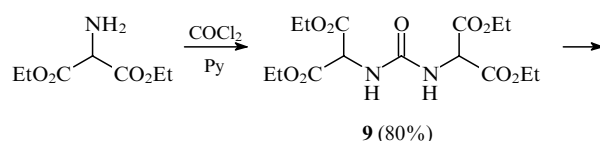


$\text{Ar} = \text{Ph, } 4\text{-MeC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, 4\text{-BrC}_6\text{H}_4, 2\text{-tetralyl.}$

For example, the reactions in boiling ethanol give ureido acids **7**, whereas the reactions in DMF yield ureido diacids **8**, which readily undergo decarboxylation.⁷²

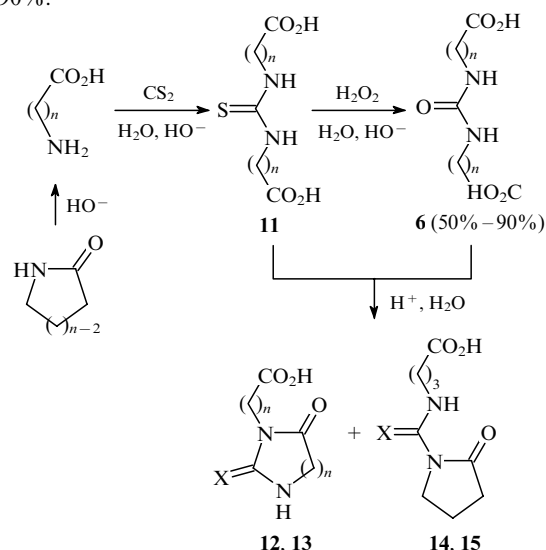
Ureido diacids can also be synthesised by the reactions of amino acid derivatives with COCl_2 , CS_2 , 1,1'-carbonyldiimidazole, 1,1'-carbonyldi(benzotriazole), etc.

The reaction of COCl_2 with diethyl aminomalonate in the presence of pyridine gives urea derivative **9**, whose hydrolysis with an alkali or an acid affords ureido diacid **6c** or hydantoinoacetic acid **10**, respectively.⁷³



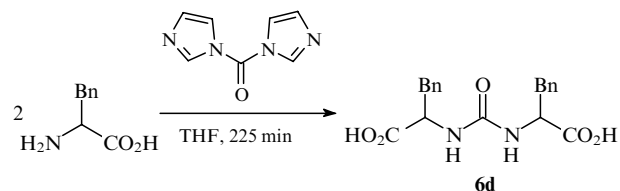
N,N' -Carbonyldi(phenylalanine) ester was synthesised⁷⁴ by the reaction of phenylalanine ethyl ester with carbon disulfide in benzene.

In the reactions of amino acids and their derivatives with CS_2 , the initially formed thioureas **11** are oxidised with hydrogen peroxide (or sodium hypochlorite) to form the corresponding ureido diacids **6**.⁷⁵ In an acidic medium, the former undergo cyclisation to give carboxyalkylthiohydantoin **12**, whereas the latter form oxygen-containing analogues **13**. In some cases ($n = 3$), the reactions afford N -substituted lactams **14** and **15** as by-products. These syntheses can be performed starting from lactams.⁷⁶ Substantial drawbacks of this method consists of the use of toxic flammable CS_2 and long reaction times (up to 12 h). The use of COS instead of carbon disulfide makes it possible to exclude oxidation of thiourea, the yields of diacids **6** being ~90%.⁷⁷



$n = 3–5$; $\text{X} = \text{S}$ (**12, 14**), O (**13, 15**).

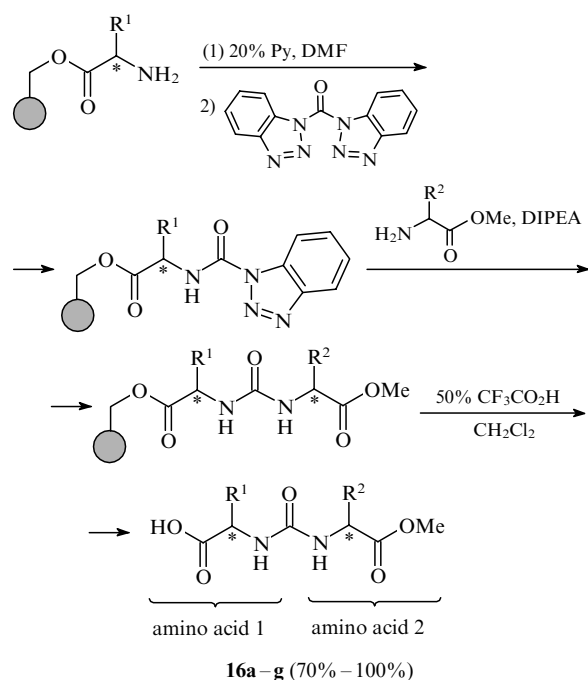
The reaction of phenylalanine with 1,1'-carbonyldiimidazole proceeds smoothly to afford ureido diacid **6d**.⁷⁸



The solid-phase synthesis, which allows one to prepare both symmetric and non-symmetric derivatives, is most promising for the synthesis of ureido diacids. The majority of procedures were developed for the preparation of 1,3,3-trisubstituted ureas on a polystyrene support (see, for example, Refs 79 and 80).

Recently, 1,1'-carbonyldi(benzotriazole) has been successfully used⁸¹ in the solid-phase synthesis of non-symmetric ureido diacids **16a–g** containing two different amino acid residues (Table 4). The products can be purified from a benzotriazole impurity by extraction with a borate buffer (pH 9.2). This method

affords ureido diacids **16a–g** in good yields and with high optical purity (see Table 4).



$R^1 = \text{Bn}$, $R^2 = \text{CH}_2\text{OBu}^t$ (**a**); $R^1 = \text{Pr}^i$, $R^2 = \text{CH}_2\text{OBu}^t$ (**b**);
 $R^1 = (\text{CH}_2)_2\text{SMe}$, $R^2 = \text{Bu}^i$ (**c**); $R^1 = (\text{CH}_2)_2\text{C}(\text{O})\text{NH}_2$,
 $R^2 = (\text{CH}_2)_3\text{NHC}(=\text{NH})\text{NHNO}_2$ (**d**); $R^1 = \text{H}$, $R^2 = \text{CH}_2\text{Ind}$ (**e**);
 $R^1 = \text{CH}_2\text{Ind}$, $R^2 = \text{CH}_2\text{Im}$ (**f**); $R^1 = \text{CH}_2\text{Im}$, $R^2 = (\text{CH}_2)_2\text{CO}_2\text{Me}$ (**g**);
 Im = 3-tritylimidazol-5-yl.

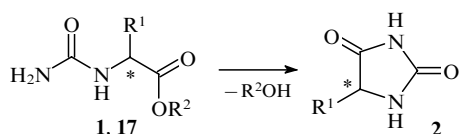
Table 4. Non-symmetric ureido diacids **16a–g**.⁸¹

Compound 16	Amino acid 1	Amino acid 2	ee (%)
a	Phe	Ser(Bu ^t)	95
b	Val	Ser(Bu ^t)	74
c	Met	Leu	80
d	Gln	Arg(NO ₂)	97
e	Gly	Trp	71
f	Trp	His(Trt)	79
g	His(Trt)	Glu(OMe)	91

III. Chemical transformations of ureido carboxylic acids

1. Mechanism of cyclisation of ureido carboxylic acids to hydantoins

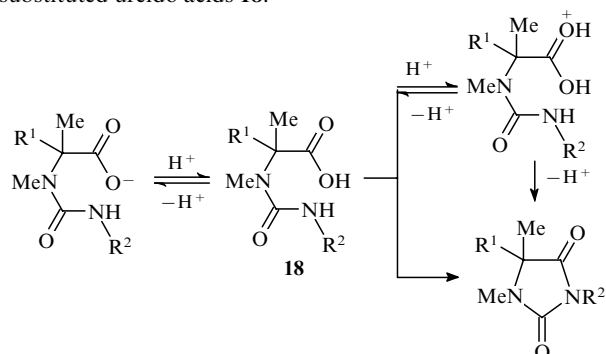
In spite of low reactivity of ureido acids, many chemical transformations involving the amino group of these compounds were documented. Cyclisation of ureido acids **1** and their esters **17** to hydantoins **2** has been the subject of the most studies.^{11, 28, 60, 61, 82–91}



$R^1 = \text{Alk}$, Ar, Het, ArAlk; $R^2 = \text{H}$ (**1**), Alk (**17**).

These reactions are generally performed in an acidic medium; more rarely, in an alkaline medium. In most cases, the reactions are not accompanied by racemisation.

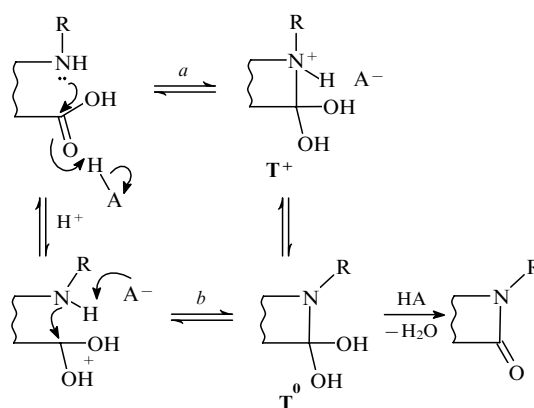
The kinetics and mechanism of cyclisation of ureido carboxylic acids giving rise to hydantoins were studied in-depth for *N*-substituted ureido acids **18**.^{11, 84}



$R^1 = \text{H}$, Me; $R^2 = \text{Me}$, Ph.

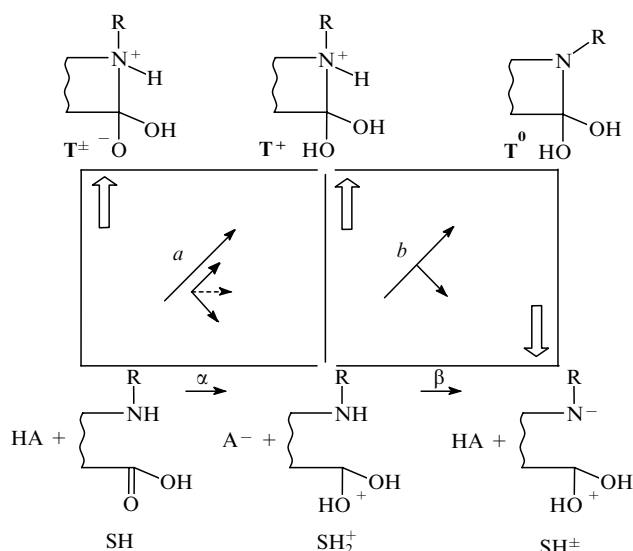
The reaction proceeds under conditions of general acid-base catalysis and involves the attack of the urea nitrogen atom on the carboxyl carbon atom.⁸⁴

Based on a detailed analysis of the mechanism of condensation under acidic conditions, it cannot be conclusively established whether general acid catalysis (pathway *a*) or kinetically equivalent specific catalysis (pathway *b*) occurs.⁸⁴

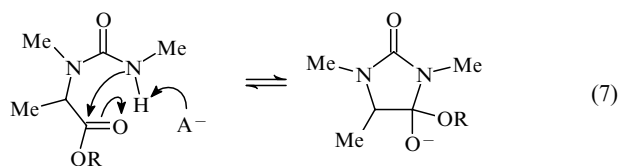


HA is acid; R = Me, Ph.

Since the cyclisation rate of ureido acids under conditions of general acid catalysis is too high to be determined precisely, the measurements were carried out for the corresponding esters, whose reactions are approximately 30 times slower due apparently to larger steric hindrance caused by the OEt group upon the formation of tetrahedral intermediates T^+ and T^0 . The substitution of the *N*-phenyl group in the ureido fragment for the *N*-methyl group would be expected to change the structure of the transition state in the ring closure reaction performed under conditions of general acid catalysis, which can be represented in the diagram using the More O'Ferrall–Jencks reaction coordinates.⁹² Blagoeva *et al.*⁸⁴ represented the alternative pathways *a* and *b* as a pair diagram, which shows that the formation of the tetrahedral intermediate T^+ is the rate-determining step in these reactions.

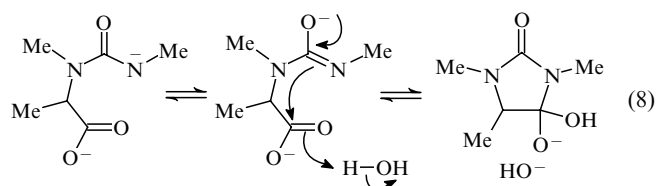


It is assumed that the initial formation of the imidazolidine ring by the reaction (7) is the rate-determining step under conditions of general base catalysis.

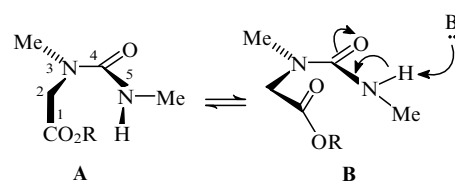


$\text{R} = \text{H}, \text{Et}.$

Therefore, the assumed mechanisms of cyclisation in the case of general base or acid catalysis involve the nucleophilic attack of the sp^2 -hybridised NH group giving rise to a C–N bond and deprotonation as either a concerted reaction [reaction (7)] or an individual step (pathway *a*). In the base-catalysed reaction, deprotonation of the urea cannot be an individual rate-determining step because this requires that reprotonation of the ureido anion be more slow than the nucleophilic addition of N^- to the CO_2R group. Although the latter reaction is very fast, reprotonation of the ureido anion should occur at a rate of at least 100 times higher. The mechanisms involving the formation of the iminol tautomer of urea [reaction (8)] can also be ruled out.



Cyclisation performed under conditions of both general base and acid catalysis is characterised by the strong influence of stereoelectronic factors. In the conformation **A** of the ground state, only the C(1) atom can deviate from the plane of the ureido group so that the formation of the bond between the C(1) and N(5) atoms is virtually impossible. For the bond between these atoms to be formed, rotation about the C(2)–N(3) bond and about one of the C–N bonds of the urea fragment must occur. Evidently, rotation about the C(4)–N(5) bond (transition $\text{A} \rightleftharpoons \text{B}$) is most efficient, because it is accompanied by violation of π -conjugation and makes accessible the partially localised lone pair of the nitrogen atom, which should act as a nucleophile.



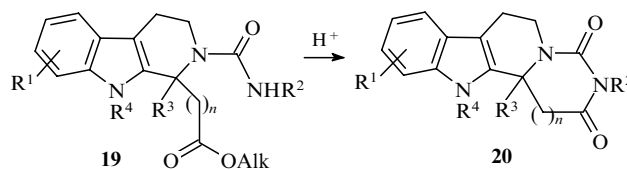
Apparently, both mechanisms considered above give rise to the conformation **B**. General base catalysis partially restores the lost delocalisation in the transition state for the subsequent addition to the CO_2R group. In the acid-catalysed reactions, the partially protonated CO_2R group is electrophilic and can react without additional activation.

It was demonstrated¹¹ that the kinetics of the process is first order with respect to ureido acid, and the reaction is substantially accelerated as pH decreases. Cyclisation of ureido acids occurs more easily as the size of the substituent in the amino acid fragment and its hydrophobicity increase.

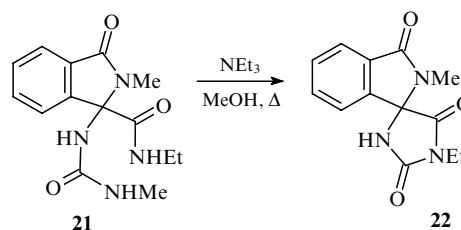
2. Reactions of ureido carboxylic acid derivatives

Cyclisation of ureido acids has attracted attention of researchers as a procedure for the preparation of various heterocyclic compounds containing the urea fragment. Hydantoins can also be used for the synthesis of acyclic ureido derivatives.

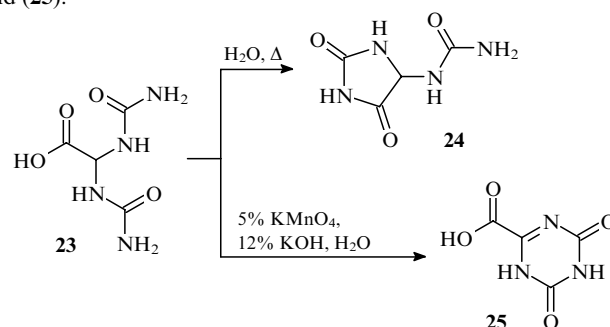
Intramolecular cyclisation of 3-carbamoyltetrahydro- β -carboline **19** in an acidic medium at high temperatures affords tetracyclic derivatives **20**, which are used as antihypoxic and psychotropic agents.⁸⁵



Heating of ureido acid amide **21** in methanol in the presence of triethylamine affords spirohydantoin **22**.⁸⁶

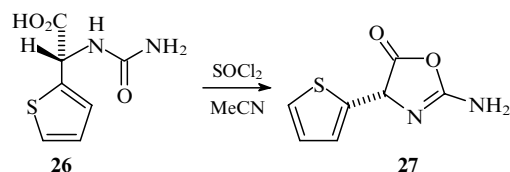


The cyclisation of diureidoacetic acid **23** gave allantoin (**24**),⁸⁷ which accelerates wound healing. Oxidation of compound **23** affords 1,4,5,6-tetrahydro-4,6-dioxo-1,3,5-triazine-2-carboxylic acid (**25**).⁸⁸



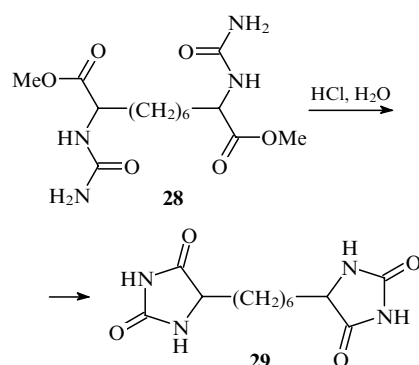
It should be noted that (*S*)-(2-thienyl)ureidoacetic acid (**26**) undergoes cyclisation under the action of thionyl chloride to form

(*S*)-2-amino-4-(2-thienyl)-4*H*-oxazol-5-one (**27**) rather than the corresponding hydantoin.⁸⁹

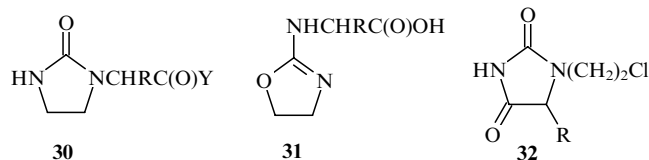


Acid-catalysed cyclisation of *N*-carbamoyl-2,2-diphenylaminoacetic acid in aqueous methanol gives 5,5-diphenylhydantoin.¹¹ The latter is known under the name difenin as an anticonvulsant and anti-arrhythmic drug.^{93–97}

The reaction of dimethyl 2,9-diureidodecanedioate (**28**) in the presence of HCl produced the corresponding 4,4'-hexamethylene-dihydantoin (**29**).⁹⁰

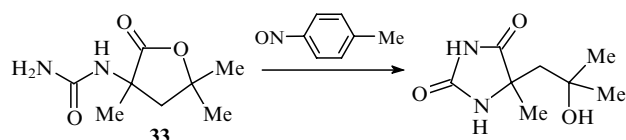


Intramolecular cyclisation of *N*-(2-chloroethylcarbamoyl) derivatives of glycine, valine and phenylalanine $\text{Cl}(\text{CH}_2)_2\text{NHC}(\text{O})\text{NHCHRC}(\text{O})\text{X}$ ($\text{R} = \text{H}$, Pr^i , Bn ; $\text{X} = \text{OH}$, Oalk , NH_2) affords imidazolidones **30**, oxazolines **31** or hydantoins **32** depending on the nature of the substituent R and the reaction conditions.⁹⁸

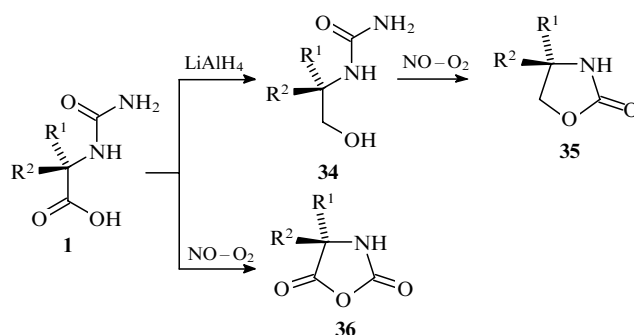


$\text{Y} = \text{OH}, \text{NH}_2$.

Like ureido acids, ureido lactone **33** was rearranged into hydantoin under the action of nitroso compounds.⁹¹



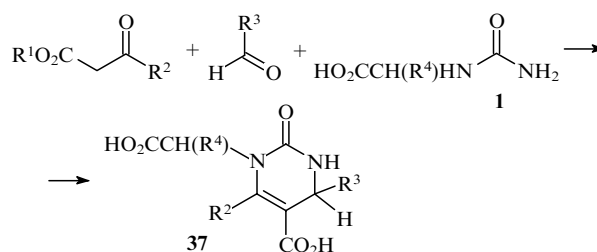
Ureido acids **1** can be used as the starting compounds in the synthesis of other heterocyclic compounds. For example, reduction of ureido acids to form ureido alcohols **34** followed by the reaction with a $\text{NO}-\text{O}_2$ mixture either in solution or in the solid phase affords oxazolidinones **35**.⁹⁹



$\text{R}^1, \text{R}^2 = \text{H}, \text{Alk}$.

Direct nitrosation of substituted ureido acids **1** (R^1 and $\text{R}^2 \neq \text{H}$) yields α -amino acid *N*-carboxyanhydrides (oxazolidine-2,5-diones) **36**, which can be used in the peptide synthesis.¹⁰⁰ The reaction is not accompanied by racemisation and gives products in quantitative yields both in solution and on a support.

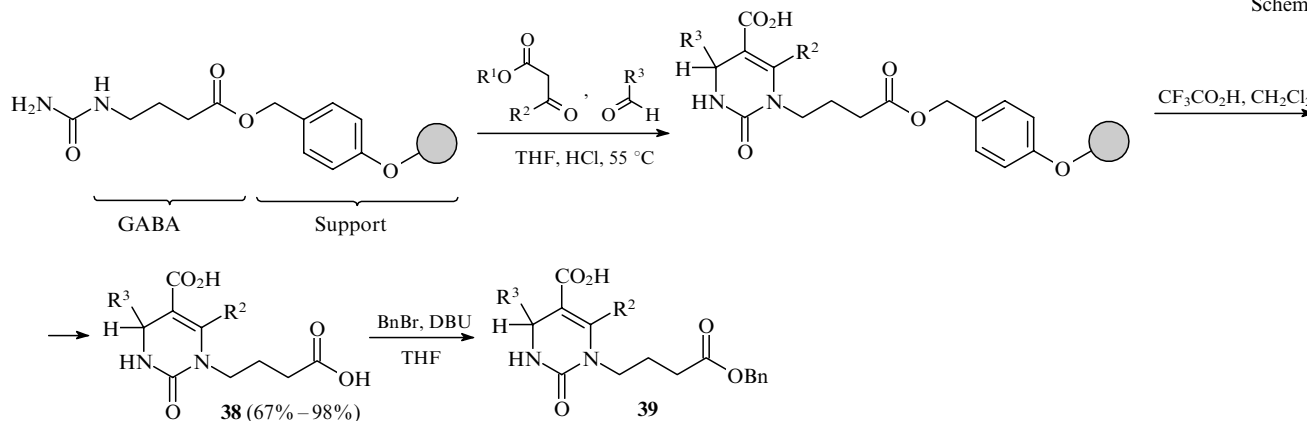
Three-component one-pot condensation of ureido acids **1**, β -keto esters and aldehydes is a very promising synthetic procedure because it affords Biginelli dihydropyrimidinones **37**.¹⁰¹ Derivatives **37** have antiviral¹⁰² and antihypertensive¹⁰³ activities and block calcium channels in cell membranes.¹⁰⁴



$\text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4 = \text{Alk}, \text{Ar}$.

The solid-phase reaction is a preferred modification, for example, in the case of GABA derivatives (Scheme 2). Products

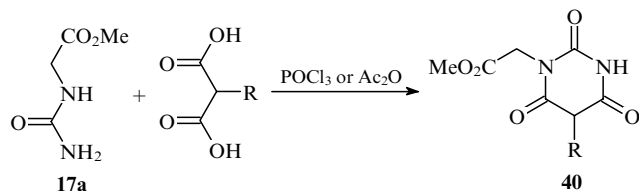
Scheme 2



$\text{R}^1, \text{R}^2, \text{R}^3 = \text{Alk}, \text{Ar}$; DBU is diazabicyclo[4.5.0]undec-4-ene.

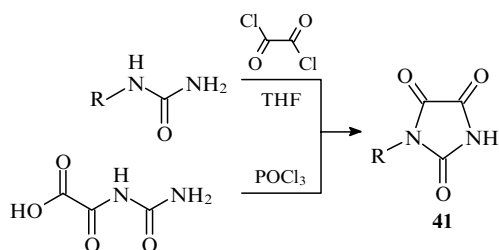
38 are formed in good yields and readily undergo benzylation at the peripheral carboxy group to give protected derivatives **39**.

The reaction of *N*-carbamoylglycine methyl ester **17a** with malonic acid derivatives in POCl₃ (or in Ac₂O) afforded 5-substituted derivatives of barbituric acid **40**,¹⁰⁵ which have a pronounced sedative effect.¹⁰⁶ On the whole, the reactions are similar to the conventional synthesis of barbituric acid¹⁰⁷ and its *N*- (see Ref. 108) and *C*(5)-substituted analogues (for example, of cyclobarbital¹⁰⁹).



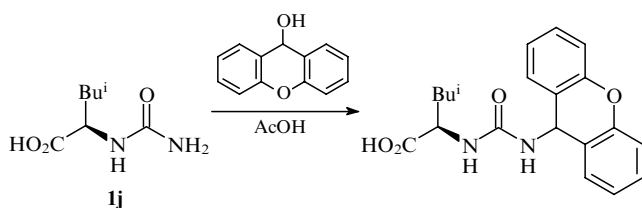
R = Alk, Ar.

N-Carbamoylglycine esters **17**, like urea,¹¹⁰ react with oxalyl chloride to form the corresponding parabanic acids **41**.^{111, 112} In POCl₃, oxalourea also undergoes cyclisation to parabanic acid.¹¹³



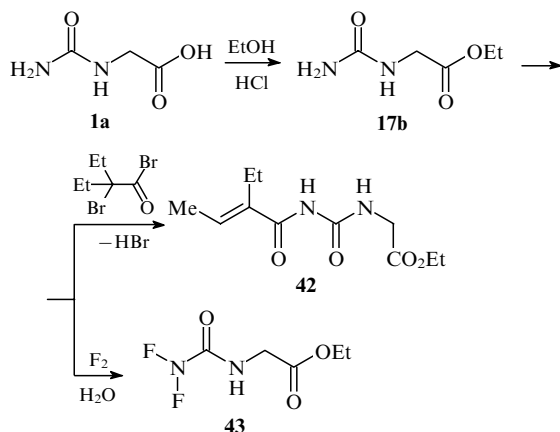
R = H, CH₂CO₂Alk.

Ureido acids **1** are alkylated at the NH₂ group with certain alcohols. For example, *N*-carbamoylleucine (**1j**) reacts with xanthen-9-ol in acetic acid.¹¹⁴

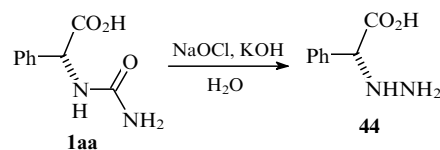


In the study,¹¹⁵ *N*-carbamoylglycine ethyl ester **17b** (Ref. 116) was acylated with substituted carboxylic acid bromides (the synthesis of derivative **42** presented below is accompanied also by elimination of HBr).¹¹⁵

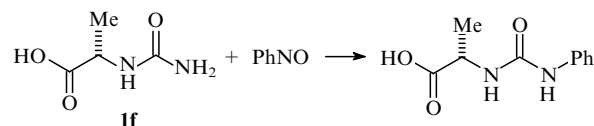
Compound **17b** gives *N,N*-difluoro derivative **43** under the action of fluorine.¹¹⁷



Oxidation of ureido acid **1aa** with sodium hypochlorite affords the corresponding hydrazine **44** in which the configuration of the chiral centre is retained.¹¹⁸



Like monomethylurea (see Ref. 107), ureido acids are nitrosated at the NH group with sodium nitrite in formic acid.¹³ The reactions of nitrosoarenes with ureido acids **1** make it possible to introduce aryl substituents into the primary amino group.¹¹⁹

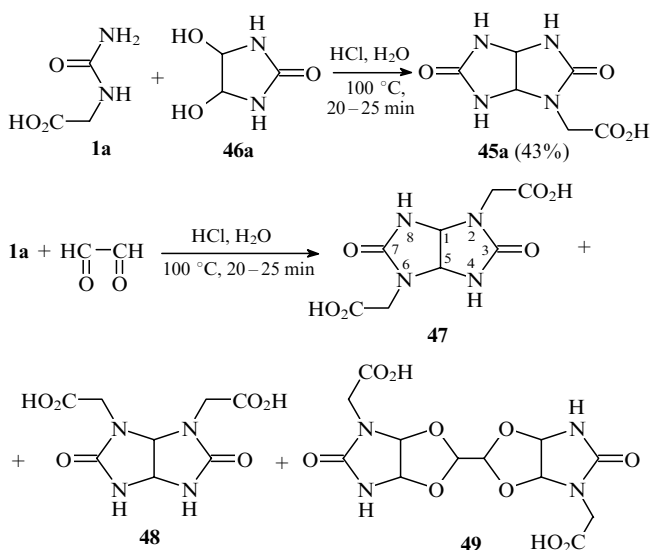


Electrochemical oxidation of ureido diacids and their thio analogues [HO₂C(CH₂)_nNH]CX (X = O or S; *n* = 3 or 5) using a lead cathode and a PbO₂ anode in sulfuric acid affords urea and succinic (*n* = 3) or adipic (*n* = 5) acid.¹²⁰

3. Ureido carboxylic acids in the synthesis of *N*-carboxyalkylglycolurils

The first synthesis of 2-mono- and 2,6-dicarboxyalkylglycolurils was described in 1962.¹²¹ 2-(Carboxymethyl)glycoluril (**45a**) was synthesised by the reaction of *N*-carbamoylglycine (**1a**) with 4,5-dihydroxyimidazolidin-2-one (DHI) (**46a**). Condensation of *N*-carbamoylglycine (**1a**) with glyoxal afforded regioisomers, viz., 2,6-bis(carboxymethyl)glycoluril (**47**) and 2,8-bis(carboxymethyl)glycoluril (**48**). However, only the 2,8 isomer was isolated from the reaction mixture (14% yield).

Recently, we have demonstrated¹²² that the reaction of *N*-carbamoylglycine (**1a**) with glyoxal gave not only bis(carboxy-alkyl)glycolurils **47** and **48** but also bis-product **49**. Bis-product **49** (20% yield) and a mixture of regioisomers **47** and **48** in a ratio of 1:1 (12% yield) were successively isolated from the reaction mixture by fractional crystallisation.



The reactions of ureido acids **1** with 4,5-dihydroxyimidazolidin-2-one **46** and its alkyl derivatives were studied in detail with the aim of extending the range of *N*-carboxyalkylglycolurils **45** and searching for the optimal reaction conditions.¹²³ The influence of the reaction time, the presence of substituents at the

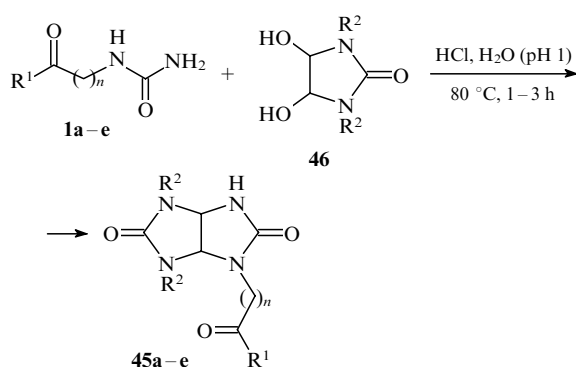
Table 5. Synthesis of *N*-carboxyglycolurils **45a–e**.¹²³

Compounds 1 and 45	<i>n</i>	R ²	Reaction time/h	Yield (%)	Symmetry group
a	1	H	3	68	<i>C2/c</i> , <i>Z</i> = 8
		Me	3	55	—
		Et	3	15	—
b	2	H	1	58	<i>P2₁/c</i> , <i>Z</i> = 4 (0.5 H ₂ O)
		Me	2	45	<i>Pna2₁</i> , <i>Z</i> = 4 (H ₂ O)
		Et	3	5	—
c	3	H	3	63	<i>P2₁/c</i> , <i>Z</i> = 8
		Me	3	39	<i>P2₁</i> , <i>Z</i> = 2
		Et	2	40	<i>Pbca</i> , <i>Z</i> = 8
d	4	H	1	52	—
e^a	1	H	1	40	—

^a R¹ = NHCH₂CO₂H; for other compounds, R¹ = OH.

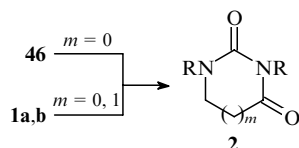
nitrogen atoms of DHI derivatives and the length of the alkyl fragment in ureido acids **1a–e** on the yields of the reaction products was examined (Table 5).¹²³

Glycolurils **45a–e** were synthesised in aqueous HCl (pH 1–2) at 80 °C (see Table 5).



Glycolurils **45a–e** were obtained in lower yields where the reactions were performed with dialkyl derivatives of DHI instead of unsubstituted DHI as well as where the length of the carboxyalkyl chain in starting ureido acids **1a–d** increased. Because of long reaction times, glycolurils **45d,e** were synthesised only from unsubstituted DHI. The optimum reaction times for the synthesis of glycolurils **45a–e** are given in Table 5.

The reactions under consideration are accompanied by the following two side processes: the rearrangement of compounds **46** and cyclisation of ureido acids **1a,b** giving rise to the corresponding hydantoins and their analogues.



m = 0: R = H, Me, Et; *m* = 1, R = H.

These processes are responsible for a decrease in the yields of the target glycolurils **45**. *N*-Carbamoyl-β-alanine (**1b**) appeared to be the least reactive in reactions with alkyl-substituted DHI **46** (R² = Me or Et). Under these conditions, compound **1b** undergoes virtually complete cyclisation to give dihydropyrimidine-2,4(1*H*,3*H*)-dione (**2b**).

The ability of glycolurils **45** to form conglomerates was investigated.^{123,124} For this purpose, glycolurils **45a–e**, which were prepared by crystallisation from H₂O, 30% aqueous MeOH and pure MeOH, were studied. Crystals suitable for X-ray diffraction study were obtained from H₂O. Compounds **45b** (R² = H, Me), **45c** (R² = H, Et) and **45d** (R² = H) crystallise as racemates in centrosymmetric space groups. 2-(Carboxypropyl)-6,8-dimethylglycoluril **45c** (R² = Me) exists as a mixture of homochiral crystals, which differ only in the optical rotation [*α*]_D = +21.92° (*c* = 1.31, H₂O) and [*α*]_D = −18.68° (*c* = 0.38, H₂O). Other physicochemical characteristics of the crystals are identical. The fact that crystallisation of glycoluril **45c** (R² = Me) gives rise to conglomerates was confirmed by X-ray diffraction (space group *P2₁*) (Fig. 1).¹²⁴

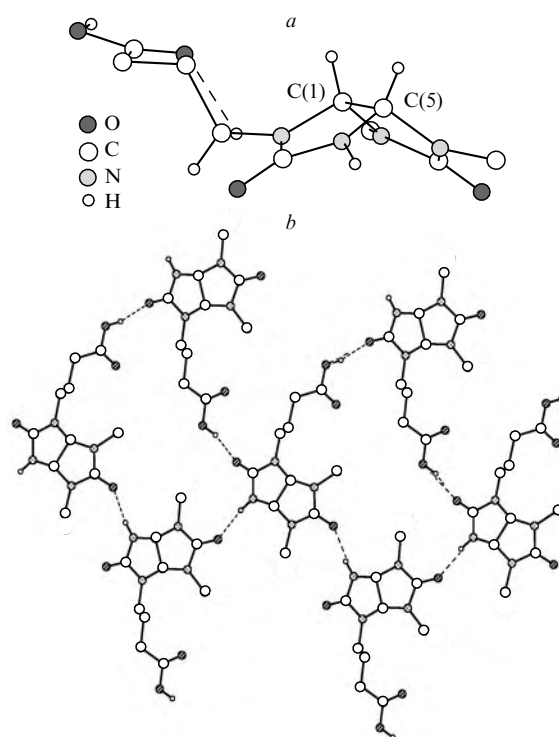
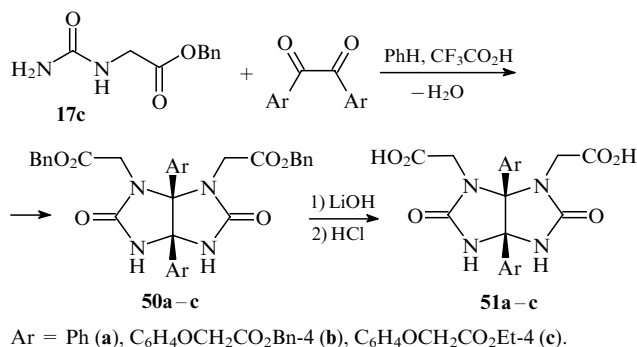


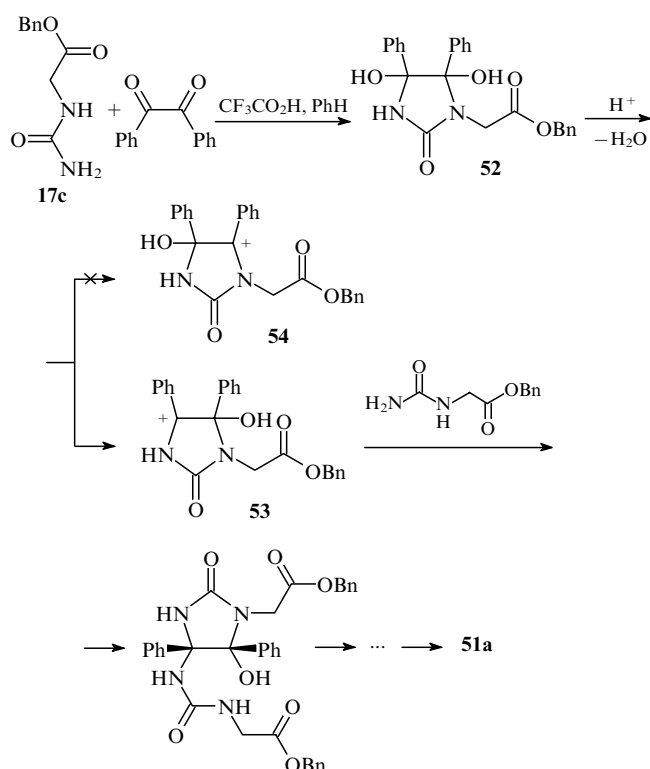
Figure 1. Molecular structure of compound **45c** (R² = Me) (a) and the scheme of formation of homochiral corrugated layers in the crystal through hydrogen bonds (b) (X-ray diffraction data, selected hydrogen atoms are shown).¹²⁴

Racemic *N*-carboxyalkylglycolurils **45** that do not form conglomerates were separated by chiral-phase HPLC. This method was used to resolve racemates of compounds **45a** (R² = H or Me) and **45b** (R² = H). It should be noted that the presence of the methyl substituents [compound **45a** (R² = Me)] results in an increase in the selectivity of enantiomer separation compared to **45a** (R² = H), whereas the presence of one more methylene unit between the carboxy group and the heterocycle [compound **45b** (R² = H)] decreases the selectivity of separation.¹²³

The synthesis of functionalised 1,5-diaryl-substituted glycolurils based on *N*-carbamoylglycine benzyl ester (**17c**) and diaryl-ethanediones was documented.¹²⁵ α-Diketones were subjected to condensation with ester **17c** in benzene with azeotropic distillation of water. Subsequent saponification of the ester groups in compounds **50** afforded substituted glycolurils **51**.

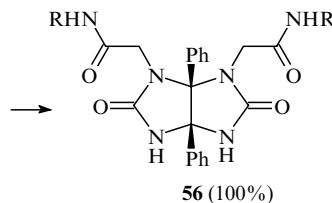
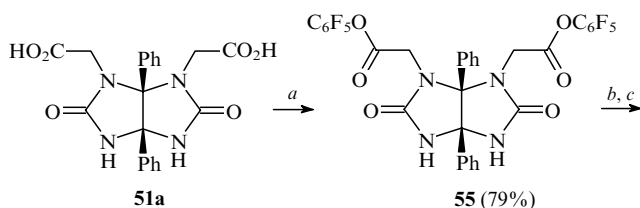


The above reactions give the 2,8-isomer of glycoluril **51** (for simplicity, the 2,6-isomer is ignored in the scheme) as the major product. If Ar = Ph, the 2,8 : 2,6 regioisomer ratio is 8 : 1. This fact can be accounted for by the following reaction mechanism:



The first step of the reaction affords 4,5-dihydroxyimidazolidin-2-one derivative **52**. After protonation, the latter can generate carbocations **53** or **54**. It was assumed¹²⁵ that it is the more electrophilic cation **53** that reacts with the more nucleophilic nitrogen atom of the urea fragment to form the 2,8-isomer of glycoluril **51a**.

In the latter study, compound **51a** (R = Ph) was subjected to esterification with pentafluorophenol to prepare bis(pentafluorophenyl) ester **55**. The reactions of the latter with amines (including amino acids and anilines) afforded derivatives **56**.



R = CH(CO₂H)Bu^s, CH(CO₂Bu^t)Bu^s;

(a) C₆F₅OH, EDC · MeI, DMAP; EDC is 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide; DMAP is 4-(dimethylamino)pyridine;

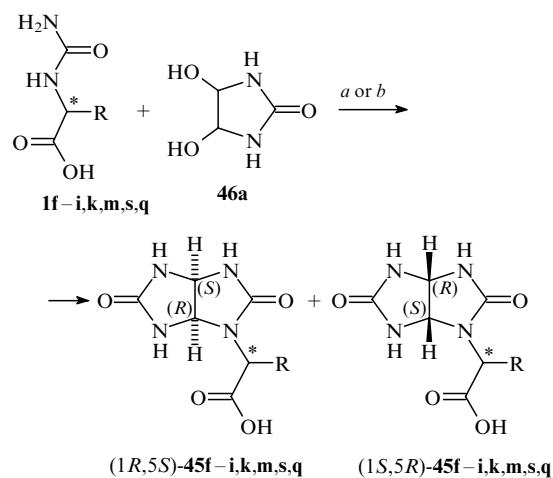
(b) (H-Leu-OBu^t) · HCl; Et₃N, CH₂Cl₂, DMF; (c) TFA.

Thus, *N*-carboxyalkylglycolurils can be prepared by condensation of *N*-carbamoyl amino acids and their esters with both DHI and α -dicarbonyl compounds.

4. Stereoselective syntheses of *N*-carboxyalkylglycolurils

The diastereoselectivity of the reaction of DHI with (*S*)-*N*-carbamoyl- α -alanine (**1f**) was described for the first time in 2001.¹³ The diastereomeric (1*R*,5*S*)- and (1*S*,5*R*)-2-(3,7-dioxo-2,4,6,8-tetraazabicyclo[3.3.0]oct-2-yl)propionic acids (**45f**) were obtained (¹H NMR spectroscopic data) in a ratio of 5 : 2.

More recently, the diastereoselective reactions of DHI with optically active *N*-carbamoyl derivatives of amino acids, viz., (*S*)-norvaline (**1h**), (*S*)- α -aminobutyric acid (**1g**), (*S*)- and (*R*)-methionines (**1m**) and (*S*)-glutamine (**1q**), and with racemic compounds **1f, h, m** were studied.¹²⁶ Cyclocondensation was carried out at pH 1–2 in water or aqueous isopropyl alcohol (depending on the solubility of the starting compounds) with heating (conditions *a*). In all cases, glycolurils **45** were obtained in 33%–40% yields (Table 6).



(a) H⁺, H₂O–PrⁱOH, 80–90 °C, 1–3 h; (b) H₃O⁺, 80 °C, 2 h.

The diastereomeric composition of the products was determined by ¹H NMR spectroscopy. It was found that glycolurils **45** were obtained as two diastereomers (major and minor), which is indicative of high diastereoselectivity of the reactions. This is evidenced by doubling of the signals for all protons, the signals for the CH protons of the major diastereomers being observed at lower field compared to the corresponding signals of the minor diastereomers. To determine the precise chemical shifts and coupling constants of the protons at the C(1) and C(5) atoms in compounds **45**, calculations were carried out by the NUMMRIT method implemented in the Xsim program (Linux OS).

Individual stereoisomers (1*R*,5*S*)-**45m** and (1*S*,5*R*)-**45m** prepared from (*S*)-*N*-carbamoylmethionine (**1m**) were separated by crystallisation from water.

The isolation of the major product obtained in the reaction of DHI with (*S*)-ureido acid **1q** (methanol, traces of HCl) was

Table 6. Diastereoselective and diastereospecific syntheses of diastereomeric and enantiomerically pure glycolurils **45**.^{126, 127}

Ureido acid 1	R	Diastereomer ratio (1 <i>R</i> ,5 <i>S</i>)- 45 : (1 <i>S</i> ,5 <i>R</i>)- 45	
		conditions (a)	conditions (b) [yield (%)]
(<i>S</i>)- 1f	Me	5 : 2	—
(<i>S</i>)- 1g	Et	5 : 1	—
(<i>S</i>)- 1h	Pr ⁿ	3 : 1	—
(<i>S</i>)- 1i	Pr ⁱ	—	100 : 0 [30]
(<i>R</i>)- 1i	Pr ⁱ	—	0 : 100 [30]
(<i>S</i>)- 1k	Bu ^s	—	100 : 0 [35]
(<i>S</i>)- 1m	(CH ₂) ₂ SMe	15 : 1	100 : 0 [37]
(<i>R</i>)- 1m	(CH ₂) ₂ SMe	1 : 15	0 : 100 [37]
(<i>S</i>)- 1s	Bn	—	100 : 0 [35]
(<i>S</i>)- 1q ^a	(CH ₂) ₂ C(O)NH ₂	15 : 1	—
(<i>R,S</i>)- 1f	Me	5 : 2	—
(<i>R,S</i>)- 1h	Pr ⁿ	3 : 1	[33]
(<i>R,S</i>)- 1m	(CH ₂) ₂ SMe	15 : 1	[37]

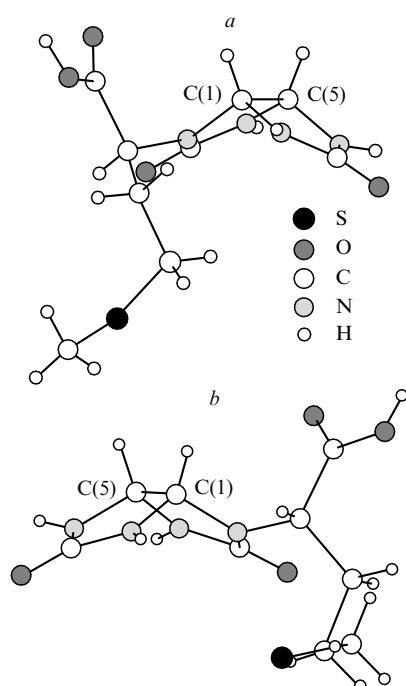
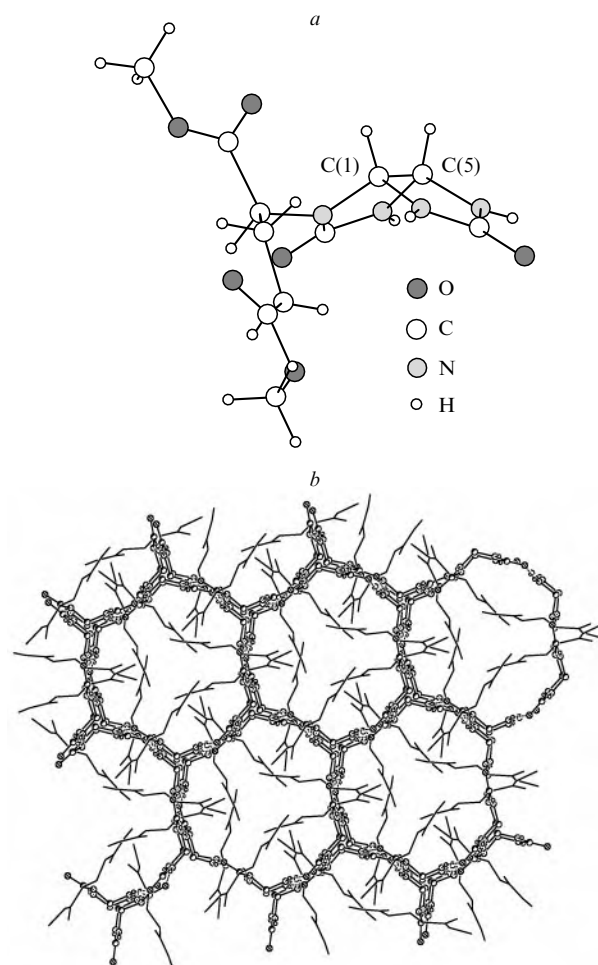
^a Product **57** was formed in the course of isolation.

accompanied by hydrolysis of the amido group to form the carboxy group followed by esterification giving rise to glycoluril methyl ester **57**. The configurations of the chiral C(1) and C(5) atoms of the major diastereomers (1*R*,5*S*)-**45m** and (1*R*,5*S*)-**57q** and the minor diastereomer (1*S*,5*R*)-**45m** (Figs 2 and 3) were established by X-ray diffraction.

The reaction of DHI with (*R*)-*N*-carbamoylmethionine [(*R*)-**1m**] also proceeded with high diastereoselectivity (the diastereomer ratio was 15 : 1), but the reaction gave (1*S*,5*R*)-**45m** as the major diastereomer, which was also isolated by crystallisation from water.

Difficulties in the separation of stereoisomers is the major problems in the diastereoselective synthesis.

With the aim of searching for the conditions of the diastereospecific reaction of DHI with (*S*)- and (*R*)-*N*-carbamoylme-

**Figure 2.** Overall view of the molecule (1*R*,5*S*)-**45m** (a) and its stereoisomer (1*S*,5*R*)-**45m** (b) (X-ray diffraction data).¹²⁷**Figure 3.** Overall view of the molecule (1*R*,5*S*)-**45q** (a) and the formation of an N—H...O-bonded honeycomb-like structure in the crystals of this compound (b).¹²⁷

thionines (**1m**), the influence of pH (from 0 to 5), temperature (40–90 °C) and the reaction time (0.5–4 h) on the reaction pathway was examined. It was found¹²⁷ that the highest diastereospecificity can be achieved with the use of 2 equiv. of HCl at 80 °C for 2.5 h (conditions b). Under these conditions, individual isomers of glycoluril **45m** were obtained (see Table 6).

These conditions were used in the reactions of DHI **46a** with other (*S*)- or (*R*)-*N*-carbamoyl- α -amino acids, *viz.*, compounds **1i**, **k**, **s**. In all cases, individual isomers of the corresponding glycolurils were synthesised.

The diastereospecific reactions of compounds **46a** with (*S*)- and (*R*)-*N*-carbamoylmethionines (**1m**) and (*S*)- and (*R*)-*N*-carbamoylvalines (**1i**) afforded enantiomers characterised by identical physicochemical parameters, including the optical rotation, which is equal in magnitude but opposite in sign. Ureidoalkylation of (*S*)-*N*-carbamoylisoleucine (**1k**) and (*S*)-*N*-carbamoylphenylalanine (**1s**) also occurs diastereospecifically to give enantiomerically pure glycolurils (1*R*,5*S*)-**45k,s** (see Table 6).

The reactions of DHI with racemic (*R,S*)-*N*-carbamoyl- α -amino acids, *viz.*, (*R,S*)-*N*-carbamoylnorvaline (**1h**) and (*R,S*)-*N*-carbamoylmethionine (**1m**), under conditions of the diastereospecific synthesis affords racemates (*R,S*)-**45h,m**, respectively.

It should be noted that all known reactions yield the corresponding hydantoins as by-products.

With the aim of confirming the absolute configurations of the chiral C(1) and C(5) atoms in glycolurils derived from (*R*)-*N*-carbamoyl- α -amino acids, the coordination compound Ni(H₂O)₆L₂(H₂O)₄ (**58**), where L is deprotonated glycoluril, was synthesised by the reaction of glycoluril (1*S*,5*R*)-**45m** with nickel

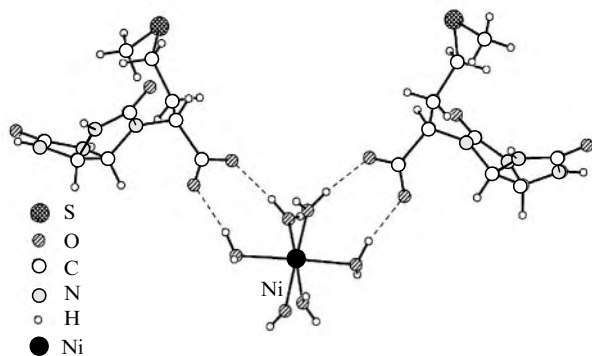


Figure 4. Solvated nickel cation and two anions of deprotonated glycoluril (1*S*,5*R*)-**45m** in the crystals of coordinated compound **58** (X-ray diffraction data).¹²⁷

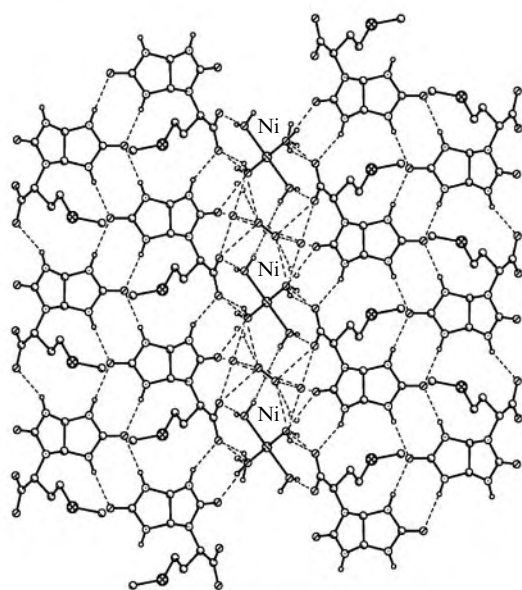


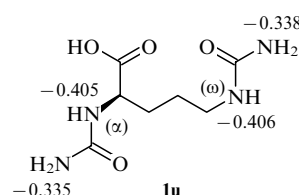
Figure 5. Projection of the molecular packing of **58** in the crystal structure illustrating alternation of the cationic layers and the anionic chains.¹²⁷

acetate in an aqueous solution. Single crystals of **58** grown from water were studied by X-ray diffraction (Figs 4 and 5). It should be noted that the metal atom in complex **58** is not involved in direct coordination to the functional groups of the ligand (see Fig. 4). In the crystal structure, the nickel cation lies on the C_2 axis

and is surrounded by six water molecules. In addition, the unit cell contains four water molecules of solvation. The presence of a large number of donors and acceptors in compound **58** results in a rather complicated supramolecular structure. The crystal structure consists of alternating inorganic (cation) and organic (anion) fragments (see Fig. 5).

5. Reactions of α,ω -diureido carboxylic acids with 4,5-dihydroxyimidazolidin-2-ones

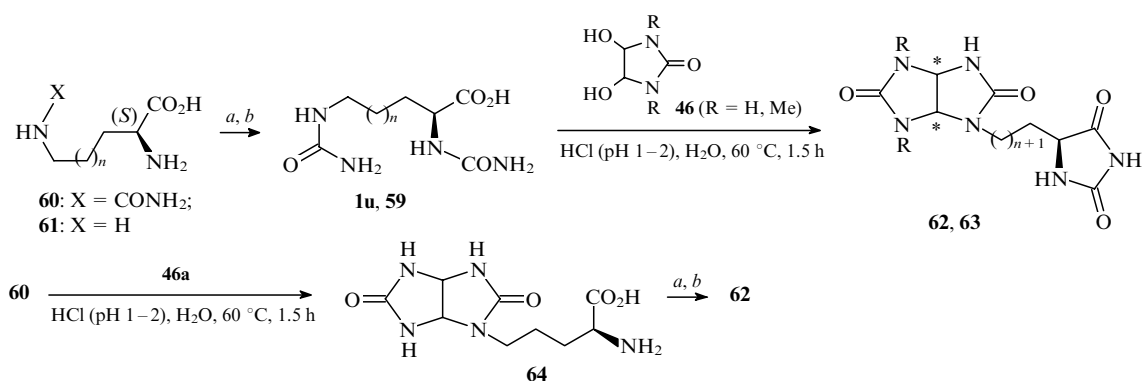
Cyclocondensation of α,ω -diureido acids with DHI derivatives **46** was studied as an access to alkylendi(glycolurils). The starting compounds **1u** and **59** were prepared by the reaction of (*S*)-citrulline (**60**) and (*S*)-lysine (**61**), respectively, with KOCN.¹²⁸ To estimate the reactivities of the α - and ω -ureido fragments in α,ω -diureido acids, the charges on the nitrogen atoms in *N* $^{\alpha}$ -carbamoylcitrulline (**1u**) were calculated by the MNDO method. The calculations demonstrated that the charges on the α - and ω -nitrogen atoms of the ureido fragments in diureido acid **1u** are virtually identical, and a preference cannot be given to a particular reaction centre.



The reaction of compound **1u** was carried out with an equimolar amount of unsubstituted 4,5-dihydroxyimidazolidin-2-one **46a**, and the reaction of diureido acid **59** was performed with dimethyl-substituted DHI **46** ($R = \text{Me}$).¹²⁸ The structures of the resulting hydantoinoalkylenglycolurils **62** and **63** were established by the independent synthesis of compound **62**. Initially, the reaction of (*S*)-citrulline (**60**) with DHI **46a** under the conditions of the diastereospecific synthesis afforded glycoluril **64**, which was used in the reaction with KOCN to form the α -ureido fragment. However, this reaction gave compound **62** instead of the expected glycolurilureido acid (Scheme 3).

The chiral centre in the starting diureido acids is remote from the ureido fragments involved in cyclocondensation due to which the reactions give mixtures of diastereomers. The structures of the reaction products were established by ^1H and ^{13}C NMR spectroscopy with the use of the highly sensitive inversion HMQC (Heteronuclear Multiple-Quantum Correlation) and HMBC (Heteronuclear Multiple-Bond Correlation) methods.

It was demonstrated¹²⁸ that the α - and ω -ureido fragments of diureido acids differ substantially in reactivity with respect to DHI. Cyclisation of the α -ureido fragment to hydantoin is more favourable, whereas the ω -fragment is more reactive with respect to DHI, which gives rise to the glycoluril fragment of compounds **62** and **63**.



Scheme 3

(a) KOCN, H_2O , 100°C , 20 min; (b) HCl, 5°C ; $n = 1$ (**1u**, **60**, **62**), 2 (**59**, **61**, **63**); $R = \text{H}$ (**62**), Me (**63**).

The stereochemical aspects of diastereoselective and diastereospecific reactions of *N*- α -carbamoylamino acids open up new possibilities for the synthesis of enantiomerically pure glycolurils.

* * *

As is evident from the above-presented data, the chemistry of ureido acids and ureido diacids continues to be developed. Apparently, the use of modern solid-phase syntheses of both the starting *N*-carbamoylamino acids and various related heterocyclic compounds is most promising in this area of chemistry. The use of optically pure ureido acids provides approaches to the diastereoselective and diastereospecific syntheses of *N*-(*N*- α -carbamoyl)-substituted glycolurils, which are potential neurotropic compounds.¹²⁹

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^a — *Pharm.-Chem. J. (Engl. Transl.)*

^b — *Russ. Chem. Bull., Int. Ed. (Engl. Transl.)*

Synthesis, reactions and structures of telluronium salts

A V Zakharov, I D Sadekov, V I Minkin

Contents

I. Introduction	207
II. Synthesis of telluronium salts	207
III. Reactions of telluronium salts	211
IV. The use of telluronium salts in organic synthesis	214
V. Crystal structures of telluronium salts	217
VI. Conclusion	223

Abstract. The published data on the synthesis, structures and properties of triorganyltelluronium salts are generalised and systematised. Special attention is given to the applications of these compounds in preparative organic synthesis. The bibliography includes 163 references.

I. Introduction

Triorganyltelluronium salts comprise compounds of the general formula $R^1R^2R^3TeX$. Depending on the nature of the electro-negative group X, solvent and the structure of the crystal lattice, the degree of ionicity of the $Te-X$ bond varies from purely ionic to covalent. Whereas the first organotellurium compound, diethyl telluride, was synthesised in 1840,¹ the first representatives of telluronium salts, *viz.*, trimethyl- and triethyltelluronium iodides, were obtained only 25 years later.²

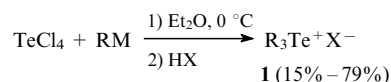
At present, triorganyltelluronium salts are widely used in preparative organic chemistry as starting materials for the synthesis of alkenes, alkylidene(or arylmethylidene)malonates, benzylic, propargylic and allylic alcohols. The trifluoromethyl derivatives are used as trifluoromethylating reagents, whereas triphenyltelluronium salts are used as catalysts in the liquid-phase oxidation of alkenes. It is recommended to use triphenyltelluronium salts as analytical reagents for Co^{2+} and Bi^{3+} ions (Refs 3 and 4); their trialkyl analogues are inhibitors of acid corrosion of iron and steel.^{5,6} Telluronium ylides generated *in situ* from telluronium salts are used in the synthesis of epoxides,⁷ cyclopropanes^{7,8} and alkenes containing electronegative substituents at the double bond.⁷

Separate chapters in the monographs^{9,10} of 1974 and 1983 are devoted to telluronium salts. However, a considerable number of papers on the synthesis and, particularly, on reactions and structures of telluronium salts have been published later. This review is intended to complement the published reviews and to

analyse the state of the art of the problem. The main attention is given to acyclic salts; the data on cyclic telluronium salts are reviewed in the monograph by Detty and O'Regan¹¹ devoted to heterocyclic tellurium derivatives, so they are mainly not included here.

II. Synthesis of telluronium salts

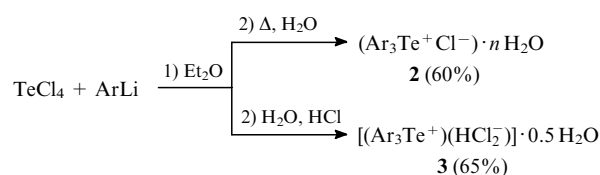
The reaction of tellurium tetrachloride with organoelement compounds is one of the main preparative methods for the synthesis of symmetrical triorganyltelluronium salts $R_3Te^+X^-$ (**1**). Diethylzinc was the first to be used for this purpose; however, it was organomagnesium ($RMgHal$) and organolithium (RLi) compounds that came in practice later.^{9,10,12,13} An attempt to obtain a triorganyltelluronium salt with the use of organocadmium compound is also reported.¹⁴ The reaction of tellurium tetrachloride with organoelement compounds is usually carried out under mild conditions and is followed by fast acid hydrolysis.



$M = MgHal, Li; X = Cl, Br, I; R = Alk, Ar.$

In the majority of cases, salts **1** were isolated as poorly soluble iodides upon treatment of the reaction mixture with an aqueous solution of potassium iodide. It should be noted that under these conditions the reaction of 2,4,6-tris(*tert*-butyl)phenyllithium with $TeCl_4$ affords the corresponding telluride $(2,4,6-Bu_3C_6H_2)_2Te$ instead of the expected telluronium salt.¹³

Recent studies have shown¹⁵ that depending on the procedure for quenching of the reaction mixture, the reaction of 2,6-dimethoxyphenyllithium with $TeCl_4$ in ether yields telluronium salts **2** or **3**. The former were isolated after hydrolysis with hot water, while the latter were isolated upon treatment of aqueous filtrates with 6 M HCl. In the latter case, bis(2,6-dimethoxyphenyl) telluride was formed as a side product (yield 15%).¹⁵



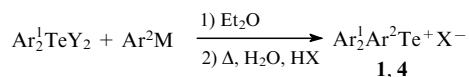
$Ar = 2,6-(MeO)_2C_6H_3; n = 2-2.5.$

A V Zakharov, I D Sadekov, V I Minkin Institute of Physical and Organic Chemistry, Rostov State University, Prosp. Stachki 194/2, 344090 Rostov-on-Don, Russian Federation. Fax (8-632) 43 46 67, tel. (8-632) 43 38 94 (A V Zakharov), tel. (8-632) 43 38 94, e-mail: sadek@ipoc.rsu.ru (I D Sadekov), tel. (8-632) 43 47 00, e-mail: minkin@ipoc.rsu.ru (V I Minkin)

Received 28 February 2005

Uspekhi Khimii 75 (3) 234–253 (2006); translated by R L Birnova

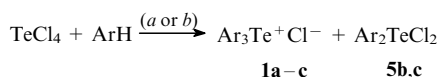
Reactions of diaryltellurium dihalides Ar_2TeY_2 ($\text{Y} = \text{Cl}^{9,10,13}$; Br , $\text{I}^{9,10}$) with arylmagnesium bromides or aryllithium compounds represent a general method for the synthesis of triaryltelluronium salts. This method was used for the preparation of both symmetrical telluronium salts ($\text{Ar}_3\text{Te}^+\text{X}^-$) (**1**) and their non-symmetrical analogues, $\text{Ar}_2^1\text{Ar}^2\text{Te}^+\text{X}^-$ (**4**).



$\text{M} = \text{MgBr}$, Li .

This reaction can obviously be used for the preparation of non-symmetrical telluronium salts of the type $\text{Ar}^1\text{Ar}^2\text{Ar}^3\text{Te}^+\text{X}^-$ from diaryltellurium dihalides $\text{Ar}^1\text{Ar}^2\text{TeY}_2$ and Ar^3M ($\text{M} = \text{MgHal}$, Li). However, no data on such a synthesis are available so far.

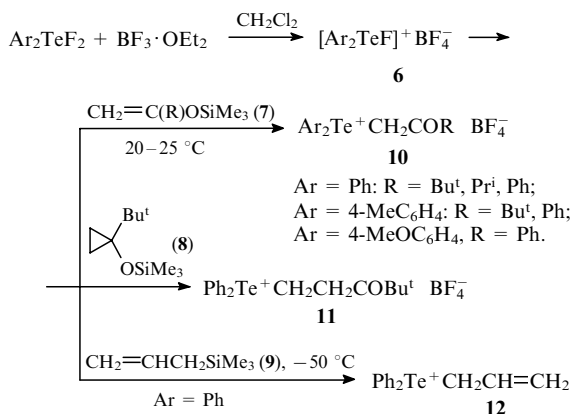
In the reactions of arenes with TeCl_4 , salts **1** or their mixtures with diaryltellurium dichlorides **5** are formed.^{10,16} Cresol derivatives of this type were obtained earlier with the use of TeOCl_2 ; however, these results seem doubtful now.⁹



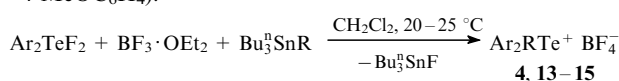
(a) AlCl_3 , Δ (for **a**); (b) 110–130 °C (for **b, c**);

$\text{Ar} = \text{Ph}$ (**a**, 60%), 2-OH-5-MeC₆H₃ (**b**), 4-OH-2-MeC₆H₃ (**c**).

A new method for the synthesis of various types of telluronium salts has been developed recently.¹⁷ It is based on the reactions of electrophilic intermediates **6** (formed upon the reaction of diaryltellurium difluorides with $\text{BF}_3 \cdot \text{Et}_2\text{O}$) with silyl derivatives **7–9**. For example, these intermediates reacted with *O*-trimethylsilyl ethers **7** and **8** at room temperature to give **2-** (**10**) and 3-oxoalkyldiaryltelluronium salts **11** in 85%–100% yields. Similarly, allyldiphenyltelluronium tetrafluoroborate **12** was obtained from allyltrimethylsilane (**9**) in quantitative yield under very mild conditions.¹⁷



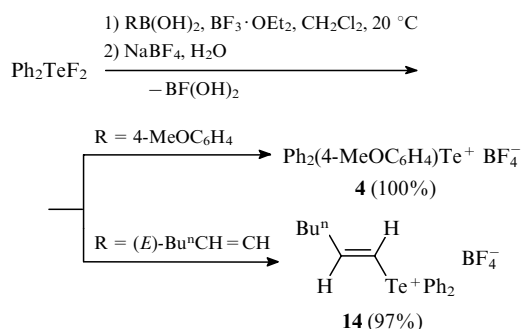
The use of tributyl(organyl)stannanes in a similar reaction enabled the synthesis of the telluronium salts $\text{Ar}_2\text{RTe}^+ \text{BF}_4^-$ containing $\text{Te}-\text{C}(\text{sp}^3)$, $\text{Te}-\text{C}(\text{sp}^2)$ and $\text{Te}-\text{C}(\text{sp})$ bonds, *viz.*, compounds **13** ($\text{R} = \text{Alk}$), **14** and **15**, respectively, as well as of non-symmetrical triaryltelluronium salts of the type **4** ($\text{Ar} = \text{Ph}$, $\text{R} = 4\text{-MeOC}_6\text{H}_4$).¹⁷



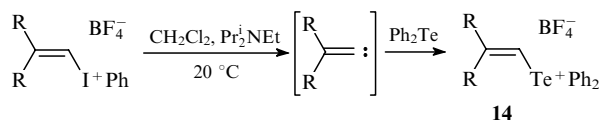
Compound	Ar	R	Yield (%)
4	Ph	4-MeOC ₆ H ₄	95
13	Ph, 4-MeOC ₆ H ₄	Bn	88–100
14	Ph	Me ₂ C=CH	87
15	Ph, 4-MeOC ₆ H ₄	PhC≡C	94–96

The method for the synthesis of telluronium salts described in Ref. 17 has a number of advantages. First, it enables preparation of diaryl(organyl)telluronium salts containing various substituents at the tellurium atom. Second, telluronium salts that are difficult to obtain by other methods are produced in high yields under mild conditions. And finally, nearly pure salts can be isolated upon evaporation of the solvent, since side reaction products, fluorotriorganylsilanes(stannanes), are volatile compounds.

Telluronium salts are synthesised from organic derivatives of boron¹⁸ and iodine.^{19,20} Thus treatment of diphenyltellurium difluoride with 4-methoxyphenylboronic acid in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ and subsequent addition of an aqueous solution of NaBF_4 to the reaction mixture results in non-symmetrical triaryltelluronium salts **4** ($\text{Ar}^1 = \text{Ph}$, $\text{Ar}^2 = 4\text{-MeOC}_6\text{H}_4$) in a nearly quantitative yield.¹⁸ Hex-1-enyl(diphenyl)telluronium tetrafluoroborate **14** [$\text{Ar} = \text{Ph}$, $\text{R} = (E)\text{-hex-1-enyl}$] was prepared using a similar approach.¹⁸

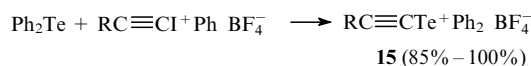


Alkenyl(diphenyl)telluronium salts **14** [$\text{Ar} = \text{Ph}$; $\text{R} = \text{Me}_2\text{C}=\text{CH}$, $(\text{CH}_2)_5\text{C}=\text{CH}$] were also synthesised by the reaction of β,β -dialkylvinyl(phenyl)iodonium tetrafluoroborates with diphenyl telluride in the presence of diisopropylethylamine at room temperature.¹⁹ This reaction proceeds through intermediate alkylidene carbenes.



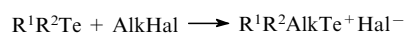
$\text{R} = \text{Me}$ (68%); $\text{R}-\text{R} = (\text{CH}_2)_5$ (89%).

The reaction of alkynyl(phenyl)iodonium tetrafluoroborates with diphenyl telluride was accompanied by transfer of the alkynyl group to the tellurium atom.²⁰ This reaction occurred under mild conditions (mixing of the reactants in CH_2Cl_2 at room temperature) and yielded alkynyldiphenyltelluronium tetrafluoroborates **15**.



$\text{R} = \text{H}$, Me , Pr^i , Bu^t , $n\text{-C}_8\text{H}_{17}$, Me_3Si , Ph .

Reactions of diorganyl tellurides (including those containing aromatic substituents) with alkyl halides represent the most general method for the synthesis of trialkyl-, dialkylaryl- and alkylaryltelluronium salts.



$\text{R}^1, \text{R}^2 = \text{Alk}$, Ar .

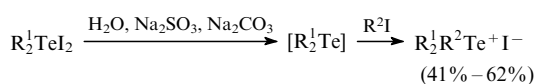
In the case of dialkyl tellurides, exothermic reactions occurred even upon mechanical mixing of the reactants.^{2,9,10,21–48} Alkyl aryl tellurides were found to be less reactive.^{9,10,49–57} Reactions of diaryl tellurides with alkyl halides usually required long-term refluxing of the reaction mixtures.^{9,10,58–60} It is noteworthy that reactions of diphenyl sulfide⁶¹ and diphenyl selenide,⁶² which are

less nucleophilic than diaryl tellurides, with alkyl halides yielded onium salts only in the presence of Ag(I) salts.

Divinyl telluride,^{63, 64} ethynyl phenyl, *tert*-butyl ethynyl, ethynyl vinyl, ethynyl propylthio and hexa-1,3-diynyl methyl tellurides¹⁰ as well as di(methyltellurio)acetylene⁶⁵ also yielded telluronium salts upon reactions with alkyl iodides.

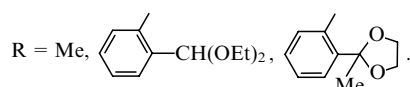
Dimethyl sulfate, together with organic bromides and iodides of various structures, *viz.*, alkyl halides, allyl bromides, propargyl bromides, benzyl halides, α -bromo ketones, α -bromocarboxylic acids, esters and *N*-substituted amides, bromoacetonitrile, alkylmono- and dibromomalonates and 1,2-dibromoethane, are used as alkylating reagents. Among chloro derivatives, only chloroacetonitrile gives telluronium salts in reactions with dialkyl tellurides.^{27, 29, 36}

Because of their very unpleasant odour and easy oxidation by atmospheric oxygen, dialkyl tellurides are sometimes prepared *in situ*. Thus the reduction of readily available dialkyltellurium diiodides with sodium sulfite and subsequent reaction with alkyl iodides were used in the synthesis of triorganyltelluronium iodides.^{9, 10}

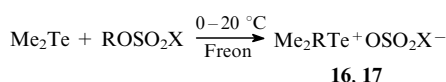


$R^1 = R^2 = Me, Pr^n$; $R^1 = Bu^n, R^2 = Me$; $R^1 = Me, R^2 = Ph$.

An alternative approach to the synthesis of these compounds is based on the treatment of lithium tellurolates with an excess of an alkylating reagent (methyl iodide) without preliminary isolation of the intermediate dialkyl(alkylaryl) tellurides.^{9, 10, 26}

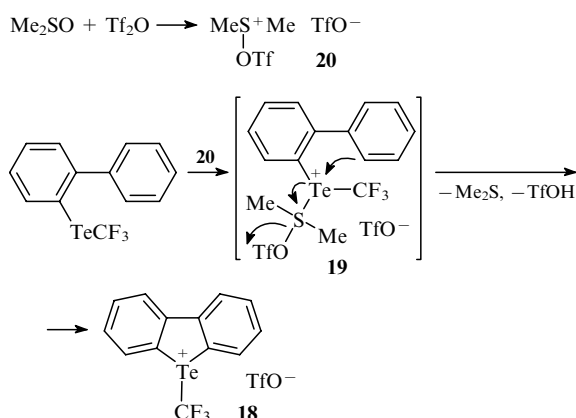


Strong alkylating reagents, such as methyl fluorosulfonate and alkyl trifluoromethanesulfonate,^{66, 67} easily form dimethyl(organyl)telluronium salts **16** and **17** from dimethyl telluride in Freon solutions in the cold.

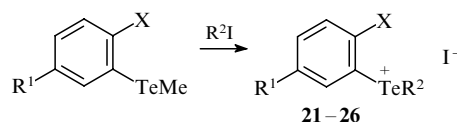


$X = F, R = Me$ (**16**); $X = CF_3, R = Me, Et$ (**17**).

5-Trifluoromethyldibenzotellurophenonium trifluoromethanesulfonate (**18**) was prepared by the reaction of trifluoromethanesulfonic anhydride (Tf_2O) with biphenyl-2-yl trifluoromethyl telluride in DMSO.^{68, 69} This reaction presumably occurs *via* intermediate **19** resulting from addition of sulfonium salt **20** to the tellurium atom.

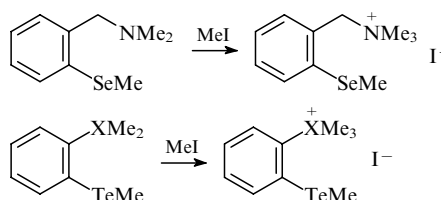


Interesting results suggestive of high nucleophilicity of the tellurium atom in alkyl aryl tellurides were obtained while studying the alkylation, by methyl iodide^{50, 59, 70} or aryl iodides (PhI, *p*-MeOC₆H₄I or *p*-EtOC₆H₄I),⁵⁹ of aromatic compounds containing various nucleophilic substituents, *viz.*, dimethylamino-methyl-,⁵⁰ dimethylamino-,^{59, 70} 2-(4,4-dimethyloxazolino)-⁵⁰ or methylthio(seleno) groups⁷⁰ in the *ortho*-position relative to organyltellurium groups. These reactions yield telluronium salts **21–26**.



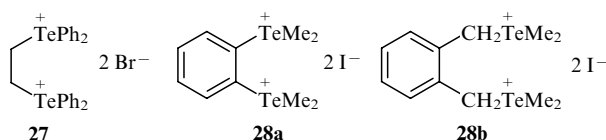
$R^1 = H, R^2 = Me$: $X = CH_2NMe_2$ (**21**), NMe_2 (**22**), SMe (**23**), $SeMe$ (**24**), 4,4-dimethyl-4,5-dihydrooxazol-2-yl (**25**); $X = NMe_2, R^1 = Me, R^2 = 4-YC_6H_4$ [$Y = H$ (**26a**), OMe (**26b**), OEt (**26c**)].

At the same time, dimethyl(2-methylselenobenzyl)amine is methylated at the nitrogen atom;⁵⁰ dimethyl(2-methyltellurophe-nyl)phosphine, -arsine and -stibine react with methyl iodide to give phosphonium, arsonium and stibonium salts, respectively.⁷⁰

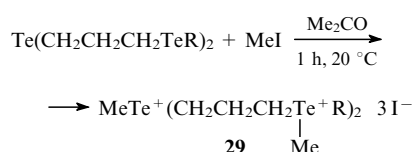


$X = P, As, Sb$.

Bis(telluronium) salts were synthesised by the reaction of 1,2-dibromoethane with diphenyl telluride (product **27**)^{9, 10} or by alkylation of compounds containing two telluromethyl groups with methyl iodide [salts **28a** (see Ref. 70) and **28b** (see Ref. 57)].

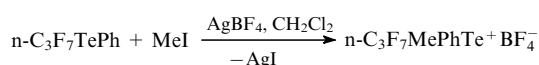


It is of note that reactions of tellurides containing three tellurium atoms with MeI yield tris(telluronium) salts **29**.⁷¹

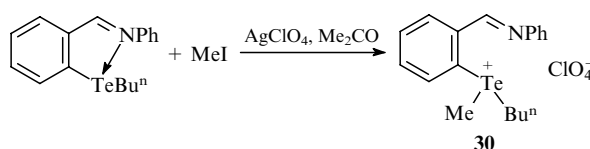


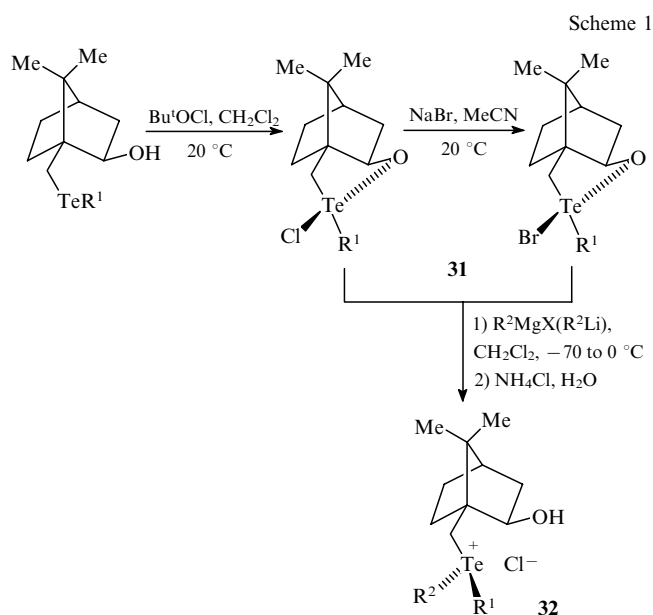
$R = Me, Ph$.

Tellurides containing electron-withdrawing perfluoroalkyl groups at the tellurium atom are alkylated only in the presence of silver tetrafluoroborate.¹⁰



Telluronium salt **30** was prepared from *N*-(2-butyltellurobenzylidene)aniline containing the intramolecular coordination bond $N \rightarrow Te$ in the presence of silver perchlorate.^{72, 73}





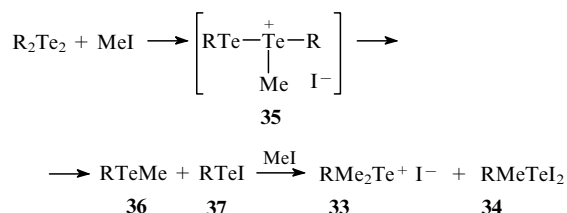
X = Cl, Br;

R¹ = Me, Et, Buⁿ, n-C₆H₁₃, Ph; R² = Me, Et, Buⁿ, Bn, CH₂CH=CH₂ (All).

A novel approach to the synthesis of trialkyl- and dialkyl-aryltelluronium salts containing a (1*S*)-2-*exo*-10-bornyl substituent has been developed (Scheme 1).^{74–76} Reactions of halooxa-telluranes **31** with organomagnesium or -lithium compounds and subsequent treatment of the reaction mixtures with aqueous NH₄Cl afforded optically pure triorganyltelluronium chlorides **32** in 60%–97% yields (for an alternative method for the preparation of chiral telluronium salts, see Section III). The structures of diastereomeric salts **32** (R¹ = Me, R² = Et; R¹ = Et, R² = Me) were confirmed by X-ray diffraction analysis.⁷⁵

The pyramidal inversion barrier of tricoordinated tellurium atoms in these compounds exceeds 30 kcal mol^{–1}. Thus 5-h refluxing of salts **32** in chloroform or methanol did not result in their epimerisation.⁷⁵

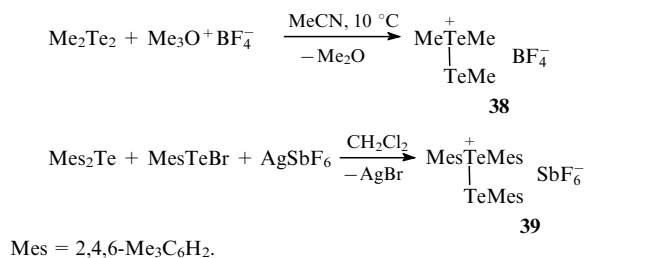
Organyldimethyltelluronium iodides **33** were formed, along with organylmethyltellurium diiodides **34** (molar ratio 1 : 1), upon treatment of diorganyl ditellurides with an excess of methyl iodide.^{9, 10, 77} The methylation of ditelluride, which obviously represents the first step in these reactions, gives intermediate organyltelluro(methyl)organyltelluronium iodides **35**. Spontaneous decomposition of these salts results in methylorganyl tellurides **36** and organyltellurenyl iodides **37**; their subsequent reactions with methyl iodide yield compounds **33** and **34**, respectively.



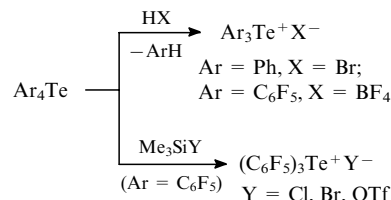
R = Me, Et, Prⁱ, Bu^t; 4-MeC₆H₄, 4-MeOC₆H₄, 4-EtOC₆H₄.

The reaction of diorganyl ditellurides with phenylacetylene in the presence of methyl iodide also seems to occur *via* salts of the type **35** and affords alkyl phenylethynyl tellurides.^{77, 78}

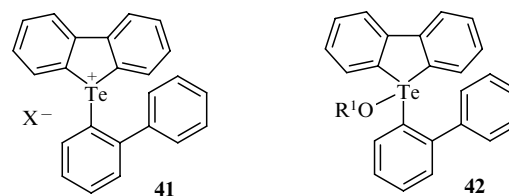
Tellurotelluronium salts with BF₄[–] and SbF₆[–] anions were isolated in the individual state, *e.g.*, compound **38**⁷⁹ and mesityl derivative **39**.^{80, 81}



The triaryltelluronium salts Ph₃Te⁺Br[–] and (C₆F₅)₃Te⁺X[–] (X = Cl, Br, OTf) were prepared in high yields by the reaction of tetraphenyltellurane Ph₄Te (see Refs 9 and 10) and tetrakis(pentafluorophenyl)tellurane (C₆F₅)₄Te (Ref. 82) with mineral acids^{9, 10, 82} or trimethylsilyl derivatives.⁸²



Reactions of a cyclic spirotetraaryltellurane, *viz.*, bis(2,2'-biphenylene)tellurane, with mineral^{9, 10} and organic acids⁸³ and phenols^{84, 85} were accompanied by the cleavage of one of the Te–C bonds. The corresponding reaction products (compounds **41** and **42**) were formed in 47%–95% yields.

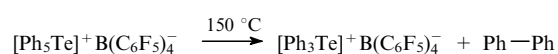


X = Cl, I, BPh₄;

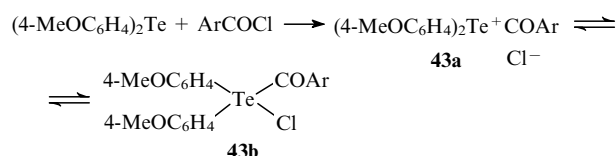
R¹ = MeCO, PhCO, 4-R²C₆H₄ (R² = H, Me, Cl, MeO₂C, Ac, NO₂), 2,4,6-Cl₃C₆H₂.

The preparative significance of these reactions is relatively low. Tetraaryltelluranes and bis(2,2'-biphenylene)tellurane are usually prepared by reactions of aryllithium derivatives with the corresponding tellurium dichlorides, which, as was shown above, can directly be converted into telluronium halides. Exchange reactions of the latter (see Section III) afford various triaryltelluronium salts including the derivatives of the type **41** and **42**.

The synthesis of triphenyltelluronium tetrakis(pentafluorophenyl)borate by thermal decomposition of a pentaphenyltelluronium-containing salt presents purely theoretical interest.⁸⁶



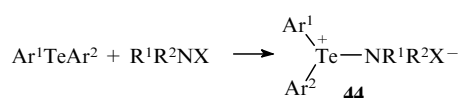
Refluxing of equimolar amounts of bis(4-methoxyphenyl) telluride and 3,5-dinitrobenzoyl chloride in neutral solvents (CH₂Cl₂ or benzene) yielded a compound with a tentative structure of telluronium salt **43a**.⁸⁷



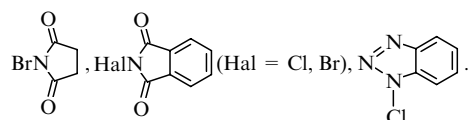
Ar = 3,5-(O₂N)₂C₆H₃.

However, low melting point of this compound and low electric conductivity of its 10⁻³ M solution in acetonitrile are in favour of the covalent structure **43b** containing a tetracoordinated tellurium atom.

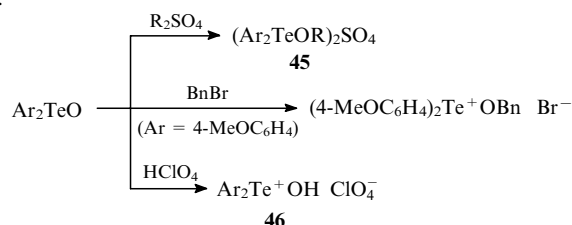
Triorganyltelluronium derivatives **44** containing two Te—C bonds and one Te—N bond are worthy of note. These salts are prepared by oxidation of diaryl tellurides by compounds that are sources of positively charged halogens (e.g., *N*-halosuccinimides^{88,89}). Derivatives **44** are high-melting crystalline compounds poorly soluble in common organic solvents.



Ar¹, Ar² = Ph, 4-MeOC₆H₄; R¹R²NX = PhCONHBr,



Diaryltellurium oxides manifest the highest basicity in the series of diarylchalcogen oxides Ar₂EO (E = S, Se, Te) and are therefore easily alkylated at the oxygen atom by dialkyl sulfates^{60,90} and benzyl bromide⁹¹ resulting in diaryl(alkoxy)telluronium salts **45**. The reaction of diaryltellurium oxides with perchloric acid yields diaryl(hydroxy)telluronium perchlorates **46**.^{60,92}

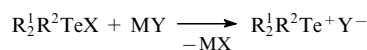


Compound	R	Ar	Ref.
45	Me	4-DC ₆ H ₄ , 4-Pr ⁱ C ₆ H ₄	90
	Me	2,6-(MeO) ₂ C ₆ H ₃	60
	Et	Ph, 4-DC ₆ H ₄ , 4-Pr ⁱ C ₆ H ₄	90
46		4-MeOC ₆ H ₄	92
		2,6-(MeO) ₂ C ₆ H ₃	60

III. Reactions of telluronium salts

Anion-exchange reactions (see the monographs^{9,10} and references cited therein, as well as Refs 12, 25, 28, 93–106) are among the most important preparative methods for the synthesis of triorganyltelluronium salts. The direction of the exchange is determined by the relative solubilities of the original and final salts, which depend on the nature of the anion. By virtue of the large radius of the tellurium atom and its low electronegativity, the telluronium cation can be regarded as a mild acid. In accordance with the HSAB principle,⁹³ the salts containing hard anions (F⁻, Cl⁻, OH⁻, NO₃⁻, CrO₄²⁻, Cr₂O₇²⁻, BF₄⁻, BPh₄⁻, ClO₄⁻, etc.) should possess better solubilities in comparison with the salts containing soft anions (Br⁻, I⁻, N₃⁻, CN⁻, SCN⁻, etc.). In particular, the solubilities of telluronium halides R₃Te⁺Hal⁻ decrease in the order: F > Cl > Br > I; therefore, the exchange can be carried out in aqueous media under the action of alkali metal halides. Compounds with solubilities exceeding those of the starting

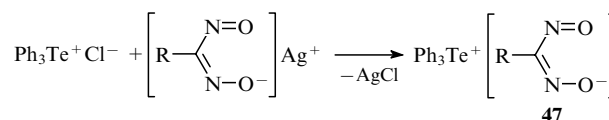
compounds are prepared using the corresponding silver salts. In this case, the direction of the exchange is determined by the relative solubilities of silver halides. The exchange reactions were used in the synthesis of many telluronium salts containing various anions.



M is an alkali metal or silver.

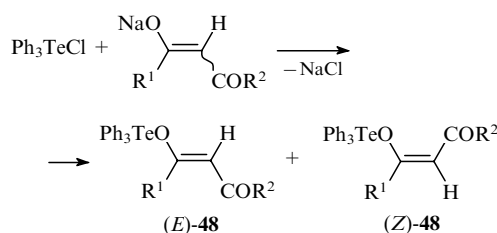
Anion-exchange reactions were also used in the synthesis of telluronium salts containing doubly charged anions.

Reactions of triphenyltelluronium chloride with silver nitro-solates afforded the corresponding triphenyltelluronium nitro-solates **47**.¹⁰⁷



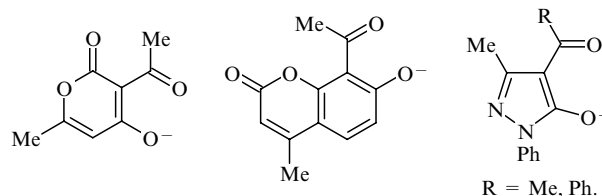
R = Me (65%), Ph (25%).

Reactions of aqueous triphenyltelluronium chloride with an excess of sodium β-diketonates resulted in triphenyltelluronium β-diketonates **48** (yields 52%–90%).¹⁰⁸ The ¹H NMR spectra suggest that these compounds exist as mixtures of *E*- and *Z*-isomers.



R¹ = R² = Me, Ph; R¹ = Me, R² = Ph; R¹ = CF₃; R² = Ph, 2-thienyl.

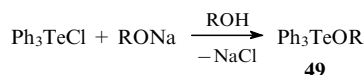
Similarly,¹⁰⁹ enolates of heterocyclic β-diketones



R = Me, Ph.

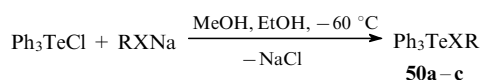
gave triphenyltelluronium derivatives.

The exchange reactions of triphenyltelluronium chloride with sodium alkoxides gave triphenyltelluronium alkoxides **49** in high yields.¹¹⁰



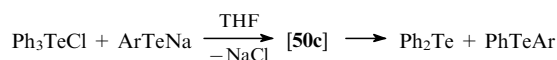
R = Me, Et, Prⁱ.

Triphenyltelluronium organylchalcogenolates **50a–c** [X = S (**a**), Se (**b**), Te (**c**)] were synthesised from triphenyltelluronium chloride.^{111–113}



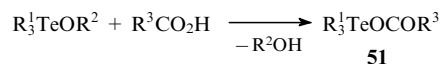
X = S: R = Et, Prⁱ, Bu^t, Bn, Ph, 4-MeOC₆H₄, 4-ClC₆H₄, 2-Py, 4-Py;
X = Se, R = 4-MeC₆H₄; X = Te: R = 4-MeC₆H₄, 4-MeOC₆H₄.

However, the reactions of Ph₃Te⁺Cl⁻ with sodium aryl-tellurolates in THF yielded diphenyl and aryl phenyl tellurides as the final products.¹¹³ Obviously, the latter were formed as a result of decomposition of intermediate compounds of the type **50c**.

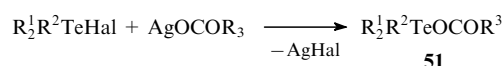


Ar = 4-MeC₆H₄, 4-MeOC₆H₄.

Treatment of triphenyltelluronium alkoxides **49** with carboxylic acids resulted in the corresponding carboxylates **51**.⁹⁷ Similar compounds were synthesised by reactions of triorganyltelluronium hydroxides with carboxylic acids⁹⁷ and of triorganyltelluronium halides with silver salts of organic acids.^{58, 94, 97}

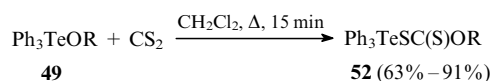


R¹ = Ph, R² = Me; R¹ = Me, R² = H; R³ = Me, CHCl₂, CCl₃, Ph.



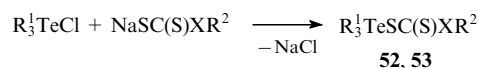
R¹, R² = Me, Ph; R³ = Me, Ph, 2-MeOC₆H₄, 3-O₂NC₆H₄.

Triphenyltelluronium xanthates **52** were prepared by the insertion of carbon disulfide into the Te—O bond of triphenyltelluronium alkoxides **49**.¹¹⁰

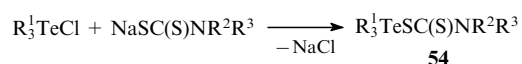


R = Me, Et, Prⁱ.

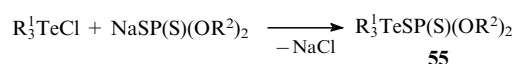
However, the exchange reactions between triorganyltelluronium chlorides and the corresponding sodium (less frequently, ammonium) salts represent the most general method for the synthesis of xanthates **52**,^{95, 110, 114–116} thioxanthates **53**,^{95, 110} dithiocarbamates **54** (Refs 95, 114, 117–119) and dithiophosphates **55**.^{112, 114, 120}



X = O (**52**), S (**53**); R¹ = Me, Ph; R² = Me, Et, Prⁿ, Prⁱ, Buⁱ, Bu^t, cyclo-C₆H₁₁ (Cy).

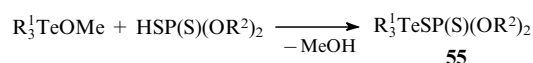


R¹ = Me; R² = R³ = Me, Et, Ph; R¹ = Ph; R² = R³ = Me, Et, Prⁱ, Ph, (CH₂)₂OH; R¹–R² = (CH₂)₅, (CH₂)₂O(CH₂)₂.



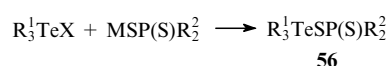
R¹ = Me, Ph; R² = Me, Et, Prⁱ, Ph.

Compounds **55** were also synthesised by the reaction of methoxytriorganyltelluranes with dialkyl dithiophosphates.¹²⁰



R¹ = Me, Ph; R² = Me, Prⁱ, Ph.

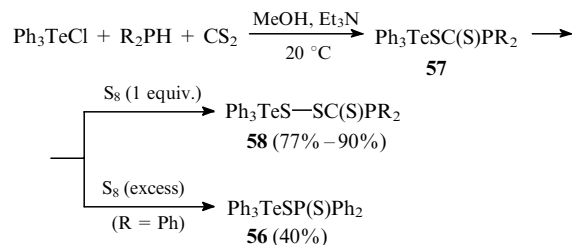
Dithiophosphinates **56** were prepared using a similar approach, *i.e.*, by the reaction of methoxytriorganyltelluranes with diorganyldithiophosphinic acid HSP(S)R₂ (Ref. 120) or the corresponding chlorides with sodium (ammonium) dithiophosphinates MSP(S)R₂ (Refs 120 and 121) (M = Na, NH₄).



X = OMe, Cl; M = H, Na, NH₄; R¹ = Me, Ph; R² = Me, Prⁱ, Ph.

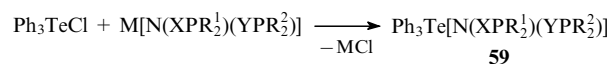
The phosphorus analogues of triorganyltelluronium dithiocarbamates **57** were formed in the reaction of triphenyl-

telluronium chloride with dialkylphosphines and carbon disulfide in the presence of triethylamine.¹²² Treatment of compounds **57** with equimolar amounts of sulfur was accompanied by the insertion of the sulfur atom into the Te—S bond resulting in derivatives **58**. At the same time, the reaction with excess sulfur in benzene at room temperature gave triphenyltelluronium diphenyldithiophosphinate **56**.¹²²



R = Prⁱ, Bn, Ph.

Triphenyltelluronium dichalcogenoimidodiphosphinates **59** were prepared by the exchange reaction of triphenyltelluronium chloride with tetraorganyl dichalcogenoimidodiphosphinates.^{121, 123}

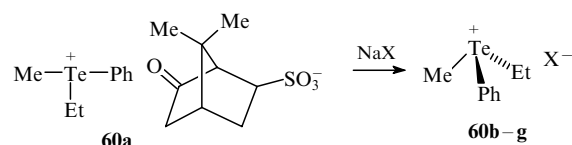


M = Na, K; X = O, S; R¹, R² = Me, Ph.

The salts **59** containing diphenylphosphine residues (R¹ = R² = Ph) were isolated from the reaction mixture and characterised by X-ray diffraction analysis. The existence of other salts in solution was established only by ¹H, ¹³C and ³¹P NMR spectroscopy.¹²³

The exchange reaction of methyl(phenyl)(*p*-tolyl) telluronium iodide (*p*-TolPhMeTe⁺I[−]) with silver D-α-bromocamphorsulfonate (D-BCS) and subsequent crystallisation resulted in compound [*p*-TolPhMeTe]⁺[D-BCS][−] with molecular rotation [M]₅₄₆₁¹⁸ = +262° in ethyl acetate (*cf.* Lowry, cited in Refs 9 and 10). This salt undergoes fast mutarotation in various solvents.

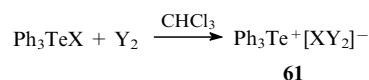
Enantiomerically pure telluronium salts **60a** containing the camphorsulfonate anion were prepared by fractional crystallisation of a diastereomeric mixture.^{54–56, 124} The absolute configurations of both isomers were established by X-ray diffraction analysis. Anion-exchange reactions of (*R*)-camphorsulfonate were used for the synthesis of the enantiomerically pure (*R*)-telluronium salts **60b–g** with various anions.^{54–56, 124}



X = ClO₄ (**b**), BF₄ (**c**), BPh₄ (**d**), *p*-ClC₆H₄SO₃ (**e**), 2,4,6-(O₂N)₃C₆H₂SO₃ (**f**), bornane-10-sulfonate (**g**).

In contrast to the methyl(phenyl)(*p*-tolyl)telluronium salt with the D-BCS anion described above, perchlorate **60b** is resistant against pyramidal inversion; no racemisation occurred even upon refluxing in methanol for 3 days.

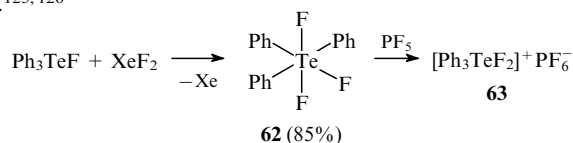
Some reactions of telluronium salts consist of conversions of the anionic fragments of the molecules. Thus reactions of triphenyltelluronium halides with halogens yield salts **61**, which contain the trihalide anion.¹⁰



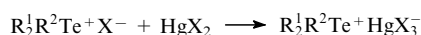
X = Cl; Y = Br, I; X, Y = Br, I.

When xenon difluoride was used instead of halogens, it was the tellurium atom that underwent the attack. For example, the

reaction of XeF_2 with triphenyltelluronium fluoride yielded *mer*- Ph_3TeF_3 **62**, a hexacoordinate tellurium derivative; this reacted with PF_5 to give the pentacoordinate tellurium derivative **63**.^{125, 126}



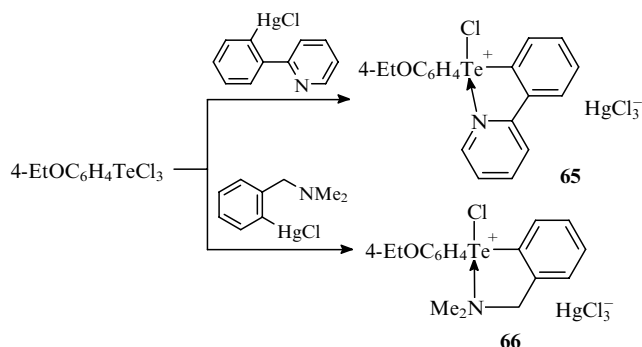
Telluronium salts form 1:1 adducts with mercuric halides^{9, 10, 127} to which the structures of triorganyltelluronium trihalomercurates **64** were ascribed based on the data from elemental analysis and IR spectroscopy.¹²⁷ However, according to X-ray structural data, the reaction product of Ph_3TeCl with HgCl_2 has a dimeric structure, *viz.*, $(\text{Ph}_3\text{Te}^+)_2[\text{Hg}_2\text{Cl}_6^{2-}]$.¹²⁸



64

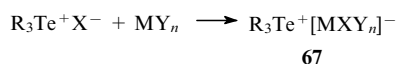
$\text{X} = \text{Cl}, \text{Br}, \text{I}; \text{R}^1 = \text{Ar}, \text{R}^2 = \text{Alk}, \text{Ar}.$

A new type of telluronium salts the tellurium atom in which is covalently bound to two organic radicals and one chlorine atom has been described.^{129–131} Reactions of aryltellurium trichlorides with arylmercury chlorides usually yield diaryltellurium dichlorides, Ar_2TeCl_2 .¹³² However, the reactions of *p*-ethoxyphenyltellurium trichloride with 2-[(2-pyridyl)phenyl]mercury chloride^{129, 130} and 2-dimethylaminobenzylmercury chloride¹³¹ unexpectedly gave telluronium salts **65** and **66**.



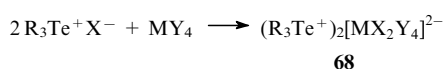
The molecules of salts **65** and **66** contain relatively short intramolecular coordination bonds $\text{N}-\text{Te}$. The length of this bond in salt **65** is equal to 2.31 Å,¹³⁰ whereas the sum of the van der Waals radii of tellurium and nitrogen is 3.65 Å.¹³³

Triorganyltelluronium halides form 1:1 adducts **67** with boron, aluminium, tin, arsenic and antimony halides and organytellurium trihalides, which have the structure of telluronium salts containing complex anions.^{9, 10, 24, 96}



$\text{X}, \text{Y} = \text{Hal}; \text{R} = \text{Me}, \text{Et}, \text{Ph}; \text{M} = \text{B}, \text{Al}, \text{As}, \text{Sb}, \text{Te}, \text{Sn}; n = 3, 4.$

As for the reactions of triorganyltelluronium halides with Lewis acids, for example SnBr_4 , SnCl_4 , TeBr_4 , TeCl_4 and TiBr_4 (molar ratio 2:1), they yield adducts **68**.^{24, 96}

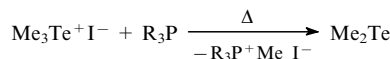


$\text{R} = \text{Et}, \text{Ph}; \text{X}, \text{Y} = \text{Cl}, \text{Br}; \text{M} = \text{Sn}, \text{Te}, \text{Ti}.$

Complexes of telluronium salts with organic donors are poorly studied. It is known¹⁰ that the triphenyltelluronium halides $\text{Ph}_3\text{Te}^+\text{X}^-$ ($\text{X} = \text{Cl}, \text{Br}$) yield 1:1 adducts with dihexyl sulfoxide. Similar products were formed upon reaction of

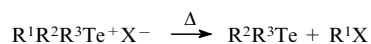
$\text{Ph}_3\text{Te}^+\text{Cl}^-$ with 1-R-4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thiones ($\text{R} = \text{Ph}, 4\text{-MeOC}_6\text{H}_4, 4\text{-O}_2\text{NC}_6\text{H}_4, \text{Bu}^n, \text{NH}_2$). It is noteworthy that it is the thionic form of the sulfur atom that is involved in the complexation.¹³⁴

Reaction of trimethyltelluronium iodide with phosphines occurs as demethylation of the original salt and results in high yield of dimethyl telluride.²⁶



$\text{R} = \text{Bu}^n, \text{Ph}.$

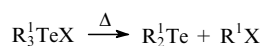
The dealkylation of telluronium salts is usually performed by heating in a solid state or in high-boiling solvents.^{9, 10, 49, 135}



$\text{X} = \text{Br}, \text{I}; \text{R}^1 = \text{Alk}; \text{R}^2, \text{R}^3 = \text{Alk}, \text{Ar}.$

In some cases, heating of salts was carried out in the presence of alkyl halide acceptors, *e.g.*, pyridine or dimethylaniline,^{9, 10} resulting in *N*-alkylpyridinium and alkyl dimethylphenylammonium salts, respectively. The thermal decomposition of telluronium salts has not been studied systematically so far. It was only noted¹⁰ that thermal stabilities of trimethyltelluronium salts depend on the anion and increase in the series $\text{F}^- < \text{Cl}^- < \text{SO}_4^{2-} < \text{Br}^- < \text{I}^-$; however, there are still no data on the effects of the leaving group, the anion and the solvent on the direction of dealkylation.

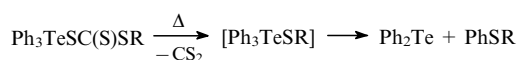
The thermal decomposition of triorganyltelluronium ethers¹¹⁰ and esters,⁹⁷ pseudohalides¹⁰ and xanthates¹¹⁰ as well as dithiocarbamates,¹¹⁷ -phosphates and -phosphinates¹²⁰ proceeds according to the same scheme as the decomposition of triorganyltelluronium halides. It is noteworthy that heating of $\text{Ph}_2\text{MeTeNCS}$ yielded Ph_2Te and MeSCN .¹⁰



$\text{R}^1 = \text{Me}; \text{X} = \text{OCOR}^2 (\text{R}^2 = \text{Me}, \text{CHCl}_2, \text{CCl}_3, \text{Ph}), \text{SP}(\text{S})\text{R}_2^2$
($\text{R}^2 = \text{Me}, \text{Pr}^i, \text{Ph}, \text{OMe}, \text{OEt}, \text{OPr}^i, \text{OPh}$);

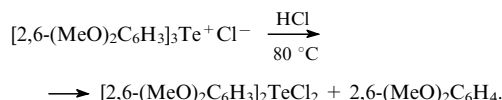
$\text{R}^1 = \text{Ph}; \text{X} = \text{OR}^2 (\text{R}^2 = \text{Me}, \text{Et}, \text{Pr}^i), \text{OCOR}^2 (\text{R}^2 = \text{Me}, \text{CHCl}_2, \text{CCl}_3, \text{Ph}), \text{CN}, \text{NCO}, \text{NCS}, \text{NCSe}, \text{SC}(\text{S})\text{NR}_2^2 (\text{R}^2 = \text{Me}, \text{Pr}^i, \text{Ph}), \text{SP}(\text{S})\text{R}_2^2 (\text{R}^2 = \text{Me}, \text{Pr}^i, \text{Ph}, \text{OPh}).$

The decomposition of triphenyltelluronium thioxanthates upon heating is somewhat different.¹¹⁰



$\text{R} = \text{Et}, \text{Pr}^i.$

Heating of tris(2,6-dimethoxyphenyl)telluronium chloride in 0.1 M HCl at 80 °C gave bis(2,6-dimethoxyphenyl)tellurium dichloride in 60% yield.¹⁵ Presumably, the thermolysis proceeded as follows:



No such conversion is reported for other telluronium salts.

In contrast to aryltellurium trihalides and diaryltellurium dihalides, which are converted into diaryl ditellurides and diaryl tellurides, respectively, under the action of sodium sulfide, heating of telluronium salts with Na_2S affords mixtures of tellurides and aromatic derivatives. The compositions of the latter depend on the structures of the original salts.^{9, 10}

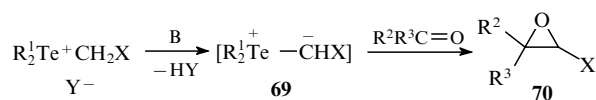
Other reactions of telluronium salts employed for the preparation of various classes of organic compounds are considered in the next Section.

IV. The use of telluronium salts in organic synthesis

Telluronium salts are widely used as precursors of non-stabilised and monostabilised telluronium ylides. The latter are prepared by treatment of the original salts with basic reagents and are introduced *in situ* into reactions with carbonyl compounds. Depending on the structure of the original salt, *i.e.*, the nature of the ylide generated, and the type of the carbonyl derivative, various classes of organic compounds are formed.^{7,8}

Diphenyltelluronium methylide **69** ($R^1 = \text{Ph}$, $X = \text{H}$) prepared from methyldiphenyltelluronium tetraphenylborate under the action of lithium 2,2,6,6-tetramethylpiperide (LiTMP) reacted with carbonyl compounds to give epoxides **70** ($R^1 = \text{Ph}$, $X = \text{H}$) in 55%–74% yields.¹⁰⁰ A similar reaction was used^{23,34} in the synthesis of α,β -unsaturated epoxides **70** ($X = \text{CH}=\text{CH}_2$). Dialkyltelluronium allylides **69** ($X = \text{CH}=\text{CH}_2$) were generated by treatment of triorganyltelluronium bromides with potassium *tert*-butoxide²³ or KOH.³⁴ The best results were achieved in reactions of the ylide prepared from allyl(diisobutyl)telluronium bromide with carbonyl compounds. The yields of vinyl epoxides did not depend on the nature of the dehydrobrominating reagent and amounted to 58%–98% for aromatic aldehydes; the yields are lower for aliphatic derivatives. Compounds **70** ($X = \text{CH}=\text{CH}_2$) are prepared as mixtures of *cis*- and *trans*-isomers, the former being slightly predominant.

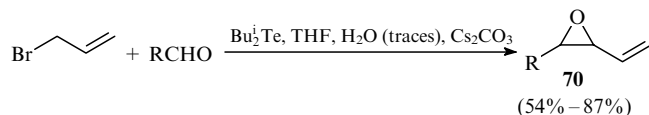
Trimethylsilylvinyl (**70**, $X = \text{CH}=\text{CHSiMe}_3$, yields 83%–89%⁴⁰) and trimethylsilylethynyl epoxides (**70**, $X = \text{C}\equiv\text{CSiMe}_3$, 80%–96%^{38,39}) were obtained in reactions of ylides **69** ($R^1 = \text{Bu}^i$; $X = \text{CH}=\text{CHSiMe}_3$, $\text{C}\equiv\text{CSiMe}_3$) with aldehydes and ketones. Ylides **69** were prepared by dehydrobromination of the corresponding telluronium salts under the action of LiTMP and used *in situ*. Trimethylsilylvinyl(or ethynyl) epoxides **70** are predominantly represented by *cis*-isomers.



B (base) = LiTMP, BuⁱOK, KOH, *etc.*

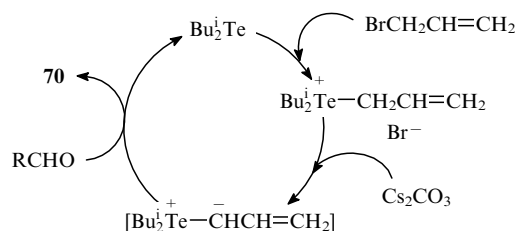
Y = BPh₄, Br; X = H, CH=CH₂, CH=CHSiMe₃, C≡CSiMe₃; R¹ = Buⁱ, Ph; R² = H, Ph; R³ = Me, n-C₅H₁₁, n-C₆H₁₃, n-C₉H₁₉, Cy, R_n⁴C₆H_{5-n} [R_n⁴ = H, 4-F, 2-Cl, 3-Cl, 4-Cl, 4-Br, 4-O₂N, 2-Me, 4-Me, 2,4,6-Me₃, 4-Ph, 2-MeO, 4-MeO, 3,4-(MeO)₂, 3,4-(OCH₂O), 6-Br-3,4-(OCH₂O)], 2-Py, 3-Py, 1-naphthyl, 2-naphthyl; R²–R³ = (CH₂)₅.

Vinyl derivatives **70** ($X = \text{CH}=\text{CH}_2$) were synthesised by catalytic epoxidation without preliminary preparation of telluronium salts.³³ Allyl bromides reacted with aldehydes in the presence of catalytic amounts of diisobutyl telluride (20 mol.%) at 50 °C.

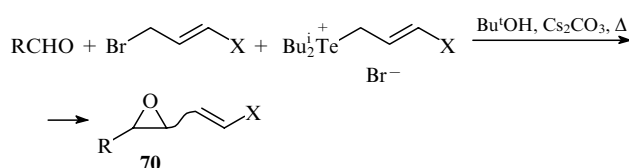


R = Cy, 4-XC₆H₄ (X = H, F, Cl, Br, NO₂, Ph), 2-naphthyl, 2-Py.

The sequence of steps resulting in epoxides **70** can be presented as a catalytic cycle. The reaction of telluride with allyl bromide yields a telluronium salt; treatment of the latter with Cs₂CO₃ leads to the generation of diisobutyl allylide, which reacts with the aldehyde to give the epoxide and Bu₂ⁱTe.

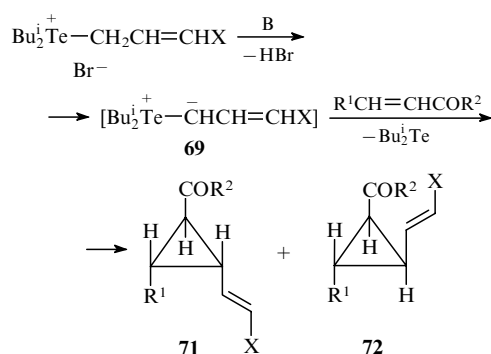


A more efficient (in comparison with diisobutyl telluride) catalyst has been proposed.¹³⁶ Vinyl epoxides **70** ($X = \text{CH}=\text{CH}_2$) were prepared by refluxing a mixture of an aldehyde, allyl bromide and catalytic amounts of a telluronium salt in the presence of solid Cs₂CO₃. Allyl(diisobutyl)telluronium bromide proved to be the catalyst of choice; the amount required was 10 times smaller (2 mol.%) than that of diisobutyl telluride (20 mol.%). However, this reaction is not stereoselective (the *cis,trans*-isomer ratio is ~1 : 1).



X = H: R = 4-ClC₆H₄; X = SiMe₃: R = n-C₉H₁₉, Cy, YC₆H₄ (Y = H, 4-Cl, 2-Cl, 4-O₂N, 4-Me), 2-naphthyl.

Telluronium ylides of the type **69** proved to be convenient synthons for the preparation of substituted cyclopropanes. Trimethylsilylvinylcyclopropanes **71** and **72** ($X = \text{SiMe}_3$, R¹ = OMe, OEt) were synthesised for the first time in >90% yields by the reaction of diisobutyltelluronium allylide **69** ($X = \text{SiMe}_3$), generated by deprotonation of the corresponding telluronium salt under the action of LiTMP, with α,β -unsaturated esters.⁴¹ The reactions of ylides **69** ($X = \text{SiMe}_3$) with β -aryl-substituted esters are characterised by high stereoselectivities and gave exclusively alkyl *trans*-2-trimethylsilylvinyl-*trans*-3-substituted cyclopropane carboxylates **71**. Reactions with methyl *trans*-but-2-enoate and methyl methacrylate are less stereoselective: mixtures of the isomers **71** and **72** were formed in 1.5 : 1 and 1 : 1 ratios, respectively.⁴¹ Later, this reaction was extended to other ylides of the type **69** ($X = \text{H}$,^{137,138} Me,¹³⁷ SiMe₃^{137–139}) and α,β -unsaturated esters^{137–139} and amides.^{137,138} Alkali metal bis(trimethylsilylamides), MN(SiMe₃)₂ (M = Na, K),¹³⁷ lithium diisopropylamide (LDA)¹³⁸ and LiTMP¹³⁹ were used as the bases.



B = MN(SiMe₃)₂ (M = Na, K), LDA, LiTMP;

X = H, Me, SiMe₃;

R¹ = Me, 2-furyl, R³C₆H₄ (R³ = H, 4-F, 4-Me, 2-MeO, 4-MeO);

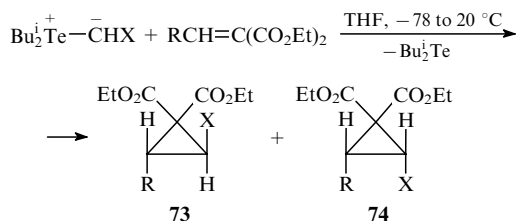
R² = OMe, OEt, N(CH₂)₄, N(CH₂)₅.

All the reactions give high yields; the stereochemistry of the reaction product is determined primarily by the nature of the base. *trans,trans*-Isomers **71** are formed exclusively in the presence of lithium cations. In other cases, the stereoselectivity of the reaction changes towards the predominant formation of *trans,cis*-isomers **72**. By varying the nature of the base, the ratio of the isomers **71**:**72** can be changed from 1:99 to 99:1. Thus the **71**:**72** isomer ratio in the reaction of diisobutyltelluronium salt ($X = \text{SiMe}_3$) with methyl cinnamate under the action of $\text{KN}(\text{SiMe}_3)_2$ was <1:99, whereas that in the presence of the $\text{LiBr}-\text{NaN}(\text{SiMe}_3)_2$ system as a base was >99:1.¹³⁷ According to the reported data,^{137, 138} the effect of the lithium cation is determined by its chelation with the carbonyl oxygen atom and the ylide carbanion and formation of a stable six-membered ring. The addition to the reaction mixture of hexamethylphosphoramide (HMPA) able to coordinate the lithium cation and to inhibit the formation of lithium chelates resulted in the formation of *trans,cis*-isomers **72** in good yields and with high selectivity.¹³⁸

The reaction of ylide **69** ($X = \text{SiMe}_3$) with diethyl fumarate and dimethyl maleate also resulted in isomers **71** ($R^1 = \text{CO}_2\text{Et}$, $R^2 = \text{Et}$; $R^1 = \text{CO}_2\text{Me}$, $R^2 = \text{Me}$).⁴¹

Ylide **69** ($X = \text{SiMe}_3$) generated from the corresponding telluronium salt under the action of LiTMP ¹³⁹ was introduced into the reaction with (–)-8-phenylmenthyl esters of α,β -unsaturated acids. This resulted in the formation of *trans*-2-trimethylsilylvinyl-*trans*-3-substituted cyclopropyl carboxylates in high yields and with high diastereoselectivities.

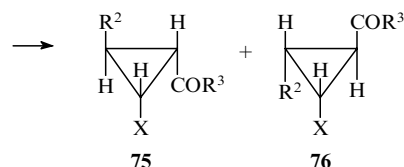
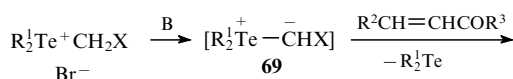
Diisobutyltelluronium ylides **69** generated by deprotonation of telluronium salts with potassium (or sodium) bis(trimethylsilylamide) reacted smoothly with diethylalkylidene- and arylmethylidenemalonates to give vinylcyclopropane-1,1-dicarboxylates **73** and **74** in high yields (81%–93%) and with high *trans*-selectivities (the **73**:**74** ratio was in the range from 71:29 to 98:2).¹⁴⁰ The addition of lithium bromide to the reaction mixture increased slightly the percentage of *trans*-isomer **73**.



$X = \text{CH}=\text{CHSiMe}_3$; $R = n\text{-C}_6\text{H}_{13}$, $\text{CH}=\text{CHPh}$, Ph , 4-MeC₆H₄;
 $R = \text{Ph}$: $X = \text{CH}=\text{CH}_2$, $\text{CH}=\text{CHMe}$, Ph .

Cyclopropanes of yet another type are formed in the reaction of telluronium ylides **69** with α,β -unsaturated ketones. The ylides generated by treatment of the corresponding telluronium salts with solid NaOH in THF,⁴² $\text{KN}(\text{SiMe}_3)_2$ (for $X = \text{Ar}$)¹⁴¹ or Cs_2CO_3 in 1,2-dimethoxyethane (DME) containing traces of water,⁴⁵ $\text{KN}(\text{SiMe}_3)_2$,¹⁴¹ Bu^tOK ¹⁴¹ (for $X = \text{CH}=\text{CHR}$ where $R = \text{SiMe}_3$, H , Me , Ph) gave rise to cyclopropyl ketones **75** and **76** (yields 52%–95%). This reaction is highly stereoselective: ketones **75** are the main products (>90% in the mixture) where the keto group and the X fragment lie on the same side relative to the plane of the cyclopropane ring.

In contrast to α,β -unsaturated esters and amides, the stereochemistry of reactions of telluronium ylides with α,β -unsaturated ketones does not depend on the presence of lithium cation. Moreover, the presence of lithium salts in reaction mixtures decreases the yields of cyclopropanes and favours the formation of epoxides.^{45, 141} The use of α,β -unsaturated aldehydes in such reactions results in complex mixtures of reaction products.⁴⁵

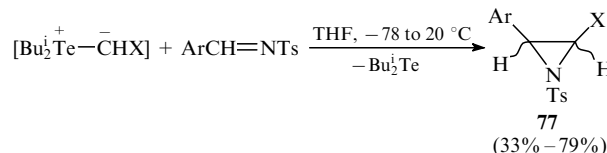


$X = \text{CH}=\text{CH}_2$, $\text{CH}=\text{CHSiMe}_3$, $\text{CH}=\text{CHMe}$, $\text{CH}=\text{CHPh}$, Ph , 4-ClC₆H₄; $R^1 = \text{Bu}^n$, Bu^t ; $R^2 = \text{R}^4\text{C}_6\text{H}_4$ ($R^4 = \text{H}$, 4-Cl, 4-Br, 4-Me, 4-Me₂N, 3-O₂N, 4-O₂N); $R^3 = \text{Bu}^t$, Ph , $\text{CH}=\text{CHPh}$.

It is of note that triphenylarsonium allylides react with α,β -unsaturated ketones to give high yields of cyclopropyl ketones with an opposite configuration of substituents in comparison with the products generated from telluronium ylides.¹⁴¹

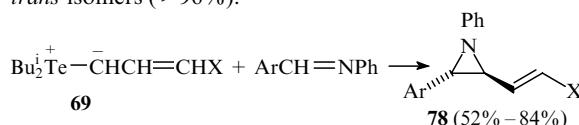
A one-pot synthesis of cyclopropanes without preliminary generation of telluronium ylides has been developed for reactions with chalcones.⁴⁵ This approach is based on the use of a biphasic system Cs_2CO_3 –THF (with traces of water) in the presence of catalytic amounts of diisobutyl telluride (20 mol.%).

Similar to sulfonium ylides, telluronium ylides react with *N*-sulfonylimines to give aziridines **77**.^{142, 143} Ylides **69** ($X = \text{CH}=\text{CHR}$,¹⁴² $\text{C}\equiv\text{CSiMe}_3$ ¹⁴³) generated from the corresponding telluronium salts under the action of potassium bis(trimethylsilylamide) in THF at low temperature react with *N*-tosylimines of aromatic aldehydes to give vinyl(or ethynyl)aziridines **77** with low stereoselectivity (the *trans*:*cis* ratio is 33:67–58:42).^{142, 143}



$\text{Ar} = 4\text{-ClC}_6\text{H}_4$; $X = \text{CH}=\text{CH}_2$, $\text{CH}=\text{CHSiMe}_3$,¹⁴²
 $\text{Ar} = \text{Ph}$; $X = \text{C}\equiv\text{CSiMe}_3$.¹⁴³

Sulfonium allylides afford aziridines only in reactions with arylimines activated by *N*-sulfonyl¹⁴² or *N*-diphenylphosphinoyl groups,¹⁴⁴ while more reactive telluronium allylides enter into aziridination reactions with less reactive imines. Thus treatment of telluronium allylides **69** ($X = \text{SiMe}_3$) prepared by deprotonation of the telluronium salt with $\text{LiN}(\text{SiMe}_3)_2$ in the presence of HMPA (toluene, –78 °C) with aryl imines gave aziridines **78**.¹⁴⁵ This reaction was highly stereoselective and yielded almost exclusively *trans*-isomers (>96%).

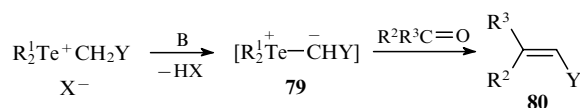


$X = \text{H}$, $\text{Ar} = \text{Ph}$; $X = \text{SiMe}_3$; $\text{Ar} = \text{Ph}$, 4-ClC₆H₄, 4-CF₃C₆H₄, 4-MeOC₆H₄, 2-MeOC₆H₄.

The reaction of diisobutylallylide **69** ($X = \text{H}$) with benzylidenedianiline results in aziridine **78** ($X = \text{H}$), however, in a lower yield (37%) and with lower stereoselectivity (the *trans*:*cis* ratio is 80:20) than in the case of the trimethylsilyl analogue **69** ($X = \text{SiMe}_3$).¹⁴⁵

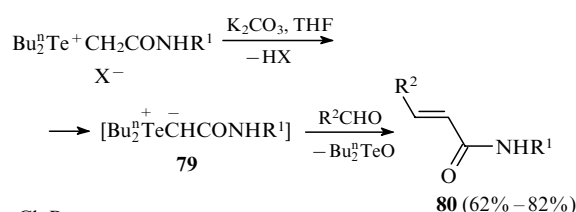
In contrast to their sulfonium analogues, stabilised telluronium ylides containing electronegative substituents at the anionic carbon atom react with aldehydes and ketones to give alkenes.^{22, 29, 30} For the first time this was demonstrated in the example of dialkyltelluronium ethoxycarbonylmethylides **79** ($R^1 = \text{Me}$, Bu^n ; $Y = \text{CO}_2\text{Et}$).²² Ylides **79** were generated from (ethoxycarbonylmethyl)dialkyltelluronium bromides under the action of potassium *tert*-butoxide and coupled *in situ* with various carbonyl compounds. This resulted in α,β -unsaturated esters **80** ($Y = \text{CO}_2\text{Et}$, yields 52%–90%), predominantly in the *E*-form.²² Later, dibutyltelluronium methylide derivatives Bu_2TeCHY ($Y = \text{COPh}$,²⁹ CN ,²⁹ CONHBu^t , see Ref. 30) were employed in

a similar reaction. The ylides were generated by deprotonation of telluronium halides under the action of Bu^tOK ²⁹ or NaH ;³⁰ their *in situ* reactions with aldehydes and ketones gave good yields (36%–83% for $\text{Y} = \text{CN}$, 74%–81% for $\text{Y} = \text{COPh}$, and 40%–71% for $\text{Y} = \text{CONHBu}^i$) of alkenes **80** with *E*-configurations of the double bonds.



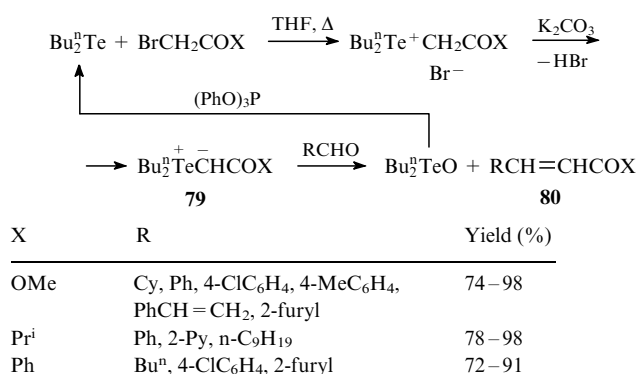
$\text{X} = \text{Br}, \text{Cl}; \text{Y} = \text{CN}, \text{CO}_2\text{Et}, \text{COPh}, \text{CONHBu}^i$;
 $\text{R}^1 = \text{Me}, \text{Bu}^n; \text{R}^2, \text{R}^3 = \text{Alk}, \text{Ar}$.

The reaction of dibutyltelluronium alkylcarbamoyl methylides **79** ($\text{Y} = \text{CONHR}$) prepared by treatment of (alkylcarbamoylmethyl)dibutyltelluronium halides with potassium carbonate in THF, with aldehydes gave α,β -unsaturated amides **80** ($\text{Y} = \text{CONHR}$) with high *E*-stereoselectivity and in good yields.¹⁴⁶



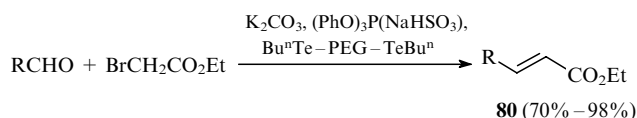
$\text{X} = \text{Cl}, \text{Br}$;
 $\text{R}^1 = \text{Pr}^i, \text{Bu}^i; \text{R}^2 = 4\text{-R}^3\text{C}_6\text{H}_4$ ($\text{R}^3 = \text{H}, \text{Cl}, \text{Me}, \text{MeO}$), $\text{CH}=\text{CHPh}$.

The synthesis of alkenes **80** from α -bromo esters or α -bromo ketones in the presence of dibutyl telluride can be carried out as a cyclic catalytic process using triphenyl phosphite as a reducing agent for the liberating Bu_2^+TeO .³¹ Catalytic amounts of dibutyl telluride react with α -bromo esters or ketones to give telluronium salts, which are converted into ylides under conditions of phase-transfer catalysis (solid K_2CO_3 , THF containing traces of water). The reaction of the ylide with aldehydes occurs in the presence of $(\text{PhO})_3\text{P}$ and yields alkenes and Bu_2^+TeO . The latter is reduced to the original dibutyl telluride, which again reacts with the bromo derivatives. Na_2SO_3 , NaHSO_3 and $\text{Na}_2\text{S}_2\text{O}_5$ can also be used as reducing agents for dibutyltellurium oxide.³¹



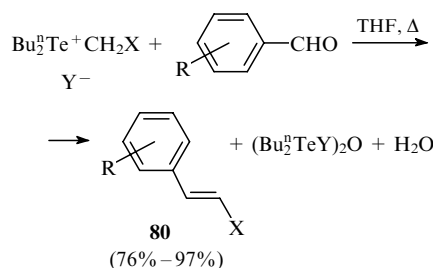
This catalytic reaction requires 20 mol.% of dibutyl telluride. The yields of alkenes decreased with a decrease in the amount of the catalyst even with the increase in the reaction time. Poly(ethylene glycol) (PEG) telluride, $\text{Bu}^n\text{Te}-\text{PEG}-\text{TeBu}^n$ (Refs 48 and 147), manifested higher catalytic activity in the olefination reaction. It was prepared by the reaction of *O*-tosyl-PEG with Bu^nTeLi (yield 83%).^{48, 147} Reactions of aromatic and aliphatic aldehydes with ethyl bromoacetate in THF or toluene in the presence of potassium carbonate as a base, $(\text{PhO})_3\text{P}$ or NaHSO_3 as a reducing agent and only 2 mol.% of $\text{Bu}^n\text{Te}-\text{PEG}-\text{TeBu}^n$,

give α,β -unsaturated esters **80**, mainly with the *E*-configured double bond (> 99% in the mixture).



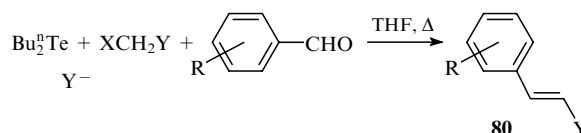
$\text{R} = n\text{-C}_9\text{H}_{19}, \text{Cy}, \text{PhCH}=\text{CH}, 4\text{-XC}_6\text{H}_4$ ($\text{X} = \text{H}, \text{Cl}, \text{NO}_2, \text{CF}_3, \text{Me}, \text{MeO}$), 2-furyl.

Due to relatively low energy and high polarity of the $\text{Te}-\text{C}$ bonds, telluronium salts enter into the reactions that do not occur with their sulfur or selenium analogues. Thus coupling of telluronium salts with aromatic aldehydes to give alkenes without the intermediate formation of ylides occurs upon refluxing in THF.^{27, 29} In some cases, the yields of *E*-alkenes **80** are even higher than the yields attained in reactions with pre-formed ylides.



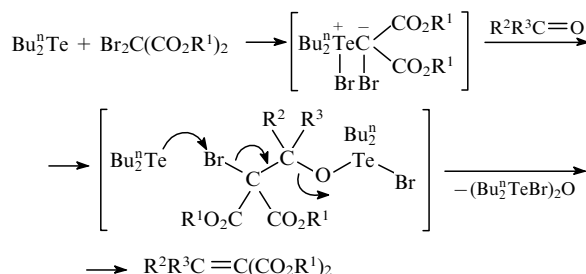
$\text{Y} = \text{Cl}, \text{Br}; \text{X} = \text{CN}, \text{CO}_2\text{Me}, \text{COPh}; \text{R} = 4\text{-Cl}, 4\text{-Br}, 3\text{-NO}_2, 4\text{-NO}_2$.

As telluronium salts are easily formed upon reactions of dibutyl telluride with α -bromo esters (or ketones) or chloroacetonitrile, the synthesis of alkenes **80** can be carried out by refluxing of equimolar amounts of dibutyl telluride, the halogen-containing substrate and the aldehyde in THF.²⁷ The yields of alkenes **80** are only slightly lower than with the use of the *in situ* prepared telluronium salts.



$\text{X} = \text{Cl}, \text{Br}; \text{Y} = \text{CN}, \text{COPh}, \text{CO}_2\text{Me}, \text{CO}_2\text{Et}$;
 $\text{R} = 4\text{-Cl}, 4\text{-Br}, 3\text{-NO}_2, 4\text{-NO}_2$.

The reaction of dibromomalonates with carbonyl compounds in the presence of dibutyl telluride (2 equiv.) is a convenient alternative to the Knoevenagel reaction.³⁷

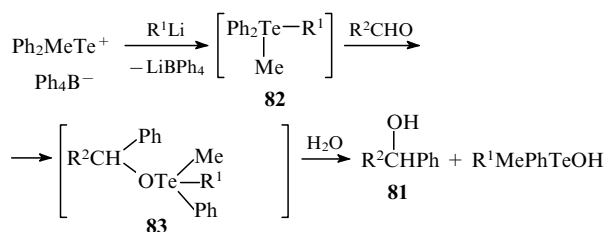


$\text{R}^1 = \text{Me}, \text{R}^2 = \text{H}, \text{R}^3 = \text{Bu}^i; \text{R}^1 = \text{Me}, \text{R}^2 = \text{R}^3 = (\text{CH}_2)_5$;
 $\text{R}^1 = \text{Et}, \text{R}^2 = \text{H}; \text{R}^3 = n\text{-C}_9\text{H}_{19}, \text{R}^4\text{C}_6\text{H}_4$ ($\text{R}^4 = \text{H}, 2\text{-Cl}, 4\text{-Cl}, 4\text{-NO}_2, 4\text{-MeO}$), 2-Py, 2-(3-bromothieryl).

This reaction proceeds under mild conditions (heating of the reaction mixture in THF at 50 °C) and results in alkylidene- and arylmethylidene α,β -unsaturated malonates in 84%–98% yields. A tentative mechanism of the reaction is reported.³⁷

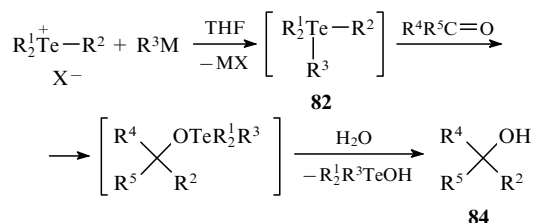
It was already mentioned that the deprotonation of methyl-diphenyltelluronium tetraphenylborate under the action of

LiTMP gave the ylide $[\text{Ph}_2\text{Te}^+\text{H}_2\text{C}^-]$ which reacted with carbonyl compounds to yield epoxides of the type **70**.¹⁰⁰ The reaction of the same salt with organolithium compounds and subsequent addition of aldehydes to the reaction mixture gave quite different results, *viz.*, secondary alcohols **81** (yields 55%–85%) were formed as the reaction products.⁹⁹ This can be attributed to the formation, from original telluronium salts and organolithium compounds, of unstable tetraorganyltelluranes **82** [similar to the formation of thermostable Ph_4Te from Ph_3TeCl and PhLi or thermally unstable tetrabutyltellurane Bu_4Te from Bu_3TeI and Bu^nLi (Refs 9, 10)]. The reactions of telluranes **82** with carbonyl compounds are accompanied by migration of one of the radicals bound to the tellurium atom to the carbonyl carbon atom resulting in intermediates **83**. In the case of methylphenyltelluronium tetraphenylborate, this reaction yields arylbenzyl alcohols **81** due to the preferential migration of the phenyl radical.⁹⁹



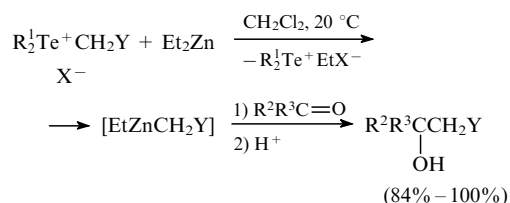
$\text{R}^1 = \text{Me}, \text{Bu}, \text{Bu}^i, \text{Ph}; \text{R}^2 = 4\text{-R}^3\text{C}_6\text{H}_4 \text{ (R}^3 = \text{H, Br, Cl, F, Me, MeO, 2-naphthyl, 2-Py.)}$

The Bn and $\text{CH}_2\text{C}\equiv\text{CSiMe}_3$ groups in tetraorganyltelluranes **82** ($\text{R}^1 = \text{Bn}$,³⁵ $\text{CH}_2\text{C}\equiv\text{CSiMe}_3$,³⁹) formed upon reaction of the corresponding telluronium salts with organolithium (or -magnesium) derivatives migrate to the carbonyl carbon atom. This yields alcohols **84** containing a benzyl³⁵ or a trimethylsilyl ethynyl-methyl³⁹ group at the α -carbon atom. A large series of β -hydroxy nitriles **84** ($\text{R}^2 = \text{CH}_2\text{CN}$) were synthesised from dibutyl(cyano-methyl)telluronium chloride using a similar approach.³⁶



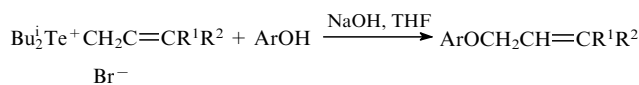
$\text{X} = \text{Cl, Br}; \text{R}^1 = \text{Bu}^n, \text{Bu}^i; \text{R}^2 = \text{Bn}, \text{CH}_2\text{C}\equiv\text{CSiMe}_3, \text{CH}_2\text{CN};$
 $\text{R}^3\text{M} = \text{MeLi}, \text{Bu}^n\text{Li}, \text{Bu}^i\text{Li}, \text{PhLi}, 4\text{-MeC}_6\text{H}_4\text{Li}, \text{MeMgI};$
 $\text{R}^4 = \text{H, Me, Ph}; \text{R}^5 = \text{Alk, Ar, Het}; \text{R}^4-\text{R}^5 = (\text{CH}_2)_5, (\text{CH}_2)_3\text{CH}=\text{CH}.$

Yet another example of the use of telluronium salts in the synthesis of alcohols is the tellurium–zinc exchange reaction between telluronium salts and diethylzinc. This reaction proceeds under mild conditions (in CH_2Cl_2 at room temperature).¹⁴⁸ The diorganylzinc derivatives formed *in situ* reacted with carbonyl compounds (aldehydes, ketones, phenacyl chlorides) and afforded secondary and tertiary alcohols in high yields after hydrolysis.¹⁴⁸



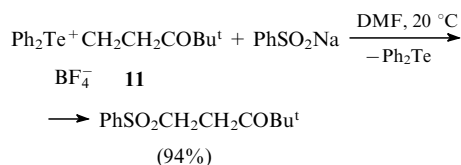
$\text{X} = \text{Cl, Br, I, BPh}_4; \text{Y} = \text{CH}=\text{CH}_2, \text{C}\equiv\text{CSiMe}_3, \text{Ph};$
 $\text{R}^1 = \text{Bu}^n, \text{Bu}^i; \text{R}^2 = \text{H, Ph}; \text{R}^3 = n\text{-C}_{11}\text{H}_{23}, \text{CH}_2\text{Cl}, \text{CH}=\text{CHPh},$
 $\text{Ph}, 4\text{-ClC}_6\text{H}_4.$

Allyl(dialkyl)telluronium bromides are efficient reagents for the allylation of phenols. The reactions of these salts with phenols in the presence of solid NaOH in THF yielded allyl aryl ethers (yields 81%–95%).⁴³



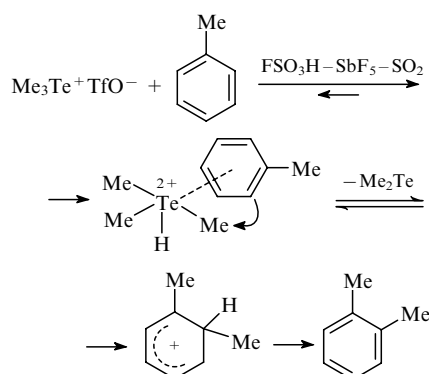
$\text{R}^1 = \text{R}^2 = \text{H, Me}; \text{R}^1 = \text{H}, \text{R}^2 = 4\text{-ClC}_6\text{H}_4; \text{Ar} = \text{Ph}, \text{R}^3\text{C}_6\text{H}_4$
 $(\text{R}^3 = 4\text{-Cl, 2-Me, 4-Bu}^i), 1\text{-naphthyl, 2-naphthyl}.$

The reaction of telluronium salt **11** with sodium phenylsulfinate yielded the corresponding alkyl phenyl sulfone.¹⁷



However, in contrast to their iodonium [*e.g.*, $\text{PhI}^+\text{CH}=\text{CR}^1\text{R}^2\text{BF}_4^-$ (Ref. 149)] and bismuthonium [$\text{Ph}_3\text{Bi}^+\text{CH}_2\text{CORBF}_4^-$ (Ref. 150)] analogues, telluronium salts **10** and **14** do not enter into this reaction. It was thus concluded¹⁷ that the nucleofugicity of the diphenyltelluronium group is lower than those of the phenyliodonium and triphenylbismuthonium groups.

In the presence of a superacid (*e.g.*, the $\text{FSO}_3\text{H}-\text{SbF}_5-\text{SO}_2$ system), trimethyltelluronium trifluoromethanesulfonate alkylated toluene under very mild conditions (-78°C) resulting in the predominant formation of *o*-xylene (yield 25%); *m*- and *p*-isomers were formed as minor products (93 : 6 : 1).⁶⁷



Dibenzotellurophenonium trifluoromethanesulfonate **18**, like its selenium and sulfuric analogues, can serve as a trifluoromethylating reagent with respect to various enolates including trimethylsilyl enolates, anilines and sodium alkanethiolates. Their trifluoromethylating activities increase in the following order: $\text{Te} < \text{Se} < \text{S}$.⁶⁹ Trifluoromethyldibenzotellurophenonium-3-sulfonate¹⁵¹ is the most convenient trifluoromethylating reagent of this class as regards the ease of isolation of the reaction products, since dibenzotellurophene-3-sulfonic acid formed is readily soluble in water.

Among other important practical applications of telluronium salts, special mention should be made of the use of triphenyltelluronium tetrafluoroborate and phosphate as catalysts of liquid-phase oxidation of alkenes.¹⁵²

V. Crystal structures of telluronium salts

The molecular and crystal structures of over 60 telluronium salts were studied using X-ray diffraction analysis. The $\text{Te}-\text{C}$ and $\text{Te}-\text{heteroatom}$ bond lengths, $\text{C}-\text{Te}-\text{C}$ bond angles, coordination numbers (CN) of tellurium atoms and references are given in Table 1, the data being sorted in accordance with the type of the anion X .

Table 1. Bond lengths and bond angles in triorganyltelluronium salts $R^1R^2R^3Te^+X^-$.

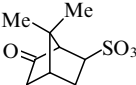
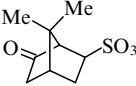
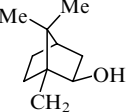
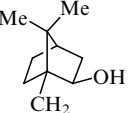
Example	X	R^1	R^2	R^3	Bond lengths /Å		Bond angle C–Te–C /deg	CN of Te atom	Ref.
					Te–C	Te–heteroatom			
85a	BPh ₄	Me	Me	Me	2.113–2.163		90.4–93.0	3	10
85b	BPh ₄	Me	Ph	Ph	2.123–2.132		91.5–97.7	3	46
85c	BPh ₄	Bu	Bu ^t O ₂ CCH ₂	PhO(CH ₂) ₃	2.098–2.205	2.926 (Te⋯OPh), 3.282 (Te⋯O=COBu ^t)	88.7–93.4	4	48
30	ClO ₄	Me	Bu ⁿ	2-(PhN=CH)C ₆ H ₄	2.121–2.148	2.75 (Te⋯N), 3.31, 3.448, 3.558 (Te⋯O)	92.5–97.8	4	72, 73
64a	HgCl ₃ ^a	Cl	4-EtOC ₆ H ₄	2-(2-Py)C ₆ H ₄	2.05–2.11	2.43 (Te–Cl), 2.31 (Te⋯N)	101.0	4	130
86	B(C ₆ F ₅) ₄	Ph	Ph	Ph	2.103–2.117	3.363 (Te⋯F)	97.1–99.2	3	86
10a	BF ₄	Bu ^t COCH ₂	Ph	Ph	2.109–2.130	2.892 (Te⋯O), 3.065 (Te⋯F)	94.8–98.9	4(5)	17
87a	SbF ₆	Mes	Mes	Mes	2.131–2.137		104.4–109.3	3	81
87b	SbF ₆ ^b	Mes	Mes	Br	2.116–2.139	2.479, 2.509 (Te–Br), 2.62, 2.66, 2.93, 3.24 (Te⋯F)	106.4–106.8	4	81
88	AuCl ₄	Ph	Ph	Ph	2.112–2.122	3.064–3.400 (Te⋯Cl)	96.5–98.7	6	106
89	PtCl ₆	Ph	Ph	Ph	2.095–2.131	3.331–3.843 (Te⋯Cl)	93.5–100.9	4	106
90	IrCl ₆	Ph	Ph	Ph	2.094–2.139	3.13–3.743 (Te⋯Cl)	94.1–100.9	4	106
91	Hg ₂ Cl ₆	Ph	Ph	Ph	2.097–2.119	3.337, 3.489, 3.574 (Te⋯Cl)	94.4–101.3	6	128
92	TeCl ₆	Ph	Ph	Ph	2.120	3.527 (Te⋯Cl)	97.72	6	153
93	MeTeI ₄	Me	Me	Me	2.007–2.127	3.84, 3.88, 3.97, 4.00 (Te⋯I)	90.7–98.6	3(4)	10
94	Ag ₄ I ₅ ^c	Et	Et	Et	2.11–2.16	3.822, 4.051, 4.166, 4.231 (Te⋯I)	91.0–96.0	3(4)	154
(R)-60a		Me	Et	Ph	2.117–2.170	2.88, 3.05 (Te⋯O)	93.7–96.6	5	54–56, 124
(S)-60a		Me	Et	Ph	2.09–2.200	3.00, 3.01, 3.03 (Te⋯O)	92.0–100.8	6	56, 124
95	OTf	C ₆ F ₅	C ₆ F ₅	C ₆ F ₅	2.062–2.142	2.61–2.68 (Te⋯O)	91.1–106.1	4	82
1a	Cl	Me	Me	Me	2.108–2.114	3.318 (Te⋯Cl)	93.9–96.2	5	28
1b	Cl	Et	Et	Et	2.15	3.448 (Te⋯Cl)	85.8	6	25
(S)-32a	Cl	Me	Et		2.082–2.165	see ^d	92.9–96.5	—	75
(R)-32a	Cl	Et	Me		2.092–2.150	see ^d	92.0–96.5	—	75

Table 1 (continued).

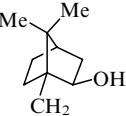
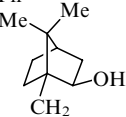
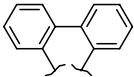
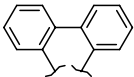
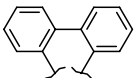
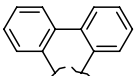
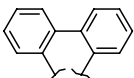
Example	X	R ¹	R ²	R ³	Bond lengths / Å		Bond angle C–Te–C /deg	CN of Te atom	Ref.
					Te–C	Te–heteroatom			
32b	Cl	Et	PhCH ₂		2.132–2.161	3.153 (Te⋯Cl), 2.841 (Te⋯O)	80.1–95.8	5	74
1c	Cl	Ph	Ph	Ph	2.115–2.144	3.142, 3.234 (Te⋯Cl)	93.4–97.1	5	28, 155
1d	Cl	C ₆ F ₅	C ₆ F ₅	C ₆ F ₅	2.108–2.207	2.670, 3.47 (Te⋯Cl)	87.8–102.3	5	156
1e	Br	Et	Et	Et	2.14	3.564 (Te⋯Br)	89.3	6	24
1f	Br	Bu ⁱ	Bu ⁱ	Ph	2.113–2.122	3.293 (Te⋯Br)	92.8–93.7	4	46
32c	Br	Me	PhCH ₂		2.122–2.161	see ^d	93.6–97.4	5	47
1g	Br ^e	C ₆ F ₅	C ₆ F ₅	C ₆ F ₅	2.13–2.21	2.834, 3.570 (Te⋯Br)	89.2–102.0	5	82
1h	I	Me	Me	Me	2.120–2.129	3.698, 3.731, 3.813 (Te⋯I)	92.2–95.7	6	28
1i	I	Et	Et	Et	2.11–2.16	3.813, 3.861, 4.494 (Te⋯I)	96.6–101.2	5	25
1j	I	Me	Me	Ph	2.128–2.132	3.659, 3.758 (Te⋯I)	93.7–95.4	5	57
1k	I ^f	Me	Me	C≡CTeMe	2.069–2.136	3.58, 3.76 (Te⋯I), 3.45, 3.70 (Te ⁺ ⋯I), 3.77 (Te ⁺ ⋯Te)	92.07–97.09	6	65
1l	I	Mes	Mes	Mes	2.134–2.148	4.128 (Te⋯I)	103.7–110.5	3	13
96	ONO ₂	Me	Me	Me	2.107–2.112	3.002, 3.018, 3.138 (Te⋯O)	94.6–95.7	6	28
42a	OCOPh	2-PhC ₆ H ₄			2.110–2.133	2.469 (Te–O), 3.182 (Te⋯O=C)	80.9–99.3	5	83
42b	OCOMe	2-PhC ₆ H ₄			2.116–2.153	2.491 (Te–O), 3.181 (Te⋯O=C)	80.3–97.2	6	83
42c	OPh	2-PhC ₆ H ₄			2.104–2.175	2.294 (Te–O)	79.7–103.9	4	84
42d	OC ₆ H ₄ NO ₂ -4	2-PhC ₆ H ₄			2.102–2.150	2.461 (Te–O)	80.2–99.1	4	85
42e	OC ₆ H ₂ Cl ₃ -2,4,6	2-PhC ₆ H ₄			2.108–2.159	2.762 (Te–O), 2.787 (Te–O)	81.3–96.5	5	85

Table 1 (continued).

Example	X	R ¹	R ²	R ³	Bond lengths /Å		Bond angle C—Te—C /deg	CN of Te atom	Ref.
					Te—C	Te—heteroatom			
50c	TeC ₆ H ₄ Me-4	Ph	Ph	Ph	2.132–2.187	3.32, 3.38, 3.53, 3.60 (Te...Te)	91.1–96.3	5	113
50c	TeC ₆ H ₄ OMe-4	Ph	Ph	Ph	2.122–2.171	3.40, 3.44, 3.45, 3.48 (Te...Te)	90.9–98.5	5	14
50b	SeC ₆ H ₄ Me-4	Ph	Ph	Ph	2.119–2.179	3.15, 3.28, 3.31, 3.34 (Te...Se)	90.8–94.9	5	113
50a	SC ₆ H ₄ Cl-4	Ph	Ph	Ph	2.120–2.170	3.02–3.64 (Te...S)	90.8–96.7	5	112
97	OC ₆ H ₂ (NO ₂) ₃ -2,4,6	Me	Me	CF ₃	2.111–2.192	2.496 (Te—O), 3.134, 3.138 (Te...O)	89.9–95.1	6	98
98a	OCN	Me	Me	Me	2.110–2.121	2.983, 3.103 (Te...N), 3.095 (Te...O)	93.3–95.4	6	104
98b	OCN	Ph	Ph	Ph	2.102–2.156	2.783, 3.005, 3.171 (Te...N), 2.891, 3.028 (Te...O)	92.8–99.0	5, 6	105
99a	SCN	Me	Me	Me	2.113–2.120	3.185 (Te...N), 3.390, 3.488 (Te...S)	92.7–96.7	6	104
99b	SCN	Ph	Ph	Ph	2.100–2.150	2.963, 3.153, 3.182 (Te...N), 3.256, 3.348, 3.527 (Te...S)	92.3–100.0	5, 6	10
100a	SeCN	Me	Me	Me	2.107–2.124	3.252 (Te...N), 3.471, 3.553 (Te...Se)	93.3–96.6	6	104
100b	SeCN ^g	Ph	Ph	Ph	2.120–2.139	3.125 (Te...N), 3.442, 3.541 (Te...S)	93.4–99.9	6	104
101a	N ₃	Me	Me	Me	2.107–2.143	2.938, 3.006, 3.018, 3.032, 3.037 (Te...N)	92.5–94.7	6	104
101b	N ₃ ^g	Ph	Ph	Ph	2.120–2.146	2.772, 2.867, 2.946, 3.00, 3.027 (Te...N)	92.7–98.8	6	104
102a	Ag(CN) ₂	Me	Me	Me	2.100–2.109	3.154, 3.270, 3.407 (Te...N)	93.6–95.9	6	104
102b	Ag(CN) ₂	Ph	Ph	Ph	2.119–2.121	3.162, 3.346, 3.501 (Te...N)	94.4–99.5	6	104
54a	SC(S)NPr ₃ ^g	Ph	Ph	Ph	2.128–2.163	3.095, 3.145 (Te...S)	92.0–97.3	5	119
52a	SC(S)OMe	Ph	Ph	Ph	2.123–2.188	3.174–3.270 (Te...S)	91.7–97.9	5	115
52b	SC(S)OBu ⁿ (see ^g)	Ph	Ph	Ph	2.142–2.172	3.123–3.535 (Te...S)	88.4–97.8	5	115
56a	SP(S)Ph ₂	Ph	Ph	Ph	2.129–2.139	3.331–3.655 (Te...S)	94.4–101.2	5	121
55a	SP(S)(OEt) ₂	Ph	Ph	Ph	2.134–2.136	3.150–3.286 (Te...S)	95.2–96.9	5	112
59a	N{P(O)Ph ₂ } ₂	Ph	Ph	Ph	2.111–2.131	2.654, 2.926 (Te...O)	94.1–97.0	5	123
59b	N{P(S)Ph ₂ } ₂	Ph	Ph	Ph	2.121–2.143	3.264, 3.451 (Te...S)	96.8–97.4	5	121
59c	N{P(O)Ph ₂ } {P(S)Ph ₂ }	Ph	Ph	Ph	2.113–2.137	2.771 (Te...O), 3.282 (Te...S)	94.5–96.3	5	123

^a The C—Te—Cl angles lie in the range 88.5–91.7° (Ref. 130); ^b the salt contains two independent ionic pairs; the C—Te—Br angles are equal to 91.6–101.8° (Ref. 81); ^c the salt was unexpectedly isolated in an attempt to obtain triethyltelluronium diethyl thiophosphate by the exchange reaction of triethyltelluronium iodide with silver diethyl thiophosphate;¹⁵⁸ ^d the data on secondary bonds are absent; ^e the solvate with benzene (1 : 1); ^f the bonds of the non-charged Te atom: Te—C(sp)³ and Te—C(sp) are 2.149 and 2.067 Å, respectively (Ref. 65); ^g the solvate with chloroform (1 : 0.5).

The nature of the Te—X bonds in the telluronium salts R_3TeX in the crystalline state varies from purely ionic to covalent and is largely determined by the nature of the electronegative group X and, to a lesser extent, by the nature of the organic radicals bound to the tellurium atom. Like other tellurium derivatives,^{157,158} telluronium salts form secondary bonds with various elements, which allows the CN of tellurium atoms to acquire values from 3 to 6. Besides, a significant role in the structures and reactivities of organotellurium compounds is played by intramolecular coordination bonds (ICB) $O \rightarrow Te$, $N \rightarrow Te$, *etc.*^{159,160} The nature of these bonds is mainly determined by the donation of the unshared electron pair (UEP) of a heteroatom in such group as CHO, COR, CO₂R, NO₂, $N=N$, $CH=N$, CH_2NR_2 , *etc.*, to the antibonding molecular orbital (σ^* -MO) of the Te—X bond. The intramolecular coordination bonds $O(or N) \rightarrow Te$ should always be taken into consideration in determining the CN for the tellurium atom, since these bond lengths are much smaller than the sum of the van der Waals radii of the elements involved in the interaction.

Salts **85a–c**, **86** containing tetraphenylborate anion and its perfluorinated analogue, as well as perchlorate **30** and trichloromercurate **64a** exist in the form of discrete cations and anions; in the majority of cases, they are not involved in significant secondary interactions with one another. The lengths of the $Te \cdots F$ bond in salt **86** (3.36 Å⁸⁶) and of the $Te \cdots O$ bond in salt **30** (average value of 3.45 Å^{72,73}) are close to the sum of the van der Waals radii for the Te, F (3.53 Å¹³³) and Te, O (3.60 Å¹³³) pairs and are not taken into consideration in the calculation of CN for the Te atom. The bonds at the Te atom in R_3Te^+ cations have a trigonal-pyramidal configuration; the CN of Te in compounds **85a,b** and **86** is 3. At the same time, the bonds at the Te atoms in salts **85c**, **30** and **64** acquire a trigonal-bipyramidal configuration as a result of which the CN increases to 4 due to the occurrence, in these salts, of ICB $O \rightarrow Te$, $N \rightarrow Te$. Their lengths are 0.7–1.3 Å smaller than the sum of the van der Waals radii of the corresponding elements. Tetrafluoroborate **10a** contains, together with ICB $O \rightarrow Te$ (2.892 Å¹⁷), an interionic secondary $Te \cdots F$ bond the length of which (3.06 Å¹⁷) is nearly 0.5 Å smaller than the sum of the van der Waals radii of Te and F (3.53 Å¹³³). With regard to this interaction, the CN of the tellurium atom increases to 5.

Secondary interionic $Te \cdots Hal$ bonds usually occur in salts containing complex halogen anions $MHal_n$ ($Hal = F, Cl$); it is noteworthy that these bonds are shorter than the sum of the van der Waals radii of the elements. Hexafluoroantimonate **87a** containing three bulky mesityl groups is an exception, it exists in the form of discrete non-interacting ions. The Te atom in this compound has the trigonal-pyramidal configuration, and its CN is 3. However, CN of the tellurium atom in bromodimesityltelluronium salt **87b** containing the shortest $Te \cdots F$ contacts is 4.⁸¹ It is of note that secondary bonds $Br \cdots F$ in this compound are relatively short (2.69–2.80 Å), *i.e.*, 0.5–0.6 Å shorter than the sum of their van der Waals radii (3.32 Å¹³³). In salt **88**, each Te atom forms secondary $Te \cdots Cl$ bonds with the chlorine atoms of three $AuCl_4^-$ anions¹⁰⁶ and, as a consequence, the CN of the tellurium atom is 6. Salts **89**, **90** containing the doubly charged anions MCl_6 ($M = Pt, Ir$) manifest three secondary interactions $Te \cdots Cl$.¹⁰⁶ However, only the shortest bonds are taken into consideration in determining the type of the coordination polyhedron of the tellurium atom (the trigonal bipyramid with allowance for the UEP of the Te atom¹⁰⁶) and its CN (equal to 4). Bis(triphenyltelluronium) di- μ -chlorobis(dichloromercurate) **91** contains symmetrical Cl-bridging dimeric $Hg_2Cl_6^{2-}$ anions.¹²⁸ Due to three secondary $Te \cdots Cl$ bonds, which are 0.24–0.47 Å shorter than the sum of the van der Waals radii, the CN of the Te atom is equal to 6.¹²⁸ The coordination number of the onium tellurium atom in bis(triphenyl)telluronium hexachlorotellurate **92** is also equal to 6.¹⁵³ In this salt, each of the two tellurium atoms in the triphenyltelluronium cations is linked to the $TeCl_6^{2-}$ anion by three secondary $Te \cdots Cl$ bonds, the average length of the bonds being 3.527 Å. The $TeCl_6^{2-}$ anion has an octahedral structure; the average length of the $Te \cdots Cl$ bonds is 3.545 Å.¹⁵³ Trimethyltel-

luronium methyltetraiodotellurate **93**¹⁰ and triethyltelluronium tetraargentatopenta iodide **94**¹⁵⁴ are made up of trigonal-pyramidal cations, Alk_3Te^+ and square-pyramidal anions $MeTeI_4^-$ or tetracoordinate Ag atoms constituting the $[Ag_4I_5]^-$ anions.¹⁵⁴ Considering that the shortest $Te \cdots I$ bonds in both salts are only 0.2 Å shorter than the sum of the van der Waals radii of Te and I (4.04 Å¹³³), the CN of the tellurium atom in these compounds can be taken equal to 3 and 4, respectively.

It is of note that the *R*- and *S*-diastereomers of ethyl(methyl)-phenyltelluronium camphor-10-sulfonate **60a** differ from one another not only in the lengths of their Te—C bonds and the C—Te—C bond angles, but also in the number of secondary interactions between the tellurium atom and the oxygen atoms of the sulfonate group. The *R*-isomer in the crystalline state was found to contain two secondary bonds $Te \cdots O$ (2.88 and 3.05 Å^{54–56,124}), which points to the square-pyramidal geometry of the Te atom (CN 5). At the same time, the *S*-isomer contains three $Te \cdots O$ bonds (3.00, 3.01 and 3.03 Å^{56,124}) with an octahedral configuration around Te (CN 6). Telluronium salt **95** containing a trifluoromethanesulfonate anion has only one $Te \cdots O$ bond (2.61–2.68 Å); the CN of the Te atom in this salt is equal to 4.⁸²

Presumably,⁵⁶ the difference in the type of secondary interactions between the optical isomers is determined by the peculiarities of the crystal packing of their molecules. It should be noted that the lengths of the $Se \cdots O$ bonds (3.03 and 3.32 Å) in (*R*)-ethyl(methyl)phenylselenonium camphor-10-sulfonate¹⁶¹ exceed those in its tellurium analogue (*R*)-**60a** despite the fact that the van der Waals and the covalent radii of selenium are smaller than those of tellurium. This suggests that the cation–anion interactions in telluronium salts are stronger than in selenonium salts.

The crystalline states of the salts containing nucleophilic halide anions are represented by several structural types. Each tellurium atom in triethyltelluronium bromide **1e** is involved in three secondary interactions with the bromine atoms (the average length of the $Te \cdots Br$ bonds is 3.56 Å;²⁴ the sum of the van der Waals radii of the elements is 3.91 Å¹³³). This favours the formation of cubane-like tetramers where the Te and Br atoms alternately occupy the vertices of the Te_4Br_4 backbone. The presence of three primary Te—C bonds and three secondary $Te \cdots Br$ bonds at tellurium atoms results in the distorted octahedral environment of Te (CN 6). Triethyltelluronium chloride **1b** has a similar structure: the average length of the $Te \cdots Cl$ bonds is 3.45 Å,²⁵ while the sum of the van der Waals radii of Te and Cl is 3.81 Å.¹³³ Trimethyltelluronium iodide **1h** was found to contain three secondary $Te \cdots I$ bonds with the average bond length of 3.75 Å²⁸ (the sum of the van der Waals radii being 4.04 Å¹³³); the CN of the Te atom is also equal to 6.

Triethyltelluronium iodide **1i** has a different structure.²⁵ Its cations form centrosymmetrical dimers linked together by bridging iodine atoms (the average length of the $Te \cdots I$ bonds is 3.84 Å). In contrast to the halides considered above, each tellurium atom is included into two secondary interactions, which is favourable for the square-pyramidal environment of the tellurium atom (CN 5). The same configurations of the bonds were found in trimethyl-(**1a**),²⁸ triphenyl- (**1c**)^{28,155} and tris(pentafluorophenyl)telluronium (**1d**) chlorides,¹⁵⁶ in tris(pentafluorophenyl)telluronium bromide (**1g**)⁸² and dimethylphenyltelluronium iodide (**1j**).⁵⁷ The CN (5) of the Te atom in the *S*-diastereomer of the optically active telluronium salt **32b** is determined by the presence of two secondary bonds: $Te \cdots Cl$ (3.153 Å) and $Te \cdots O$ (2.842 Å),⁷⁴ their lengths are much smaller than the sum of the van der Waals radii of the corresponding elements. All the three nitrogen atoms in tris(2-dimethylaminobenzyl)telluronium chloride (not included into the Table) are coordinated by the tellurium atom, which favours the formation of the octahedral environment of the latter¹⁴ (CN 6). The length of ICB $N \rightarrow Te$ in this compound slightly exceeds that in salts **30** and **64a**, which contain sp^2 -hybridised nitrogen atoms. Chlorine atoms are not involved in second-

dary interactions [the shortest distance $\text{Te}\cdots\text{Cl}$ is 4.72 Å, which exceeds the sum of the van der Waals radii of Te and Cl (3.81 Å)¹³³ by 0.9 Å]. Each iodine atom in (methyltelluroethynyl)dimethyltelluronium iodide (**1k**) forms secondary bonds with four tellurium atoms.⁶⁵ The $\text{Te}^+\cdots\text{I}$ bonds (3.45 and 3.70 Å) are shorter than the $\text{MeTe}\cdots\text{I}$ bonds (3.58 and 3.76 Å). The crystals of **1k** were found to contain relatively short $\text{Te}^+\cdots\text{Te}$ bond; their lengths (3.77 Å) are about 0.4 Å smaller than the sum of the van der Waals radii of the elements (4.12 Å).¹³³ The CN of the onium Te atom with consideration of these interactions is 6, that for the tellurium atom bound to $\text{C}(\text{sp}^3)$ - and $\text{C}(\text{sp})$ -atoms is 5.⁶⁵

The presence of bulky mesityl radicals in trimesityltelluronium iodide (**1l**) may account for the fact that this salt is not characterised by any significant secondary interactions involving the tellurium atom. The length of the $\text{Te}\cdots\text{I}$ bond is 4.13 Å,¹³ *i.e.*, exceeds the sum of the van der Waals radii of Te and I (4.04 Å)¹³³ by nearly 0.1 Å.

Biphenyl-2-yl(dibenzotellurophenium) benzoate (**42a**)⁸³ has a trigonal-bipyramidal structure characteristic of σ -telluranes R_2TeX_2 ($\text{X} = \text{Hal}, \text{OCOR}, \text{ONO}_2$, *etc.*)¹⁶² containing covalent bonds $\text{Te}-\text{X}$. The apical positions are occupied by the O atom and one of the $\text{Te}-\text{C}$ bonds of the dibenzotellurophene fragment (the angle between the apical substituents is 159.9°). The length of the $\text{Te}-\text{O}$ bond (2.469 Å) is 0.3 Å greater in comparison with diphenyl telluroacetate $\text{Ph}_2\text{Te}(\text{OCOCH}_3)_2$ (2.16 Å)¹⁶³. The secondary $\text{Te}\cdots\text{O}$ bond between the tellurium atoms and the carbonyl oxygen atom of this molecule (3.182 Å) is about 0.4 Å smaller than the sum of the van der Waals radii of the elements. With consideration of this bond, the CN of the Te atom is 5. Benzoate **42a** exists as a monomer in the crystalline state, while the acetate **42b** is a dimer due to the presence of secondary $\text{Te}\cdots\text{O}$ bonds with carbonyl oxygen atoms of not only its own molecule (2.491 Å), but also the adjacent molecule (3.181 Å).⁸³ If these bonds are taken into consideration, the CN of the Te atom becomes equal to 6. The difference between the structures of benzoate **42a** and acetate **42b** can be attributed to the effects of steric factors, *i.e.*, the different sizes of the OCOPh and OCOME groups.⁸³

2,2'-Biphenylene(biphenyl-2-yl)telluronium phenolates **42c**⁸⁴ and **42d**⁸⁵ have identical structures. The coordination polyhedra of the tellurium atom in these compounds are distorted trigonal bipyramids the apical positions in which are occupied by the oxygen atoms and by one of the $\text{Te}-\text{C}$ bonds of dibenzotellurophene (the angles between the apical substituents in both compounds are equal to 159.6°). The $\text{Te}-\text{O}$ bond in 4-nitrophenoxy derivative **42d** (2.461 Å) is nearly 0.2 Å longer than that in the unsubstituted derivative **42c** (2.294 Å). The lack of secondary interactions in the crystals of compounds **42c,d** makes the CN of the Te atom equal to 4. In contrast to the monomeric phenoxy derivatives **42c,d**, salt **42e** containing a 2,4,6-trichlorophenoxy substituent exists in the form of a dimer.⁸⁵ In the latter case, the lengths of the primary $\text{Te}-\text{O}$ bonds (2.762 Å) and secondary $\text{Te}\cdots\text{O}$ bonds between the tellurium atom and the oxygen atom of the adjacent molecule (2.787 Å) are virtually identical, the tellurium atom has a distorted square-pyramidal configuration of the bonds (CN = 5). Presumably,⁸⁵ the gradual increase in the lengths of the $\text{Te}-\text{O}$ bonds in phenolates **42c-e** reflects the gradual changes in the nature of the $\text{Te}-\text{X}$ bonds from predominantly covalent to ion-like.

Similarly to phenolate **42e**, triphenyltelluronium chalcogenolates **50b-c** exist as dimers with virtually planar cyclic fragments Ar_8Te_4 and $\text{Ar}_8\text{Te}_2\text{Se}_2$.¹¹³ The average lengths of four secondary interactions $\text{Te}\cdots\text{Te}$ are 3.451 (**50c**, $\text{X} = \text{TeC}_6\text{H}_4\text{Me-4}$) and 3.441 Å (**50c**, $\text{X} = \text{TeC}_6\text{H}_4\text{OMe-4}$), *i.e.*, much smaller than the sum of the van der Waals radii of the Te atoms (4.40 Å)¹³³. The lengths of the $\text{Te}\cdots\text{Se}$ bonds in selenolate **50b** (3.269 Å) are about 0.2 Å smaller than the $\text{Te}\cdots\text{Te}$ bonds and 0.7 Å smaller than the sum of the van der Waals radii of Te and Se (3.96 Å)¹³³. Thus, the CN of the Te atom in the above tellurolates and selenolates is equal to 5. At the same time, it is suggested¹¹² that triphenyltel-

luronium 4-chlorophenylthiolate **50a** exists in a solid state as a tetramer each tellurium atom in which forms two secondary bonds with sulfur atoms (the CN of Te is 5); the $\text{Te}\cdots\text{S}$ distances lie in the range 3.02–3.64 Å.

The structure of dimethyl(trifluoromethyl)telluronium 2,4,6-trinitrophenolate (**97**) differs from those of **42c-e** and **50a-c**.⁹⁸ The coordination polyhedron of the tellurium atom in **97** (with consideration of the UEP) represents a distorted pentagonal bipyramid. The apical positions are occupied by the trifluoromethyl group (the lengths of the $\text{Te}-\text{C}$ bonds reach 2.192 Å) and the phenol oxygen atom (the length of the $\text{Te}-\text{O}$ bonds is 2.496 Å), whereas two methyl groups (the average length of the $\text{Te}-\text{C}$ bonds is 2.113 Å), two oxygen atoms of the nitro groups of two neighbouring molecules (the lengths of secondary $\text{Te}\cdots\text{O}$ bonds are equal to 3.134 and 3.138 Å) and the UEP of the tellurium atom occupy the equatorial positions. Thus, the CN of the Te atom in phenolate **97** is 6.

With consideration of secondary interactions, salts **98a**, **99a**, **100a,b** containing the chalcogenocyanate anions XCN ($\text{X} = \text{O}, \text{S}, \text{Se}$) are characterised by the octahedral environment of the bonds around the Te atom (CN = 6).¹⁰⁴ As the XCN anions are ambident, both $\text{Te}\cdots\text{N}$ and $\text{Te}\cdots\text{X}$ interactions take place in the crystals of these compounds. In salts **99a** and **100a,b** containing soft S and Se atoms,⁹³ two bonds of these atoms with soft Te atom take place along with one secondary $\text{Te}\cdots\text{N}$ bond. Only one secondary $\text{Te}\cdots\text{O}$ bond (3.10 Å) and two secondary $\text{Te}\cdots\text{N}$ bonds (2.98 and 3.10 Å) are found in trimethyltelluronium cyanate (**98a**) containing a harder oxygen atom. Triphenyltelluronium cyanate (**98b**)¹⁰⁵ and thiocyanate (**99b**)¹⁰ were found to contain secondary $\text{Te}\cdots\text{X}$ bonds ($\text{X} = \text{O}, \text{S}$) and $\text{Te}\cdots\text{N}$ bonds of approximately the same lengths as in the corresponding trimethyltelluronium salts.¹⁰⁴ Cyanate **98b** contains discrete tetramers two Te atoms in which have distorted square-pyramidal environment (CN = 5), while the other two have distorted octahedral environment (CN = 6). Triphenyltelluronium thiocyanate **99b** is made up of dimers containing Te atoms with CN = 5, and tetramers the Te atoms in which are penta- and hexacoordinate.

In trimethyltelluronium (**101a**)¹⁰⁴ and triphenyltelluronium (**101b**)¹⁰⁴ azides, the tellurium atoms are linked to terminal nitrogen atoms of nearly linear azido groups, resulting in a distorted octahedral environment of the Te atom (CN = 6). The average length of secondary $\text{Te}\cdots\text{N}$ bonds is 3.0 Å, *i.e.*, 0.65 Å less than the sum of the van der Waals radii of Te and N. Such a coordination of tellurium atoms was observed in triorganyltelluronium dicyanoargentates **102a,b**.¹⁰⁴ The Te atoms form two shorter secondary $\text{Te}\cdots\text{N}$ bonds (3.15 and 3.27 Å in the trimethyltelluronium salt **102a** and 3.16 and 3.35 Å in its phenyl analogue **102b**) and one more extended $\text{Te}\cdots\text{N}$ bond (3.41, 3.50 Å, respectively). The latter are only 0.15–0.25 Å shorter than the sum of the van der Waals radii of Te and N.

Telluronium salts containing 1,1-dithio ligands $\text{SC}(\text{S})\text{X}$ ($\text{X} = \text{NR}_2$, OR) (**52a,b**, **54a**) are represented by two major structures. Triphenyltelluronium dithiocarbamate (**54a**)¹¹⁹ and triphenyltelluronium alkyl xanthate (**52a**)¹¹⁵ are dimeric in the crystalline state due to the formation of secondary $\text{Te}\cdots\text{S}$ bonds. This results in the distorted octahedral (with consideration of UEP) environment of the Te atom (CN = 5). The lengths of the $\text{Te}\cdots\text{S}$ bonds in salts **52a** and **54a** vary from 3.10 to 3.27 Å. In contrast to these salts, triphenyltelluronium isobutyl xanthate (**52b**) is monomeric.¹¹⁵ The xanthate fragment is chelated by only one tellurium atom. The length of one of the two secondary $\text{Te}\cdots\text{S}$ bonds (3.535 Å) exceeds that of the other bond (3.123 Å) by nearly 0.4 Å. The difference in the structures of methyl and isobutyl xanthates seems to be due to the steric hindrance created by the isobutyl groups in the dimer formation.

Salts **55a**, **56a** and **59a-c** with various phosphorus-containing ligands are always monomeric. The tellurium atom in compounds **55a** and **56a** containing dithiophosphoric substituents [$\text{SP}(\text{S})(\text{OEt})_2$ ¹¹² and $\text{SP}(\text{S})\text{Ph}_2$ ¹²¹], is pentacoordinate and has a distorted square-pyramidal environment. In addition to three

primary Te—C bonds, each tellurium atom forms two secondary Te...S bonds. It is noteworthy that the Te...S bonds (3.15 and 3.29 Å) in salt **55a** are somewhat shorter than those in salt **56a** (3.33 and 3.66 Å).

Six-membered chelate rings $\text{TeX}_2\text{P}_2\text{N}$ ($\text{X} = \text{O}, ^{123} \text{S}^{121}$) and $\text{TeOSP}_2\text{N}^{123}$ are formed in triphenyltelluronium dichalcogeno-imidodiphosphinates **59a–c**.¹²³ The distorted square-pyramidal geometry of the bonds at the tellurium atom ($\text{CN} = 5$) is determined by secondary bonds $\text{Te}\cdots\text{O}$ (2.65–2.93 Å) and $\text{Te}\cdots\text{S}$ (3.26–3.45 Å).

Hence, the structural diversity of telluronium salts suggests the existence of different types of interactions of tellurium atoms in crystalline states.

VI. Conclusion

The reviewed data suggest that the chemistry of telluronium salts has advanced considerably in the past two decades. This is manifested in the development of novel efficient methods for the synthesis of telluronium derivatives and preparation of hitherto unknown types of telluronium salts. Considerable progress has been achieved in the application of telluronium salts in preparative organic chemistry. Telluronium ylides prepared by deprotonation of telluronium salts and used *in situ* react with various carbonyl compounds and compounds with multiple bonds to give cyclopropanes, aziridines, oxiranes, alkenes, benzylic and propargylic alcohols and β -hydroxy nitriles. The majority of these reactions proceed in good yields and with high stereoselectivity. Of special interest is the synthesis of alkenes containing electron-withdrawing substituents (CO_2R , COR, CN) at the double bond by the reaction of dialkyl tellurides with the corresponding organobromine derivatives and aldehydes. Such reactions have no analogies in the chemistry of sulfonium and selenonium salts. X-ray diffraction analysis of more than 60 telluronium salts revealed that the coordination number of the tellurium atom varies from 3 to 6 due to its ability to form secondary bonds with various heteroatoms.

Further progress in the chemistry of telluronium salts seems to be associated with the development in three major areas, *viz.*, (i) development of novel preparative methods for telluronium salts from organoelement compounds, in the first place, from organomercury, organosilicon and organotin derivatives and highly electrophilic organotellurium intermediates; (ii) search for novel reactions aimed at the synthesis of various organic derivatives based on telluronium salts. This task is attainable due to the ease of cleavage of $\text{C}—\text{Te}^+$ bonds. Special attention should be given to further improvement of one-pot processes where catalytic amounts of telluronium salts or their precursors (diorganyl tellurides) can be used. And finally, (iii) the continuation of X-ray diffraction studies of telluronium salts containing various types of intramolecular coordination bonds ($\text{O} \rightarrow \text{Te}$, $\text{N} \rightarrow \text{Te}$) may result in the discovery of novel structural types of these compounds.

This review has been written with the financial support of the programme 'Leading Scientific Schools of the RF' (Grant NSh-945.2003.3).

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^a — *Protect. Met. (Engl. Transl.)*

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^e — *Russ. J. Coord. Chem. (Engl. Transl.)*

Chiral hydroxy phosphonates: synthesis, configuration and biological properties

O I Kolodiaznyy

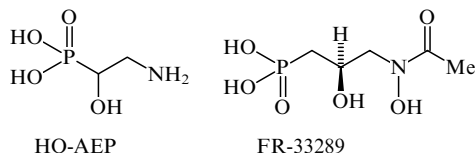
Contents

I. Introduction	227
II. Asymmetric synthesis of hydroxy phosphonates	227
III. Determination of the absolute configuration of hydroxy phosphonates	246
IV. Biological activities of hydroxy phosphonates	247
V. Conclusion	249

Abstract. Published data on the synthesis, absolute configurations and biological properties of chiral hydroxy phosphonates are generalised and described systematically. Examples of asymmetric synthesis of hydroxy phosphonates by the phospho-aldol reaction, reduction of keto phosphonates, chemo-enzymatic approach, and so on are discussed. Methods for determination of the optical purity and absolute configuration of hydroxy phosphonates using modification by chiral reagents, NMR, circular dichroism, GLC and HPLC on columns with chiral sorbents are considered. The significance of hydroxy phosphonates as promising compounds for the development of new drugs and bioregulators is demonstrated. The bibliography includes 263 references.

I. Introduction

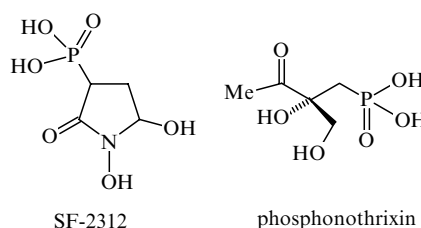
Hydroxy phosphonic acids form an important class of compounds, some of which are encountered in nature. Organophosphorus compounds of natural origin with a C–P bond were unknown before 1959,^{1–3} when Horiguchi and Kandatsu³ first discovered them in living organisms. Soon after this, substantial amounts of amino and hydroxy phosphonates have been isolated from natural sources. The best known natural hydroxy phosphonic acids include 1-hydroxy-2-aminoethylphosphonic acid (HO-AEP), 3-(*N*-acetyl-*N*-hydroxyamino)-2-hydroxypropylphosphonic acid (FR-33289), 1,5-dihydroxy-2-oxopyrrolidin-3-ylphosphonic acid (SF-2312), phosphonothrixin, *etc.*^{1,2} Many of these compounds attract attention due to their interesting biological properties as antibacterial, antiviral and antitumour agents, antibiotics, enzyme inhibitors, amino acid mimetics and pesticides.^{4–8}



O I Kolodiaznyy Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences of Ukraine, Murmanskaya ul. 1, 02094 Kyiv, Ukraine. Fax (38-044) 573 25 52, tel. (38-044) 573 25 55, e-mail: oiko1123@ukr.net

Received 25 February 2005

Uspekhi Khimii 75 (3) 254–282 (2006); translated by Z P Bobkova



The physiological activity of hydroxy phosphonates is due, on the one hand, to their structural similarity to biologically important phosphates with the P–O bond being replaced by P–C and, on the other hand, to the structural analogy between α -hydroxy-alkylphosphonic and α -hydroxy carboxylic acids. The replacement of the carboxy group in hydroxy carboxylic acids by a phosphonate group results in hydroxy phosphonic acids exhibiting an inhibitory effect with respect to enzymes and receptors to which natural hydroxy carboxylic acids usually bind. The biological activities of phosphonic acids are largely determined by the absolute configuration of the stereogenic α -carbon atom. For example, of the four possible diastereomers of the antibiotic alaphospholine, the *S,R*-diastereomer exhibits the highest activity with respect to the pathogenic microorganisms.⁹

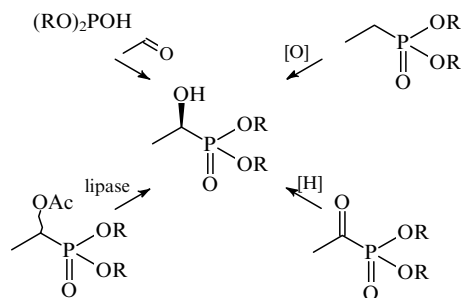
At present, hydroxy phosphonates with various structures containing one or several hydroxy groups in the organic radical have been synthesised and studied in detail; these include derivatives of carbohydrates, purine bases, nucleotides, and so on. The most studied compounds are α - and β -hydroxy phosphonates, β -amino α -hydroxy phosphonates, polyhydroxy phosphonates and fluorine-containing hydroxy phosphonates, which are isosteric analogues of natural compounds exhibiting high biological activity.

The vast factual material accumulated to date on the synthesis, properties and practical application of hydroxy phosphonates still requires systematisation, some contradictory data calling for critical consideration. This stimulated us to write a review paper in which we generalise for the first time the published data on the methods of preparation and properties of chiral hydroxy phosphonates, as well as their applications as biologically active substances or pharmaceutical agents. Hopefully, information surveyed in this review will be useful for chemists engaged in various aspects of organic chemistry and stereochemistry.

II. Asymmetric synthesis of hydroxy phosphonates

The vigorous development of the chemistry and biology of hydroxy phosphonates in the last decade is due to the develop-

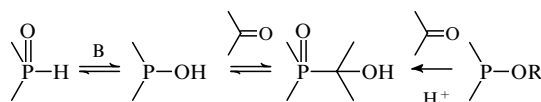
ment of highly efficient methods for their preparation.^{10, 11} Chiral hydroxy phosphonic acids can be prepared by a number of methods including kinetic resolution of racemic mixtures or enzymatic and asymmetric synthesis. The most important approach to the synthesis of hydroxy phosphonates is phosphorylation of carbonyl compounds leading to formation of a C–P bond (phosphorylation). Two methods for asymmetric phosphorylation of carbonyl compounds are known: phospho-aldol addition and the reaction of phosphonate carbanions with aldehydes or ketones. The phospho-aldol condensation (the Abramov reaction) occupies a leading position in this series, being a highly convenient method for the synthesis of chiral α -hydroxyalkylphosphonates.^{12, 13}



In recent years, the chemo-enzymatic method for the synthesis of optically active hydroxy phosphonates has been used more and more often.¹⁴ Other routes to these compounds are the enantioselective reduction of keto phosphonates,¹⁵ enantioselective hydroxylation of phosphonate-stabilised carbanions¹⁶ and [2,3]-sigmatropic Wittig rearrangements.¹⁷

1. Phospho-aldol condensation (the Abramov reaction)

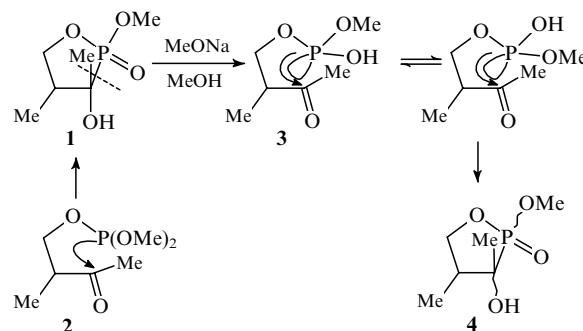
Two types of phospho-aldol condensation are known, namely, the reaction of dialkyl phosphites with carbonyl reagents in the presence of a basic catalyst, which shifts the tautomeric equilibrium of dialkyl phosphites towards the P(III)-form, and the reaction of phosphorous triesters with carbonyl compounds in the presence of a proton-donor reagent (phenol, carboxylic acid, tertiary amine hydrochloride, aniline, and so on) or a Lewis acid. Phosphorous triesters react with carbonyl compounds in two steps: first, the reversible addition of a carbonyl reagent to the trivalent phosphorus atom gives a carbon–phosphorus bond and then the ester group at the phosphorus atom is hydrolysed to give α -hydroxy phosphonate.^{12, 18–20}



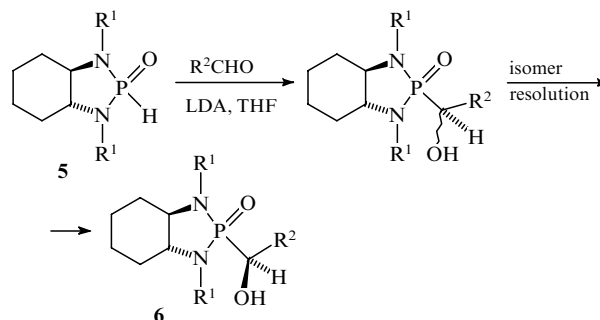
B is base.

In the presence of tertiary amines and some other bases, hydroxyalkylphosphonates decompose into the initial dialkyl phosphite and carbonyl components. This transformation is called the retro-Abramov reaction. Nuclear magnetic resonance^{21, 22} and kinetic studies^{19, 20} have shown that the retro-Abramov reaction has a substantial influence on the stereochemistry of the resulting hydroxy phosphonates. For example, the stereochemistry of the sodium methoxide-catalysed decomposition of the diastereomers of 3-hydroxy-2-methoxy-3,4-dimethyl-1,2-oxaphospholan-2-one (**1**) obtained by cyclisation of phosphite **2**, has been studied.²³ Under the action of sodium methoxide in methanol, diastereomerically pure hydroxy phosphonates **1** underwent racemisation. Presumably, the reaction mechanism includes cleavage of the P–C bond (retro-Abramov reaction) and epimerisation of the chiral P-anion **3**, which bring about the formation of a mixture of diastereomers **4** upon the subsequent

cyclisation. One more possible reason for racemisation is cleavage of the endocyclic P–O bond in compound **1**.



Chiral phosphonites and phosphinites, having a stereogenic phosphorus atom, and phosphites that contain residues of optically active alcohols, amino alcohols or amines at the phosphorus atom can serve as asymmetric inductors in the Abramov reaction. Phosphites based on chiral 1,2-diaminocyclohexane, ephedrine, binol, menthol, *etc.*, are used most often. The addition of chiral dialkyl phosphites and their anions to achiral aldehydes gives rise to α -hydroxy phosphonates with a moderate stereoselectivity.^{24–40} For example, the reaction of bicyclic chiral phosphorous diamides **5** with aldehydes yields α -hydroxyalkylphosphonamides **6** in good yields. The presence of bulky substituents in phosphoramidite and aldehyde molecules increases the reaction stereoselectivity.^{24–29}

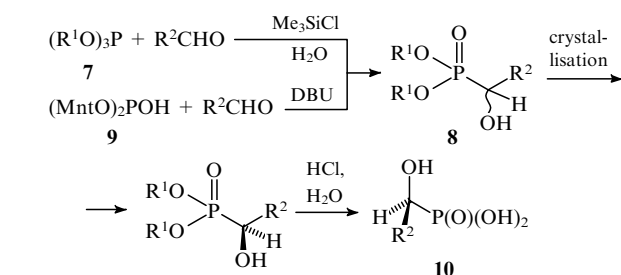


LDA = LiNPr₂.

R ¹	R ²	dr	Ref.
2-MeC ₆ H ₄ CH ₂	PhCH = CH	1 : 1	24
Bn	CH ₂ = CH	1.4 : 1	24
1-NaphCH ₂	PhCH = CH	1.5 : 1	24
(S)-PhMeCH	Ph	1.8 : 1	29
Bn	PhCH = CH	4.0 : 1	24
Bu ^t CH ₂	PhCH = CH	7.9 : 1	24
Bu ^t CH ₂	Ph	25 : 1	24

dr is the diastereomer ratio.

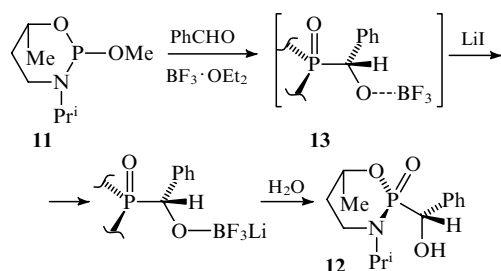
The nature of the chiral alkoxy groups at the phosphorus atom has a pronounced effect on the stereoselectivity of the phospho-aldol condensation. For instance, the reaction of tris(glucosyl) phosphite **7** with benzaldehyde in the presence of chlorotrimethylsilane proceeds with good stereoselectivity to give hydroxy phosphonate **8** mainly as a single isomer with a diastereomeric excess (*de*) of 84%. Meanwhile, trimethyl and tribornyl phosphites react with aldehydes with low stereoselectivity, giving rise to mixtures of hydroxy phosphonate diastereomers **8**.^{30, 31} The reaction of dimethyl phosphite (**9**) with aromatic and aliphatic aldehydes in the presence of 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) as the catalyst has a moderate stereoselectivity. The diastereomers **8** were separated and, after hydrolysis of ester groups, acids **10** were formed with enantiomeric purity (*ee*) 96%–98%.^{30–33}



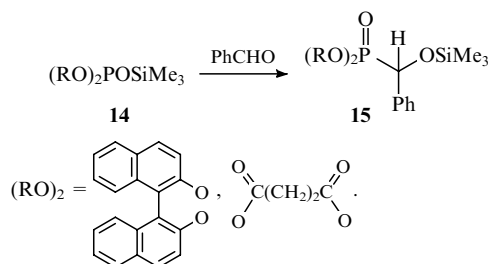
R ¹	R ²	de (%)	Ref.
GF	Ph	84	31
Mnt	Pr ⁱ	60	31
Mnt	4-Me ₂ NC ₆ H ₄	40	31
Mnt	4-MeOC ₆ H ₄	35	30
Mnt	Ph	33	31
Brn	Ph	33	30

GF is (–)-1,2,5,6-di-*O*-isopropylidene-D-glucofuranos-3-yl, Mnt is (1*S*,2*R*,5*S*)-menthyl, Brn is *endo*-bornyl.

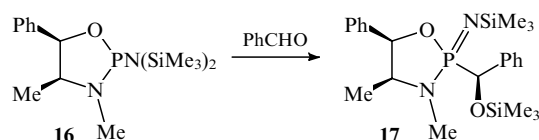
Gordon and Evans have established³⁴ that the reaction of 2-methoxy-1,3,2-oxazaphosphinane **11** with benzaldehyde in the presence of boron trifluoride etherate affords 2-(α -hydroxybenzyl)-2-oxo-1,3,2-oxazaphosphinane diastereomers **12** in 1 : 2 – 1 : 4 ratio. It was suggested that the reaction proceeds *via* a highly reactive complex of boron trifluoride etherate with benzaldehyde, which reacts with the phosphite to give complex **13**. The reaction stereoselectivity is determined first of all by the step affording complex **13**, which is converted into hydroxyalkylphosphonate **12** after treatment with lithium iodide and hydrolysis.



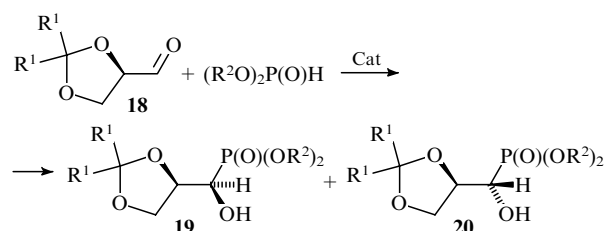
The phospho-aldol reaction of chiral silyl phosphites **14** with benzaldehyde at room temperature gives silyloxy phosphonates **15** with relatively low stereoselectivity.³⁵



The addition of chiral diazaphospholidines, which are ephedrine derivatives, to carbonyl compounds also proceeds with moderate stereoselectivity.^{36–39} An exception is the modified Mukayama reaction of silylated λ^3 -diazaphospholidines **16** with aldehydes, which furnishes only one diastereomer, the adduct **17** (*ee* > 98%).³⁶ Compound **17** is easily converted into α -hydroxy phosphonate, which possesses a pharmacological activity.^{37,38}

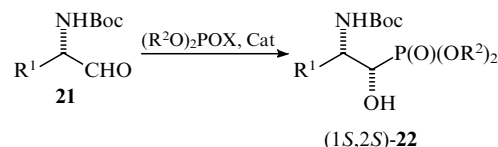


The stereoselectivity of condensation of achiral phosphites with chiral aldehydes is low. For example, the reaction of dialkyl phosphites with 2,3-*O*-protected D-glyceraldehyde **18** in the presence of catalysts such as triethylamine or lithium or cesium fluoride yields mixtures of hydroxy phosphonate diastereomers **19** and **20** in 45 : 55 – 35 : 65 ratio. The use of lithium diethyl phosphite somewhat increases the reaction stereoselectivity.⁴¹ Enantiomerically pure isopropylidene- and cyclohexylidene-protected 1,2,3-trihydroxypropylphosphonates (1*R*,2*R*)-**19** and (1*S*,2*R*)-**20** can be isolated from the diastereomer mixture by column chromatography.^{42–44}



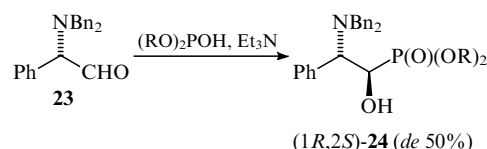
R¹ = Me₂, (CH₂)₅; R² = Et, Prⁱ; Cat = DBU, Et₃N, CsF, LDA.

Phosphonylation of chiral α -amino aldehydes is the most convenient and versatile method for the preparation of optically pure stereomeric α -hydroxy- β -aminoalkylphosphonic acids.^{45–55} The reaction stereochemistry depends crucially on the number of substituents at the nitrogen atom. For example, the addition of dialkyl phosphites to *N*-*tert*-butoxycarbonyl-(*S*)-phenylglycinal (**21**, R¹ = Ph) yields (1*S*,2*S*)-2-amino 1-hydroxy phosphonate **22**,⁴⁸ the phosphonate analogue of the side chain of a natural antitumour agent, paclitaxel. The phosphonylation of *N*-benzoyl-(*S*)-phenylglycinal occurs in a similar way. Meanwhile, the reaction of dialkyl phosphites with *N,N*-dibenzylphenylglycinal (**23**) gives mainly (1*R*,2*S*)-diastereomer **24**.⁴⁹



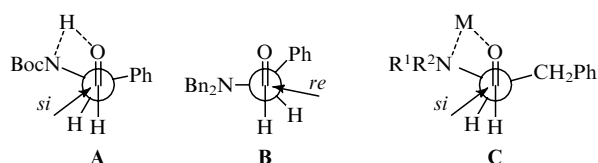
Boc = Bu^tOC(O).

R ¹	R ²	X	Cat	dr	Ref.
Ph	Me	Li	–	74 : 26	48
Bn	Et	SiMe ₃	TiCl ₄	60 : 40	47, 50
Ph	Me	SiMe ₃	–	83 : 17	48
Bn	Et	SiMe ₂ Bu ^t	TiCl ₄	98 : 2	47
Bn	Et	SiMe ₃	SnCl ₄	74 : 26	50
Bu ^t OC ₆ H ₄ CH ₂	Et	H	KF	80 : 20	50
Bu ^t	Et	H	KF	81 : 19	50



R = Me, Et.

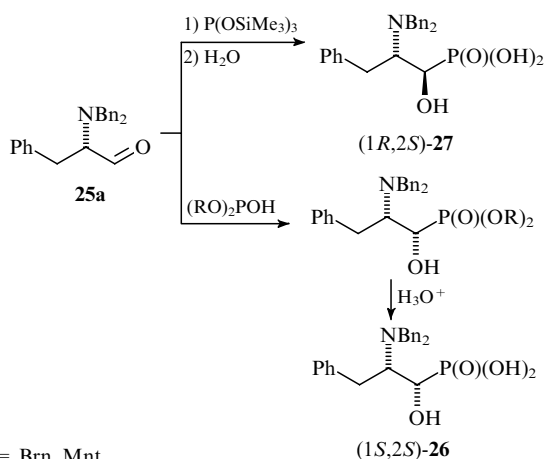
The different stereochemistry of the reaction is due to the fact that in the molecule of (*S*)-*N*-Boc-derivative **21**, the intramolecular hydrogen bond stabilises conformation A; therefore, the *si*-stereofacial attack of the dialkyl phosphite on the carbonyl group gives rise to the *S*-adduct. In the case of (*S*)-*N,N*-dibenzyl derivative **23**, no intramolecular hydrogen bond is formed; therefore, phosphite attacks preferably the *re*-side of the carbonyl group (model B).



M = Ti, Sn.

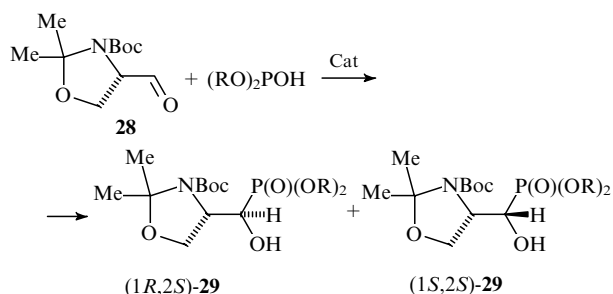
The stereoselectivity of the reaction of phosphites with aldehydes depends on not only the structure of the initial reactants but also the catalyst.^{47–52} For example, titanium and tin tetrachlorides efficiently catalyse the reaction of silyl phosphites with chiral (*S*)-aldehydes **21** and **23** and promote the formation of (1*S*,2*S*)-diastereomers. In this case, the *si*-stereofacial attack is governed by the formation of chelate **C**.^{47, 50}

The reaction of chiral aldehyde **25a** with dimethyl and dibornyl phosphite followed by hydrolysis affords optically pure 2-amino-1-hydroxyalkylphosphonic acid (1*S*,2*S*)-**26**, whereas the addition of the same aldehyde to tris(trimethylsilyl) phosphite results in (1*R*,2*S*)-diastereomer **27**, which was isolated in the crystalline state.⁵⁵



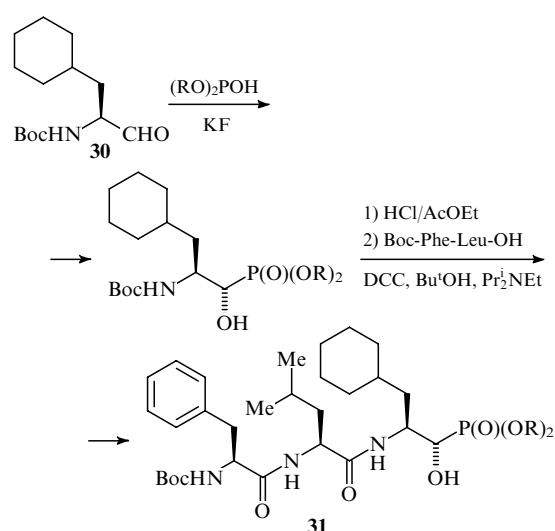
R = Brn, Mnt.

The condensation of dialkyl phosphites with the Garner aldehyde **28** in the presence of triethylamine results in the formation of (1*R*,2*S*)-diastereomers of hydroxy phosphonates **29** (de 80%), which were purified by column chromatography. The reaction with titanium(IV) isopropoxide as the catalyst gives a mixture of (1*R*,2*S*)- and (1*S*,2*S*)-diastereomers **29** in ~1 : 1 ratio; pure (1*S*,2*S*)-diastereomer **29** was isolated by column chromatography on silica gel.⁵³



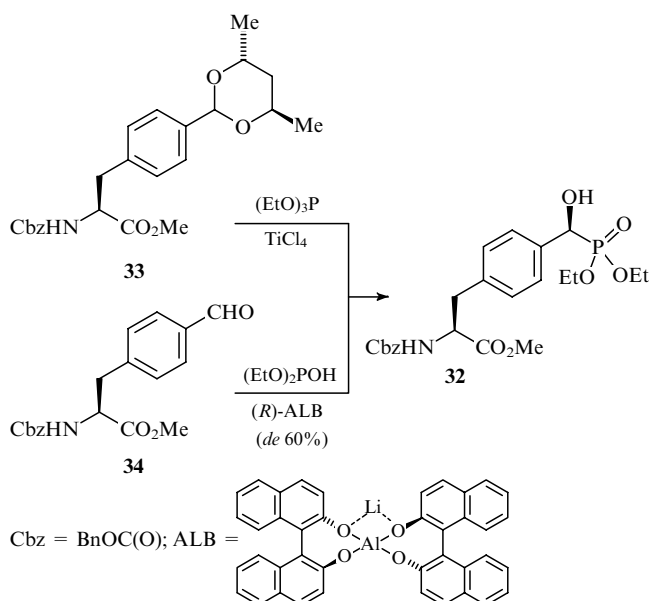
R = Me, Et; Cat = Et₃N, Ti(OPrⁱ)₄.

Patel *et al.*⁸ used the reaction of dialkyl phosphites with chiral aldehyde **30** for the preparation of enantiomerically pure phosphonate analogues of tripeptides, α -hydroxy phosphonates **31**, which are highly efficient renin inhibitors.

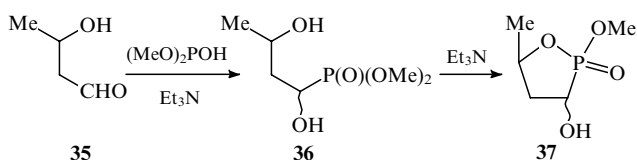


R = Me, Et; DCC = cyclo-C₆H₁₁–N=C=N–C₆H₁₁–cyclo.

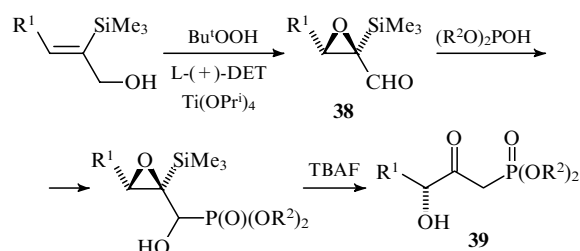
Shibuya and co-workers⁵⁴ developed stereocontrolled methods for the synthesis of the hydroxy phosphonate analogue of tyrosine **32** based on the reaction of chiral pentane-2,4-diol acetal of protected 4-formyl-L-phenylalanine **33** with triethyl phosphite in the presence of titanium tetrachloride and by the reaction of diethyl phosphite with methyl ester of *N*-benzyloxy-carbonyl-4-formyl-L-phenylalanine (**34**) in the presence of a chiral heterobimetallic catalyst ALB.



The addition of dimethyl phosphite to 3-hydroxybutanal (**35**) results in a diastereomer mixture of 1,3-dihydroxybutylphosphonates **36** in 3 : 7 ratio. The absolute configurations of the C(1) and C(3) atoms in these diols were determined by ¹³C NMR spectroscopy of their *O*-benzylidene derivatives. The intramolecular cyclisation of phosphonates **36** in the presence of triethylamine gives a mixture of 3-hydroxy-2-methoxy-5-methyl-1,2-oxaphospholan-2-one diastereomers (**37**).⁵⁶

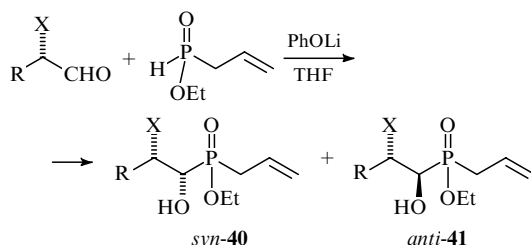


Chiral epoxy aldehydes **38** obtained by asymmetric Sharpless epoxidation of 2-trimethylsilylalk-2-enols reacted with dialkyl phosphites, yielding γ -hydroxy- β -oxo phosphonates **39** with *ee* 96%–97%.⁵⁷



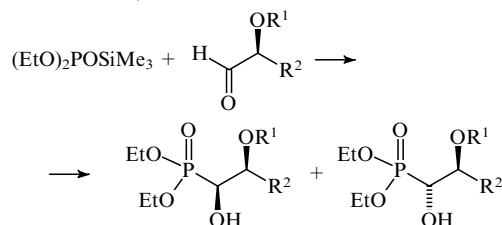
$R^1 = n\text{-C}_4\text{H}_9, n\text{-C}_{10}\text{H}_{21}$; $R^2 = \text{Me, Ph}$;
DET is diethyl tartrate; TBAF = $\text{Bu}_4\text{N}^+\text{F}^-$.

β -Substituted α -hydroxy phosphinates **40** and **41** are prepared by lithium phenoxide-catalysed reaction of protected α -hydroxy and α -amino aldehydes with ethyl allylphosphinate.⁵⁸



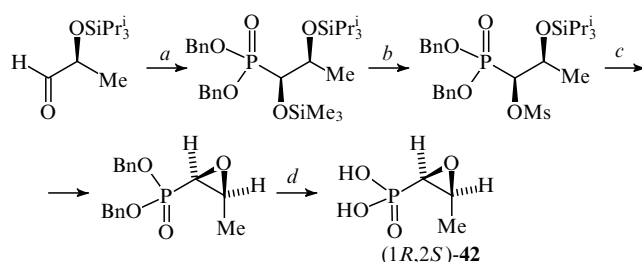
$R = \text{Me, Bu}^t, \text{Ph, Bn}$; $X = \text{OSiMe}_2\text{Bu}^t, \text{NBn}_2$.

The phosphonylation of α -silyloxy aldehydes with silyl phosphites was accomplished by Bongini *et al.*^{59,60} The reaction stereoselectivity increases with an increase in the bulk of the trialkylsilyl substituents in the phosphite and aldehyde molecules (*dr* 33 : 67–92 : 8).



$R^1 = \text{SiEt}_3, \text{SiPr}_3^i, \text{SiMe}_2\text{Bu}^t$; $R^2 = \text{Me, Pr}^i, n\text{-C}_5\text{H}_{11}, \text{Ph}$.

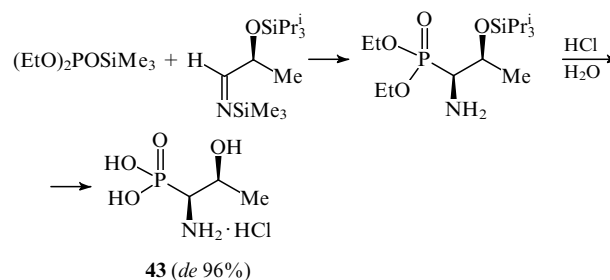
This reaction was used to develop a method for the synthesis of phosphomycin **42**, which is an efficient antibiotic of the natural origin. Phosphomycin **42** was obtained by stereoselective addition of dibenzyl trimethylsilyl phosphite to *O*-triisopropylsilyl-(*S*)-lactaldehyde.⁶¹



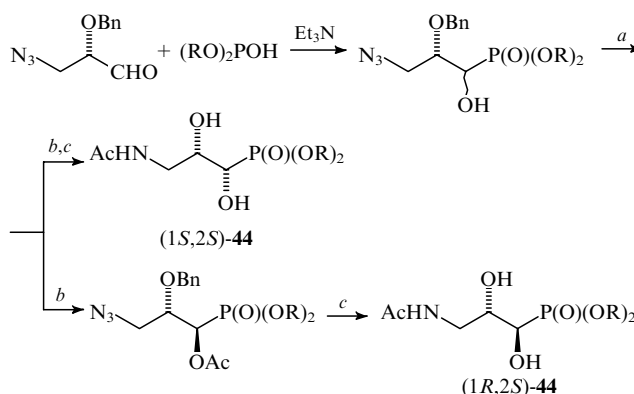
(a) $(\text{BnO})_2\text{POSiMe}_3$; (b) MeSO_2Cl (MsCl), Et_3N , CH_2Cl_2 ;
(c) TBAF, SiO_2 , THF, 20 °C; (d) H_2 , Pd/C;

(1*S*,2*S*)-Phosphothreonine (**43**) with a high diastereomeric purity was prepared in a similar way by the reaction of diethyl

trimethylsilyl phosphite with silylated *N*-trimethylsilylimino-(*S*)-lactaldehyde.⁶² The other phosphothreonine stereoisomers were prepared by the addition of diethyl trimethylsilyl phosphite to lactaldehyde followed by the Mitsunobu inversion of the corresponding α -hydroxy β -silyloxy phosphonate.⁶³

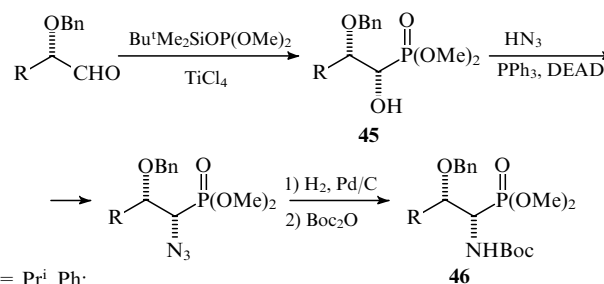


Diastereomerically pure (1*R*,2*S*)- and (1*S*,2*S*)-3-amino-1,2-dihydroxypropylphosphonates **44** are prepared by a multistep synthesis, which includes the reaction of (*S*)-3-azido-2-benzyloxypropanal with dialkyl phosphites, chromatographic separation of the stereoisomers on a column with silica gel and debenzoylation with hydrogen in the presence of HPd/C.⁶⁴



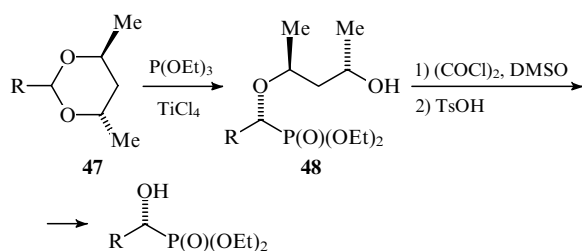
$R = \text{Me, Et}$;
(a) chromatography on SiO_2 ; (b) Ac_2O , Et_3N , DMAP; (c) H_2 , Pd/C;
DMAP =

The stereoselective hydrophosphonylation of α -benzyloxy aldehydes catalysed by titanium tetrachloride is used in the synthesis of the phosphonic analogues of amino hydroxy acids. Shibuya and co-workers^{65,66} used the phospho-aldol reaction to prepare β -benzyloxy α -hydroxy phosphonates **45**; their reactions with hydrazoic acid followed by reduction and protection gave substituted α -amino β -hydroxy phosphonates **46**.



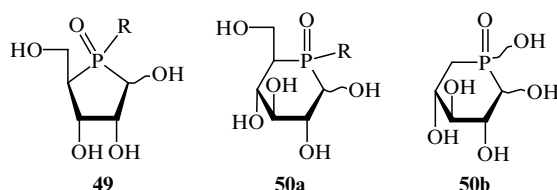
$R = \text{Pr}^i, \text{Ph}$;
DEAD = $\text{EtO}_2\text{CN}=\text{NCO}_2\text{Et}$.

The reaction of triethyl phosphite with homochiral (2*S*,4*S*)-pentanediol acetals **47** in the presence of titanium tetrachloride results in diastereoselective formation of alcohols **48** (*dr* = 93 : 7). The Swern oxidation followed by treatment with *p*-toluenesulfonic acid yields hydroxy phosphonates (*ee* 95%).⁶⁷ Yamamoto and co-workers⁶⁸ used this strategy to prepare chiral (2*R*)-1-amino-1-deoxy-1-phosphinyglycerols.

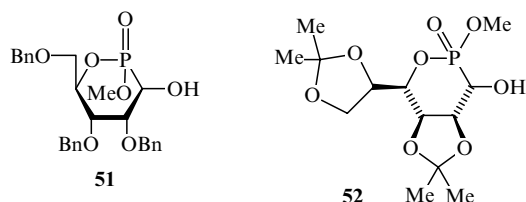


R = Prⁱ, Buⁿ, Bu^t; Ts = 4-MeC₆H₄SO₂.

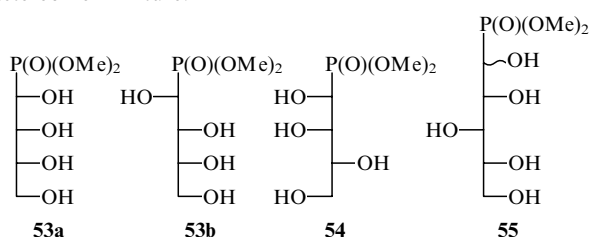
The Abramov reaction was used to prepare phosphorus-containing D-ribofuranose (compounds **49**) and D-glucopyranose (**50a**) analogues and 5-deoxy-5-C-phosphinyl-D-xylose (**50b**). These compounds were converted into pseudo-carbohydrate nucleoside derivatives that may possess biological activity.^{69–71}



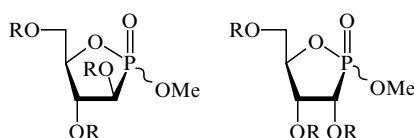
The Abramov reaction is also utilised to prepare stereochemically pure δ -phostones **51** and **52**⁷² the structures of which were proved by X-ray diffraction analysis.⁷³



Polyhydroxyalkylphosphonates **53a,b** and **54** were synthesised⁷⁴ by the phospho-alcohol reaction of dimethyl phosphite with 2,4-*O*-benzylidene derivatives of D-erythrose and D-threose, while the addition of dimethyl phosphite to 2,3:4,5-di-*O*-isopropylidene-D-xylose afforded polyhydroxyalkylphosphonate **55** as a diastereomer mixture.⁷⁵

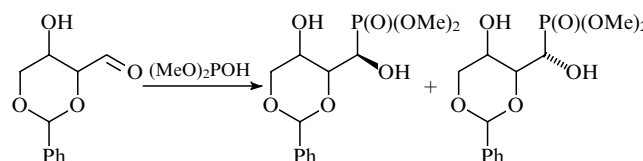


Wróblewski^{76–79} synthesised analogues of D-tetralose, D-ribose and some other carbohydrates containing phosphorus in the anomeric position. The addition of ethyl trimethylsilyl phosphite to 1,3-di-*O*-benzyl-4-*O*-(*tert*-butyldimethylsilyl)-D-tetralose results in the formation of hydroxy phosphonate diastereomers. The acid-catalysed cyclisation of (1*S*)- and (1*R*)-1-*C*-(dimethoxyphosphoryl)-D-erythritols produces methyl D-arabino- and D-ribofuranoside analogues containing phosphorus in the anomeric position.^{77–79}



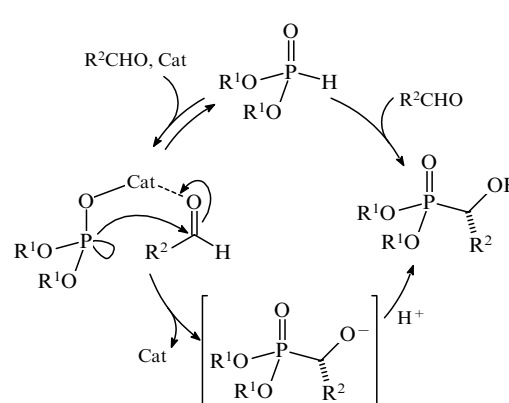
R = Me, Ph.

A mixture of (1*S*)- and (1*R*)-2,4-*O*-benzylidene-1-(dimethoxyphosphoryl)-D-threitol diastereomers in 1:9 ratio was obtained by the addition of dimethyl phosphite to 2,4-*O*-benzylidene-D-threose in the presence of triethylamine.⁷⁹



Similarly, (1*S*)- and (1*R*)-diastereomeric 2,4-*O*-benzylidene-1-(dimethoxyphosphoryl)-D-erythritols were prepared in 1:1 ratio starting from 2,4-*O*-benzylidene-D-erythrose.

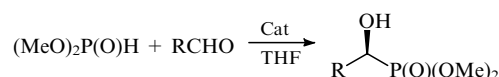
In recent years, asymmetric catalysis of the phospho-alcohol condensation gained strong impetus. Scheme 1 shows the tentative reaction mechanism involving an asymmetric catalyst.⁸⁰



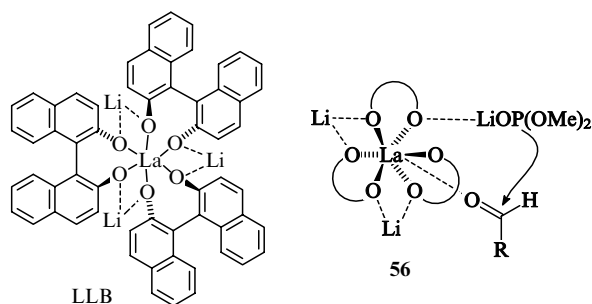
Scheme 1

R¹ = Alk, R² = Alk, Ar, etc.

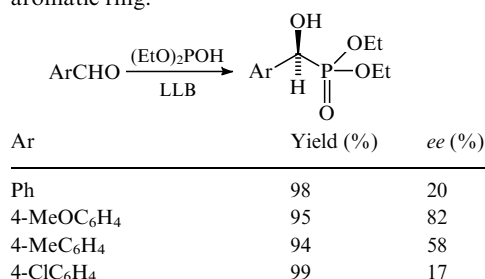
Several types of asymmetric catalysts have been proposed for the stereochemical control of the phospho-alcohol reaction. Shibasaki and co-workers⁸¹ reported that heterobimetallic complexes LLB and ALB containing chiral binaphthol ligands efficiently catalyse asymmetric hydrophosphonylation of aromatic aldehydes. The optical purity (*ee*) of the resulting α -hydroxy phosphonates reaches 95%. The reaction proceeds *via* an intermediate complex of the catalyst with the phosphite and aldehyde (for example, complex **56** in the case of LLB), the nucleophilic attack by the trivalent phosphorus on the aldehyde carbonyl carbon atom taking place within this complex.



R	Cat = LLB, –78 °C		Cat = ALB, –40 °C	
	yield (%)	ee (%)	yield (%)	ee (%)
Ph	88	79	95	90
4-MeC ₆ H ₄	93	78	82	86
4-Me ₂ NC ₆ H ₄	88	95	–	–
4-MeOC ₆ H ₄	87	93	88	78
4-NO ₂ C ₆ H ₄	85	36	85	71
4-ClC ₆ H ₄	80	63	80	83
PhCH=CH	90	84	85	82
PhCH=C(Me)	94	92	47	56
n-C ₅ H ₁₁	88	61	95	16



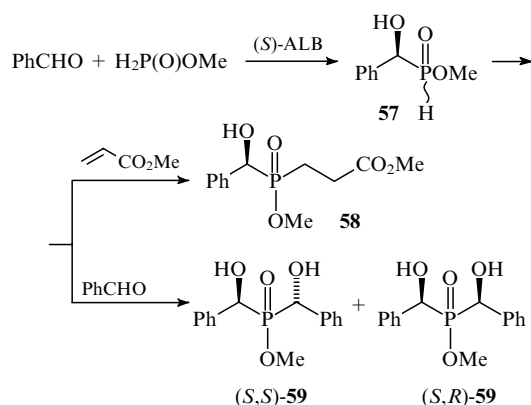
Shibuya and co-workers,^{82,83} who carried out the same reaction, found that the enantioselectivity of hydrophosphonylation of arylaldehydes in the presence of LLB depends on the electronic nature of the substituent in the *para*-position of the aromatic ring.



Spilling and Rath²⁸ reported that the addition of dialkyl phosphites to cinnamaldehyde catalysed by (*R*)-LLB affords (*S*)-hydroxy phosphonates in good yields but the enantioselectivity (*ee*) is only ~30%. Subsequently, for increasing the reaction stereoselectivity, it has been proposed⁸⁰ to add the aldehyde to the reaction mixture very slowly, over a period of several hours.

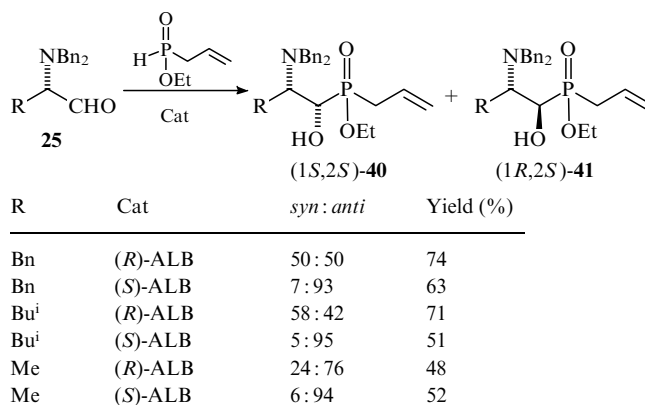
The complexes obtained from titanium(IV) isopropoxide and some chiral diols efficiently catalyse the addition of diethyl phosphite to aromatic aldehydes. For example, the complex obtained from titanium(IV) isopropoxide and diisopropyl L-tartrate ensures the formation of (*R*)-hydroxy phosphonates with *ee* 36%–53%. The reaction enantioselectivity depends on the diol structure, the electronic nature of the substituent at the carbonyl group and the donor properties of the solvent.^{83,84}

The addition of methyl hypophosphite to achiral aldehydes in the presence of the ALB catalyst proceeds with a moderate diastereoselectivity, yielding diastereomer mixtures of (*S*)- α -hydroxy-H-phosphinates **57**, which cannot be isolated in a pure state. Compounds **57** react with methyl acrylate and benzaldehyde to give hydroxy phosphinates **58** and an (*S,S*)- and (*S,R*)-diastereomer mixture of α,α' -dihydroxy phosphinates **59**, from which pure (*S,S*)-stereoisomer was isolated after acylation.⁸⁵



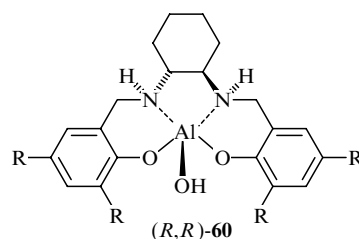
The reaction of hypophosphorous acid with aldehydes initiated by microwave radiation giving rise to bis(α -hydroxyalkyl)-phosphinic acids has been reported.⁸⁶

The catalytic hydrophosphinylation of chiral α -amino aldehydes **25** in the presence of ALB results in β -amino α -hydroxy phosphinic acid derivatives with moderate stereoselectivity.^{87–89}



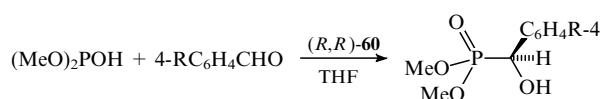
The formation of a complex diastereomer mixture in the reaction is due to the presence of three asymmetric centres in the product molecule, namely, the α - and β -carbon atoms and the phosphorus atom. Nevertheless, diastereomers (*1S,2S*)-**40** and (*1R,2S*)-**41** can be separated by column chromatography.^{54,87,88}

Chiral aluminium salcyan complexes catalyse the enantioselective route of the phospho-aldol reactions.⁹⁰ For example, the use of the chiral catalyst (*R,R*)-**60** in the reaction of dimethyl phosphite with substituted benzaldehydes results in *S*-isomers of the adducts with *ee* ~50%.



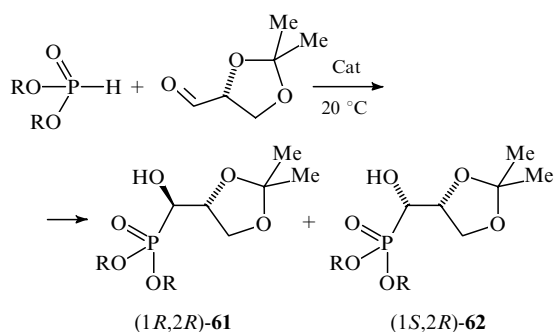
R = H, Bu^t.

R	H	Me	OMe	NO ₂	NMe ₂
ee (%)	52	57	47	18	22



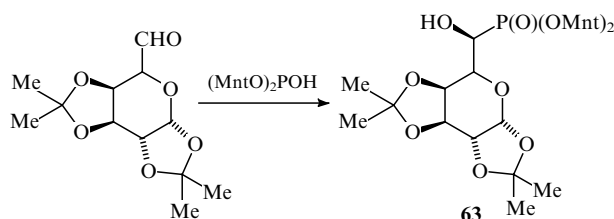
Optically active quinine catalyses the reaction of *ortho*-nitro-benzaldehyde with dialkyl phosphites giving *S*-enantiomers of hydroxy phosphonates with *ee* 80%.^{91,92}

Multiple asymmetric induction, *i.e.*, a reaction proceeding under the stereochemical control of two or more chiral inductors, is an efficient method for increasing the stereoselectivity of the phospho-aldol condensation.^{93–98} Thus the reaction of the optically active di-(*1R,2S,5R*)-menthyl phosphite with 2,3-*O*-isopropylidene-D-glyceraldehyde (both reactants are chiral inductors) occurs with a higher stereoselectivity than the reaction involving one chiral inductor and gives a diastereomeric mixture of α -hydroxy phosphonates **61** and **62** with predominance of the *anti*-stereoisomer (*de* 60%).⁴³ The introduction of the third asymmetric inductor, the chiral catalyst ALB, increases the stereoselectivity to 90%.⁴² The ratio of isomers formed in the reaction depends on the natures of the solvent and the base and on the temperature. The resulting diastereomers (*R,R*)-**61** and (*S,R*)-**62** were separated by crystallisation and column chromatography on silica gel. The (*1S,2R*)-configuration of the adduct was confirmed by X-ray diffraction analysis.



R	Cat	Solvent	syn : anti	Ref.
Et	DBU	—	45 : 55	43
Pr ⁱ	DBU	—	45 : 55	43
Mnt	DBU	—	20 : 80	43
Mnt	DBU	MePh	20 : 80	43
Mnt	DBU	THF	28 : 72	43
Mnt	DBU	CH ₂ Cl ₂	35 : 65	43
Mnt	NaOH	THF	30 : 70	43
Mnt	(S)-ALB	THF	5 : 95	42
Mnt	(R)-ALB	THF	22 : 78	42

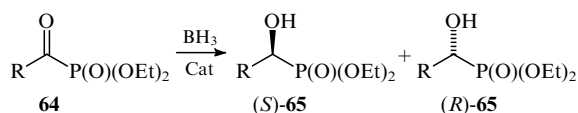
The reaction of dimethyl phosphite with *galacto*-hexodialdose proceeds with high stereoselectivity, owing to double asymmetric induction, resulting in the formation of C(6)-phosphorylated galactose derivative **63** with *de* ~ 100%. The adducts was isolated as optically pure crystalline compound.⁹⁸



2. The reduction of keto phosphonates

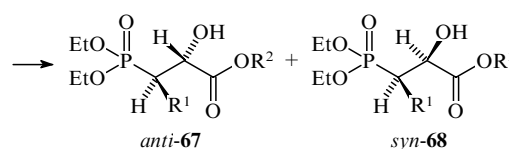
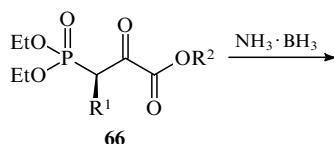
The enantioselective reduction of keto phosphonates is a very convenient method for the synthesis of chiral hydroxy phosphonates. Keto phosphonates with optically active substituents, chiral reducing agents or catalysts can serve as asymmetric inductors in this reaction.

The reduction of diethyl α -keto phosphonates **64** with borane in the presence of chiral β -butyloxazaborolidines as catalysts yields diethyl (*S*)- and (*R*)-1-hydroxyalkylphosphonates **65** in good yields and satisfactory enantiomeric excesses (*ee* 53%–83%).⁹⁹



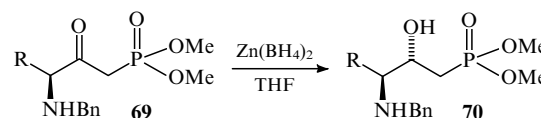
R = Et, Buⁿ, Buⁱ; Cat — β -butyloxazaborolidine.

The reduction of keto phosphonates **66** with the borane–ammonia complex affords hydroxyphosphonate diastereomers **67** and **68** in 25 : 1 ratio.¹⁰⁰



R¹ = Me, Et, Prⁿ, Buⁿ, n-C₅H₁₁; R² = Et, Prⁱ.

The reaction of γ -*N*-benzylamino β -keto phosphonates **69** with zinc borohydride gives *anti*- γ -amino β -hydroxy phosphonates **70** with good diastereoselectivity.¹⁰¹

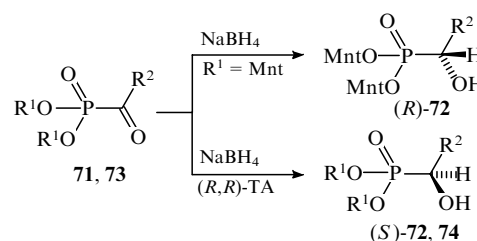


R = Prⁱ, Ph.

This strategy has been used to prepare 1,5-dihydroxy-2-oxopyrrolidine-3-phosphonic acid (SF-2312), which is active against Gram-positive and Gram-negative bacteria.¹⁰²

Sodium borohydride reduces sodium acylphosphonates and bis(acylphosphonates) to the corresponding hydroxyalkylphosphonates and dihydroxyalkylenebis(phosphonates).¹⁰³

The reduction of dimethyl keto phosphonates **71** with sodium borohydride in THF has a low stereoselectivity, (*R*)-1-hydroxybenzylphosphonates **72** were obtained with *de* ~ 30%–35%.¹⁰⁴ The stereoselectivity can be increased through the formation of the chiral complex of sodium borohydride with natural D-tartaric acid. The enantioselective reduction of diethyl aroylphosphonates **73** with chiral NaBH₄–(*R,R*)-TA complex affords diethyl (*S*)-1-hydroxybenzylphosphonates **74** with *ee* ~ 60%, whereas the reduction of dimethyl aroylphosphonates **71** yields (*S*)-dimethyl 1-hydroxybenzylphosphonates **72** with the diastereomeric excess (*de*) 80%–93%.¹⁰⁵

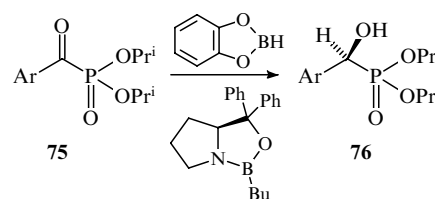


R¹ = (1*R*,2*S*,5*R*)-Mnt (**71**, **72**), Et (**73**, **74**);

R² = Ph, C₆H₄F, C₆H₄OMe; TA is tartaric acid.

Higher stereoselectivity observed in the reduction of dimethyl aroylphosphonates is due to the double asymmetric induction effect, because in this case the inductions by the menthyl residues and tartaric acid are combined.

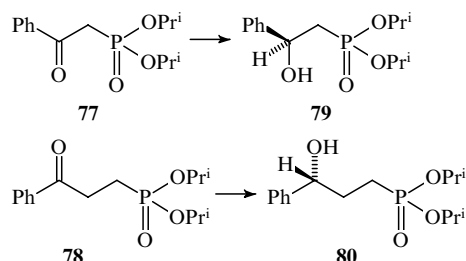
It has been proposed^{15, 106, 107} to prepare chiral α -, β - and γ -hydroxy phosphonates by the reduction of aroylphosphonates with catecholborane or a borane–dimethyl sulfide complex in the presence of 1,3,2-oxazaborolidine as the catalyst. The enantioselective reduction of diisopropyl α -keto phosphonates **75** with



Ar = 2-MeOC₆H₄, 2-MeC₆H₄, 2-ClC₆H₄, 3-ClC₆H₄, 4-ClC₆H₄, 2-FC₆H₄, 2-BrC₆H₄.

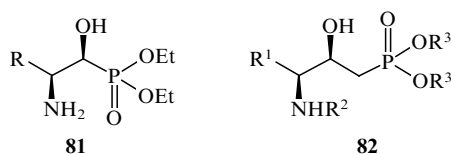
borane or catecholborane controlled by (*S*)-oxazaborolidines leads to (*S*)-1-hydroxybenzylphosphonates **76** with 53%–83% enantiomeric excess.

Conversely, the reduction of β - (**77**) and γ -keto phosphonates **78** under the same conditions affords β - and γ -hydroxyalkylphosphonates (**79** and **80**) with *R* absolute configuration.



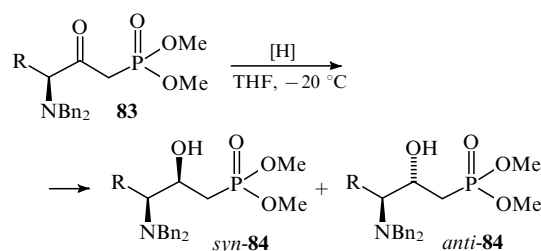
Treatment of α -keto phosphonates **75** with (–)-chlorodiisopinocampheylborane affords diisopropyl (*S*)-1-hydroxybenzylphosphonates **76** with higher enantiomeric excesses than the reaction with catecholborane in the presence of oxazaborolidine.¹⁵

The reduction of α -keto β -phthalimido phosphonates with catecholborane in the presence of oxazaborolidine as the catalyst followed by deprotection of the amino group results in β -amino α -hydroxy phosphonates **81** with a high diastereoselectivity and in good yields.¹⁰⁸ The same procedure was used to convert γ -amino β -keto phosphonates into 3-amino 2-hydroxy phosphonates **82**, which are phosphate mimetics stable against hydrolysis.¹⁰⁹



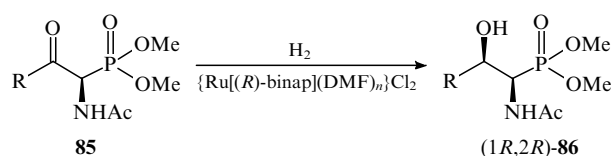
R = Me, Prⁱ, Buⁱ, Bn, 4-BnOC₆H₄CH₂.

The diastereoselectivity of the reduction of γ -*N,N*-dibenzyl-amino β -keto phosphonates **83** does not depend on steric factors, which are determined by the size of the substituent at C(3). The configurations of hydroxy phosphonates **84** were confirmed by X-ray diffraction analysis and NMR spectroscopy.¹¹⁰



R	Reducing agent	Yield (%)	syn : anti
Pr ⁱ	AlHBu ₂ ⁱ (DIBAL-H)	50	82 : 18
Pr ⁱ	NaBH ₄	44	85 : 15
Pr ⁱ	catecholborane	69	> 98 : 2
Me	catecholborane	85	> 98 : 2
Bn	catecholborane	89	> 98 : 2
Ph	catecholborane	82	90 : 10

The hydrogenation of (*R*)- α -acetamido β -keto phosphonates **85** in the presence of the chiral ruthenium binaphthyl complex gives hydroxy phosphonates (1*R*,2*R*)-**86** with good enantio- and diastereoselectivity.¹¹¹



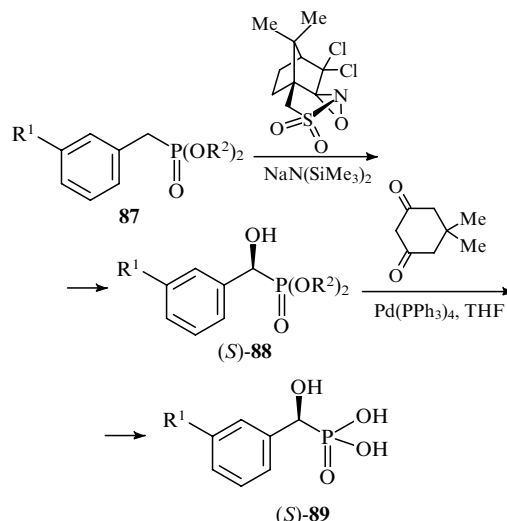
binap is 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl.

Tomioka *et al.*¹¹² carried out photoreduction of dialkyl keto phosphonates, which results in α -hydroxy phosphonates in ~60%–70% quantum yields.

3. Oxidation

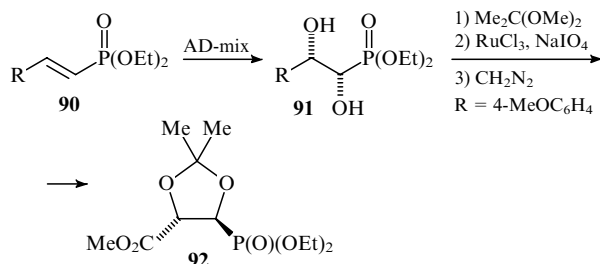
The oxidation of alkyl- and alkenylphosphonates is widely used in the synthesis of hydroxy phosphonates. This method has found wide use since oxidation of double carbon–carbon bonds in the asymmetric epoxidation or the Sharpless dihydroxylation in the case of organophosphorus compounds gives products in high yields and with high optical purity.

The stereoselective oxidation of benzylphosphonates **87** with chiral oxaziridines gives α -hydroxy phosphonates **88** with a rather high optical purity, *ee* can reach 69%–98%. De-esterification of α -hydroxy phosphonates **88** with dimedone in the presence of the palladium catalyst occurs with almost no racemisation and affords α -hydroxy phosphonic acids **89** with *ee* 90%–96%.^{16, 113}



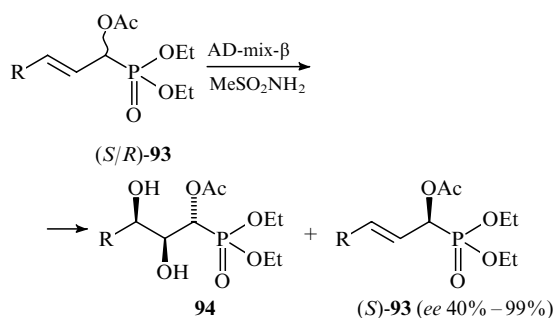
R ¹	R ²	The <i>ee</i> of 88 (%)	Ref.
H	Me	93	16
NO ₂	Me	80	16
Cl	Me	87	16
OMe	Me	81	16
CF ₃	Et	98	113
H	CH ₂ =CHCH ₂	96	113
OPh	CH ₂ =CHCH ₂	98	113

The asymmetric dihydroxylation of (*E*)-alkenylphosphonates **90** by AD-mix- α or AD-mix- β reagents, which represent mixtures of phthalazine adducts with dihydroquinine or dihydroquinidine, potassium ferricyanide, potassium carbonate and potassium osmate, results in the formation of optically active *threo*- α,β -dihydroxy phosphonates **91**.^{114–116} The highest enantioselectivity (*ee* > 88%) is attained upon the oxidation of (*E*)-alkenylphosphonates containing an aromatic substituent at the double bond. Diol **91** (R = 4-MeOC₆H₄) was converted into dioxolane **92** upon the Martin catalytic oxidative degradation of the *p*-methoxyphenyl group. Dioxolanes of type **92** are convenient chiral intermediates for the synthesis of phosphonates containing a heteroatom at the α -carbon atom.¹¹⁴



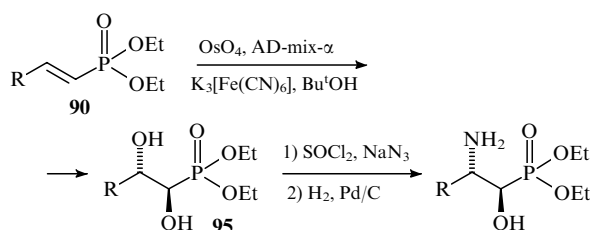
R	AD-mix	The yield of 91 (%)	ee (%)
Ph	AD-mix- α	42	91
4-MeOC ₆ H ₄	AD-mix- α	71	95
4-MeOC ₆ H ₄	AD-mix- β	69	98
3-MeOC ₆ H ₄	AD-mix- α	67	96
4-ClC ₆ H ₄	AD-mix- α	65	98
1-Naphthyl	AD-mix- α	80	93
2-Furyl	AD-mix- α	17	88
n-C ₇ H ₁₃	AD-mix- β	63	84

The racemic mixture of (*S/R*)-1-acetoxy-2-(*E*)-alkenylphosphonates **93** can be resolved by kinetically controlled dihydroxylation with AD-mix- α or AD-mix- β .¹¹⁷ The stereochemistry of dihydroxylation depends on the configuration of the α -carbon atom and the nature of substituents at the double bond. For example, AD-mix- β oxidises mainly the (*R*)-enantiomer of compound **93**; hence, in addition to the optically active (1*R*,2*S*,3*R*)-1-acetoxy-2,3-dihydroxyphosphonate **94** formed, the reaction mixture contains non-consumed (*S*)-acyloxyphosphonate **93**, which can be isolated with a good optical purity.

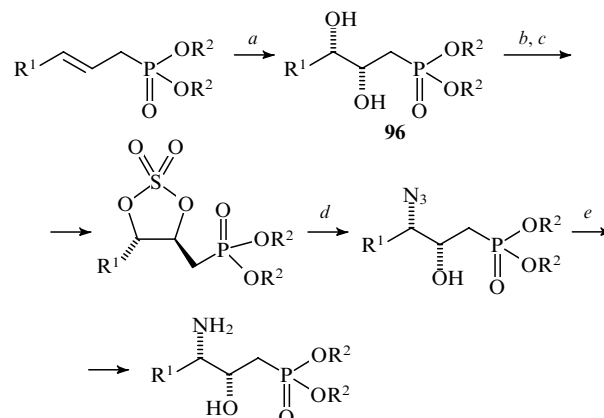


R = H, Ph, 4-MeOC₆H₄.

Dihydroxyalkylphosphonates **95** and **96** are prepared by asymmetric dihydroxylation of vinyl- and allylphosphonates. Dihydroxy derivatives **95** and **96** are converted into 2-amino-1-hydroxy- and 3-amino-2-hydroxyalkylphosphonates through formation of azido derivatives and the catalytic reduction of the azide group.^{116–119} Chiral 3-amino-2-hydroxyalkylphosphonates are used in the synthesis of phosphocarnitine analogues.¹¹⁸

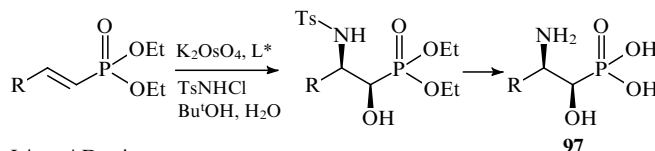


R = H, Ph, 4-BrC₆H₄, 4-O₂NC₆H₄, 4-MeOC₆H₄.



R¹ = H, Me, 4-MeOC₆H₄CO₂CH₂; R² = Et, Bn;
(a) AD-mix- α , K₂OsO₄; (b) SOCl₂, Py; (c) NaIO₄, RuCl₂;
(d) NaN₃, H₂SO₄; (e) PPh₃, H₂O.

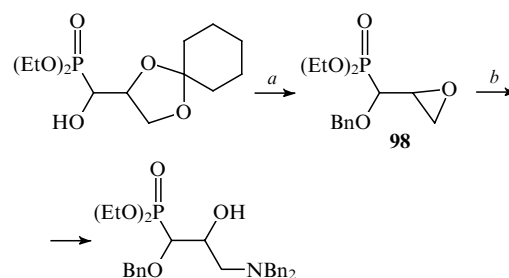
The asymmetric aminohydroxylation of diethyl (*E*)-styrylphosphonates with potassium osmate(VI), tosylamine and AD-mix- α as the chiral inductor results in (1*R*,2*S*)-threo-2-amino-1-hydroxyphosphonic acids **97**.^{119, 120}



L* = AD-mix- α

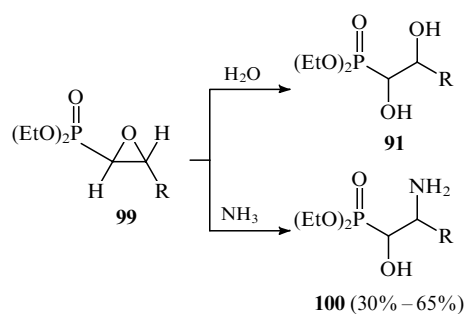
R	Yield (%)	ee (%)
Ph	65	60
4-BrC ₆ H ₄	71	75
4-O ₂ NC ₆ H ₄	75	92
4-MeOC ₆ H ₄	72	45
H	55	15

The diastereomeric diethyl (1*R*,2*R*)- and (1*S*,2*R*)-1-benzoyloxy-2,3-epoxypropylphosphonates (**98**) were synthesised from 2,3-*O*-cyclohexylidene-1,2,3-trihydroxypropylphosphonate; its reaction with dibenzylamine yielded (1*R*,2*R*)- and (1*S*,2*R*)-3-dibenzylamino-1-benzoyloxy-2-hydroxypropylphosphonates.¹²¹



(a): (1) BnBr, Ag₂O; (2) HCl, dioxane; (3) MeC(OMe)₃, PPTS;
(4) AcBr, K₂CO₃, MeOH; (b) NHBn₂;
PPTS is pyridinium *p*-toluenesulfonate.

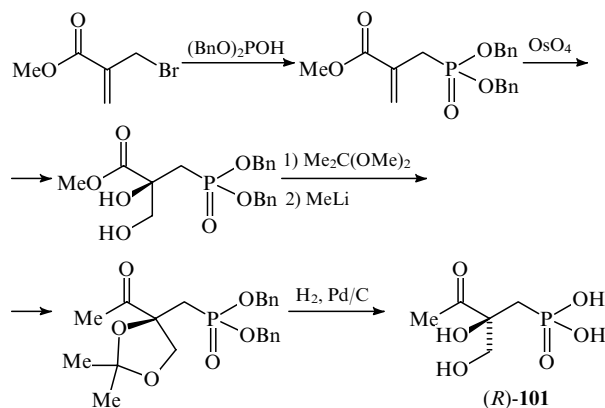
Cristau and co-workers^{122, 123} obtained 1,2-dihydroxyethylphosphonates **91** by hydrolysis of ethyl 1,2-epoxy alkylphosphonates **99**. Opening of the oxirane ring in compound **99** by amines resulted in 2-amino-1-hydroxyalkylphosphonates **100**, analogues of HO-AEP.



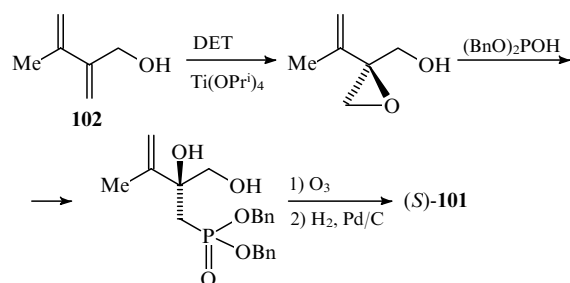
R = H, Bu^n , Ph, 2- MeC_6H_4 , 3- MeC_6H_4 , 4- MeC_6H_4 , 2- MeOC_6H_4 , 1-naphthyl.

Amino hydroxy phosphonates were also prepared by catalytic methanolysis of 2-phosphorylaziridine.¹²¹

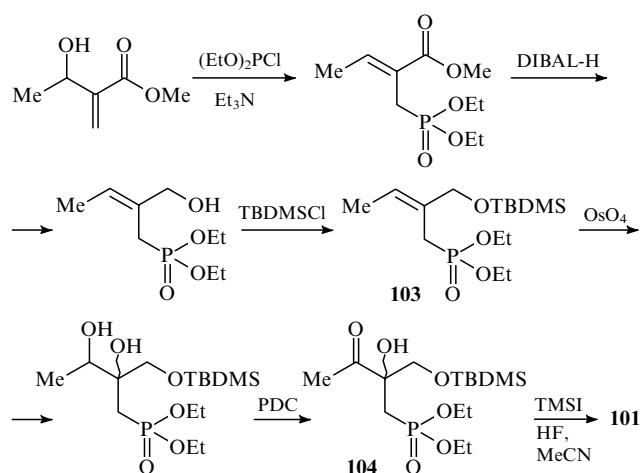
Nakamura *et al.*¹²⁴ developed the synthesis of phosphonothrixin (**101**) starting from methyl bromomethacrylate, which was first converted into allylic phosphonate by the Michaelis–Becker reaction and then hydroxylated with osmium tetroxide. The dihydroxyalkylphosphonate thus formed was converted into (*R*)-phosphonothrixin (**101**), as shown in the scheme.



Another synthetic route to phosphonothrixin, which was also proposed by Nakamura *et al.*,^{124, 125} starts with the asymmetric Sharpless epoxidation of the dienic alcohol **102** to give chiral (*R*)-epoxy alcohol (*ee* 92%), which reacts with dibenzyl phosphite to give dihydroxyalkylphosphonate. The subsequent ozonolysis and debenzylation of the dihydroxyalkylphosphonate furnish (*S*)-phosphonothrixin (**101**) with *ee* 92%. The (*R*)-enantiomer of phosphonothrixin was also synthesised by this method.

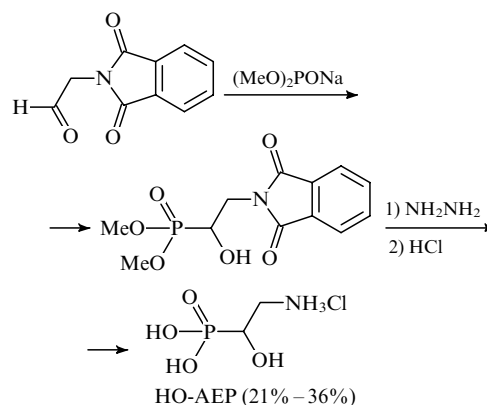


The total six-step synthesis of phosphonothrixin (**101**) was developed on the basis of commercially available methyl 3-hydroxy-2-methylidenbutyrate, which reacts with diethyl phosphorochloridite in the presence of triethylamine; this is followed by reduction of the ester group and yields allylic phosphonate **103** in 60% yield.¹²⁶ Dihydroxylation of phosphonate **103** with osmium tetroxide and subsequent oxidation of the secondary alcohol group gives the protected phosphonothrixin **104** in 80% yield. After removal of the protecting groups, free phosphonothrixin (**101**) was obtained in an overall yield of 24%.^{126, 127}

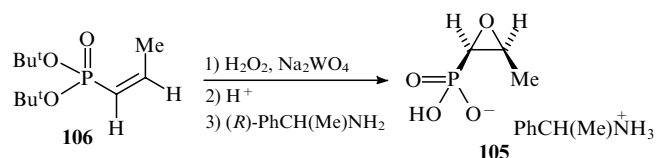


TBDMS = $\text{Bu}^t\text{Me}_2\text{Si}$; TMS = Me_3Si ; PDC is pyridinium dichromate.

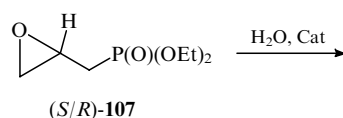
Natural 1-hydroxy-2-aminoethylphosphonic acid (HO-AEP), which was isolated from the membrane of the soil amoeba *Acanthamoeba castellanii*, is synthesised by the addition of sodium dimethyl phosphite to *N*-(2-oxoethyl)phthalimide followed by removal of the phthaloyl group with hydrazine and acid hydrolysis of the ester groups.¹²⁸

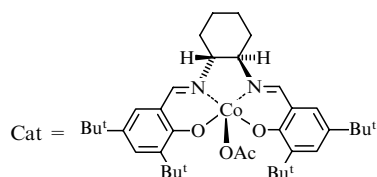
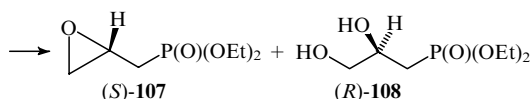


Phosphomycin, (1*R*,2*S*)-(Z)-1,2-epoxypropylphosphonic acid (**105**), was prepared by catalytic epoxidation of vinylphosphonate **106** with subsequent hydrolysis and resolution of racemic phosphomycin into enantiomers using (+)- α -phenylethylamine.¹²⁹

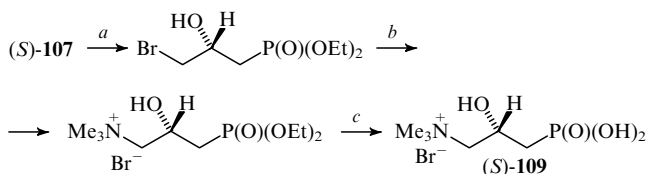


Kinetically controlled hydrolysis was proposed for the enantioselective resolution of racemic epoxyalkylphosphonates.^{117–130} The conventional acid hydrolysis of epoxide (*S*)-**107** gives diol (*S*)-**108** with *ee* of only 72%. However, partial kinetically controlled hydrolysis of racemic epoxide (*S*/*R*)-**107**, which occurs in the presence of cobalt (*R,R*)-salen complex, affords chiral diethyl (*R*)-2,3-dihydroxypropylphosphonate **108** with *ee* 98%.^{131, 132} Epoxide (*S*)-**107** with *ee* 82% remains in the reaction mixture.





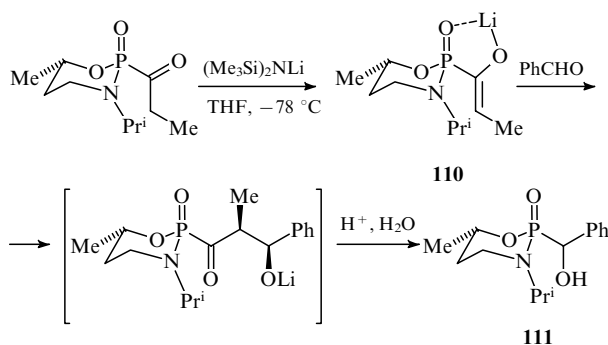
Diethyl (*S*)-2,3-epoxypropylphosphonate **107** is converted into phosphocarnitine (*S*)-**109** according to the following scheme:¹³²



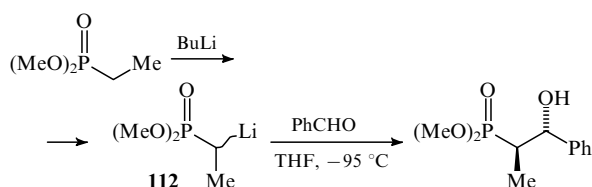
(a) MgBr₂, (b) Me₃N, (c) HCl, H₂O.

4. C-Modification

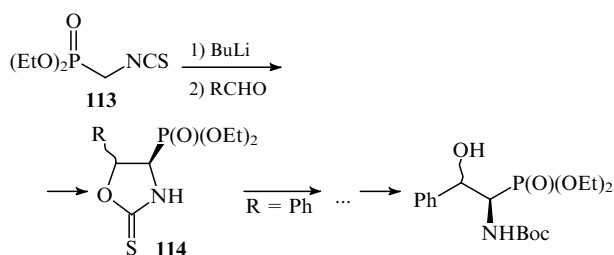
The addition of lithium derivative of (*S,S*)-2-(α -hydroxypropenyl)-2-oxo-1,3,2-oxazaphosphorinane **110** to benzaldehyde results in a diastereomer mixture of α -hydroxy-2-oxo-1,3,2-oxazaphosphorinanes **111** in 3 : 1 ratio.¹³³



The reaction of the lithium derivative of dimethyl ethylphosphonate **112** with aromatic aldehydes in THF provides β -hydroxyalkylphosphonates with 85% diastereoselectivity.¹³⁴



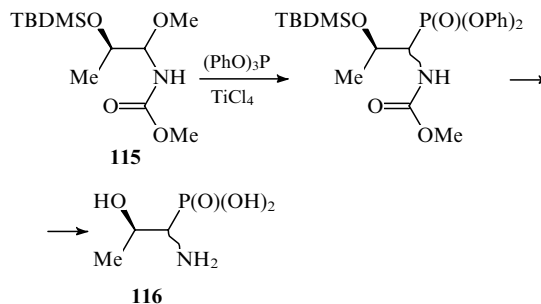
Diethyl isothiocyanomethylphosphonate **113** reacts with butyllithium to give a carbanion, which add to aldehydes yielding a diastereomer mixture of 2-thioxo-1,3-oxazolidin-4-ylphosphonates **114**.



R = Prⁱ, Bu^t, Ph, PhCH=CH, 1-furyl.

phosphonates **114**; these are converted into *N*-Boc-protected 1-amino-2-hydroxyalkylphosphonates in three steps.¹³⁵

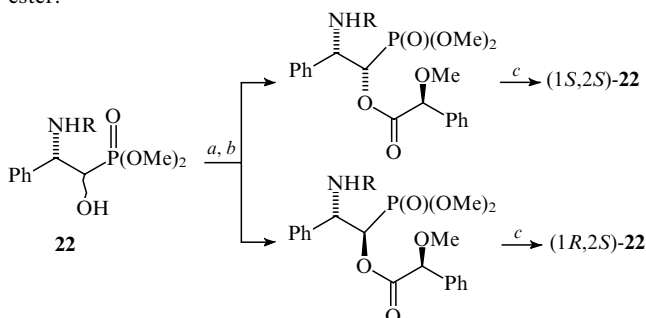
N,O-Acetals **115** containing a chiral group react with triphenyl phosphite in the presence of TiCl₄ to give a mixture of (*R,R*)- and (*S,R*)-diastereomeric α -amino- β -hydroxypropylphosphonates **116** in 2 : 1 ratio. Pure diastereomers are obtained by fractional crystallisation.¹³⁶



5. Chromatographic separation

The resolution of racemic hydroxy phosphonates into enantiomers (in the form of diastereomers) by column chromatography is used rather often to obtain chiral hydroxy phosphonates.^{137–140} Good results can be attained by using silica gel Merck 60 (70–230 mesh); the course of separation is monitored by TLC. Iodine vapour or, whenever possible, an ultraviolet detector is used to visualise the plates.

Wróblewski and Piotrowska^{45,46} separated dimethyl 2-*tert*-butoxycarbonylamino- and dimethyl 2-benzoylamino-1-hydroxy-2-phenylethylphosphonate stereoisomers (**22**) upon esterification with (*S*)-*O*-methylmandelic acid followed by chromatography of the resulting diastereomer mixtures on silica gel. The yield of the less polar diastereomer was 43% and that of the more polar diastereomer, 36%, the latter being obtained in the crystalline state. Enantiomerically pure phosphonates (1*S*,2*S*)-**22** and (1*R*,2*S*)-**22** are formed in good yields upon ammonolysis of the ester.^{45,46}

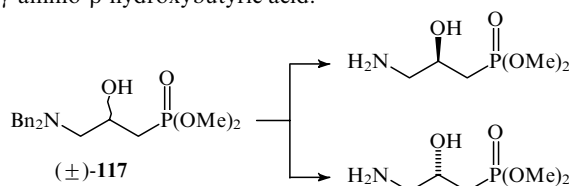


R = Boc, PhC(O);

(a) (*S*)-PhCH(OMe)CO₂H, DCC, DMAP; (b) chromatography;

(c) 25% NH₃, H₂O.

By using a similar approach, Ordóñez *et al.*¹³⁸ resolved racemic (*S/R*)-2-hydroxy-3-(*N,N*-dibenzylamino)propylphosphonate **117** into optically pure enantiomers, which are analogues of γ -amino- β -hydroxybutyric acid.



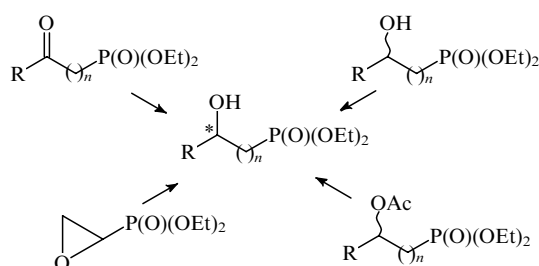
Enantiomeric diethyl hydroxy(aryl)methylphosphonates containing *para*- or *ortho*-substituted benzene or other aromatic rings (naphthalene, thiophene) are separated by HPLC on a chiral stationary phase.¹³⁹ The resolution of enantiomers of diethyl

α -hydroxyfarnesylphosphonate, which is a precursor of a farnesyl protein transferase inhibitor, is attained by semipreparative HPLC on a chiral chromatographic column Chiralcel OD.¹⁴⁰

The separation of stereoisomeric 1-amino-2-hydroxy- and 2-amino-1-hydroxypropylphosphonic acid by capillary electrophoresis using chiral quinine carbamate has been described.¹⁴¹

6. Enzymatic synthesis

Enzymatic synthesis is an efficient alternative to the standard chemical synthesis of optically active hydroxy phosphonates. Bacteria, fungi and enzymes can be used as biocatalysts for the preparation of enantiomerically pure hydroxy phosphonates.^{142, 143} The following general approaches to the enzymatic synthesis of hydroxyalkylphosphonates are best developed: biocatalytic reduction of keto phosphonates; enantioselective acylation of racemic hydroxy phosphonates using microorganisms or enzymes for the separation of stereoisomers; enantioselective hydrolysis of acyloxyalkylphosphonates and epoxyethylphosphonates.

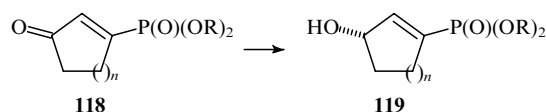


$n = 0, 1, 2$.

Ketophosphonates are reduced successfully using baker's yeast and some fungi. Baker's yeast is most convenient due to its ready availability, versatility and the ease of application.

Baker's yeast has been used^{144–146} for the enantioselective reduction of diethyl β -, γ - and δ -oxoalkylphosphonates, which yielded hydroxy phosphonates with a high optical purity ($ee > 95\%$). The reactions were carried out under aerobic conditions. In the case of low reactive compounds, anaerobic reduction was used.¹⁴⁵ This method has also been used to synthesise optically active β -keto γ - and δ -hydroxy phosphonates.¹⁴⁷

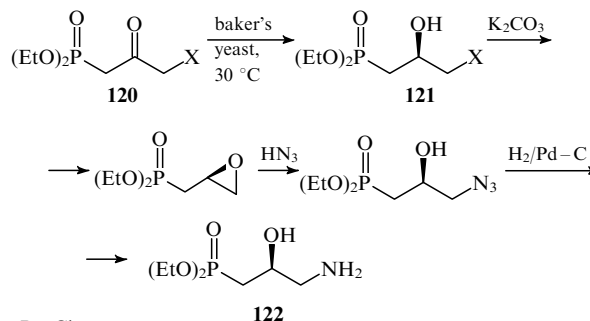
Maffei and co-workers¹⁴⁸ studied the enantioselective reduction of dialkyl 3-oxocycloalk-1-enylphosphonates **118** with baker's yeast and obtained dialkyl (*S*)-3-hydroxycycloalk-1-enylphosphonates **119**, which are important intermediates in the synthesis of a number of biologically active compounds. It was concluded that the reduction of six-membered cyclic keto phosphonates proceeds with a higher enantioselectivity (ee 76%) than that involving five- and seven-membered analogues. The highest stereoselectivity is achieved in the reduction of six-membered cyclic keto phosphonates in organic solvents (hexane, benzene, *tert*-butyl methyl ketone); in this case, hydroxy phosphonates **119** are formed with ee 65%–82%. An increase in the bulkiness of alkoxy groups at phosphorus (from methoxy to isopropoxy) increases the optical purity of dialkyl 3-hydroxycycloalk-1-enylphosphonates to ee 95% irrespective of the reduction conditions.



$R = \text{Me, Et, Pr}^i; n = 1–3$.

Solvent	The yield of 119 (%)	ee (%)
$n\text{-C}_6\text{H}_{14}$	84	65
$\text{MeC}(\text{O})\text{Bu}^t$	15	82
C_6H_6	7	69

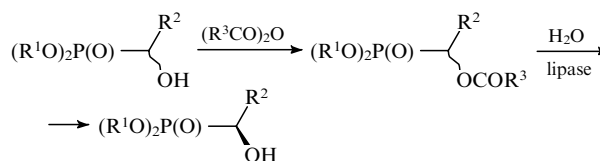
Yuan *et al.*¹⁴⁹ performed the enantioselective reduction of 3-halo-2-ketopropylphosphonates **120** with baker's yeast; this gave optically active 3-halo-2-hydroxy propylphosphonates **121** in moderate yields and a satisfactory optical purity. Compounds **121** are used in the synthesis of 3-amino-2-hydroxypropylphosphonates **122**.



$X = \text{Br, Cl}$.

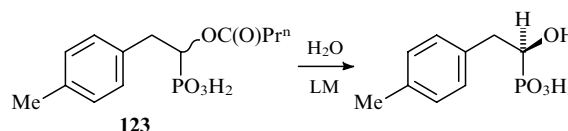
Enzyme-catalysed acylation or hydrolysis constitute convenient methods for the separation of racemic hydroxy phosphonates.^{150–161}

Optically pure *S*-enantiomers of the hydroxy phosphonate series have been obtained^{154, 157} in satisfactory yields with high enantiomeric excess by enzymatic hydrolysis of the acyl derivatives of racemic hydroxy phosphonates catalysed by lipases from *Aspergillus niger*, *Rhizopus oryzae* and *Candida rugosa*.

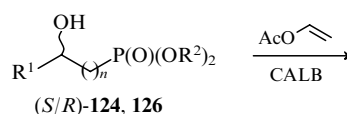


$R^1 = \text{Et, Pr}^i; R^2 = \text{Et, Pr}^n, \text{Pr}^i, \text{Bu}^n, \text{Bu}^i, \text{Bu}^t, n\text{-C}_5\text{H}_{11};$
 $R^3 = \text{ClCH}_2, \text{Me, Et}.$

Hydrolysis of racemic 1-butyryloxyalkylphosphonic acid **123** with lipolytic microorganisms (LM), namely, the bacteria *Pseudomonas fluorescens* or the fungi *Penicillium citrinum*, leads to optically pure (*S*)-hydroxy phosphoric acid.^{143, 152}



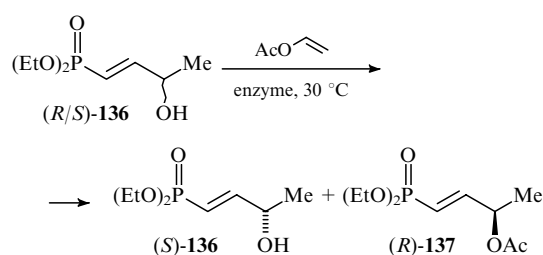
Racemic α -hydroxyalkylphosphonates **124** are subjected to acetylation catalysed by lipases from *Candida antarctica* B (CALB) and *Candida rugosa* (CRL); after that, the remaining *R*-isomer of hydroxy phosphonate **124** is separated from the *S*-isomer of acetyl derivative **125**.¹⁴⁷ Yuan and co-workers¹⁵³ used CALB in organic solvents for the enantioselective acetylation of racemic β -hydroxyalkylphosphonates **126**. The subsequent separation of the non-consumed alcohol (*S*)-**126** from ester (*R*)-**127** gives pure stereoisomers. In both cases, vinyl acetate was used as the acylation agent. This method for the preparation of chiral hydroxyalkylphosphonates is characterised by high enantioselectivity and experimental convenience.



phosphonates are converted into L-phosphoisoserine (**134**) and L-phosphoserine (**135**) using catalytic hydrogenation and the Staudinger reaction.

A similar method has been used to prepare chiral methyl sulfides (*ee* 93%–97%) from racemic α -hydroxy phosphonates, which are resolved using enzymatic hydrolysis of acyl derivatives.¹⁶⁶ The enzymatic acetylation of racemic diisopropyl α -hydroxy phosphonates with isopropenyl acetate in *tert*-butyl methyl ether allows one to obtain (*S*)-diisopropyl-1-hydroxy-(2-thienyl)methyl-, -1-hydroxyethyl-, -1-hydroxycyclohexylmethyl-phosphonate and (*R*)-2-hydroxypropylphosphonate acetates with enantiomeric excesses reaching 99%. Using enzymatic hydrolysis, (*S*)-2-hydroxy-2-phenylethyl- and (*S*)-2-hydroxy-3-methylbutyl-phosphonates can be converted into (1*R*,2*R*)-2-amino-1-hydroxy-phosphonic acids.^{167–169} Enzymatic hydrolysis was used in the synthesis of phosphomycin.^{169, 170}

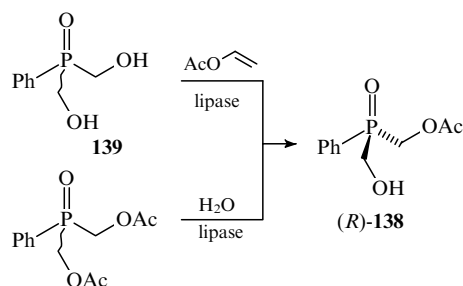
Acetylation of racemic diethyl 3-hydroxybut-1-enylphosphonate (**136**) catalysed by various enzymes and subsequent separation of the components of the reaction mixture affords enantiomerically pure diethyl (*S*)-3-hydroxybut-1-enylphosphonate **136** and diethyl (*R*)-3-acetoxybut-1-enylphosphonate **137** with enantiomeric excesses reaching 99%.¹⁷¹



Enzyme	<i>ee</i> (%)	
	(<i>S</i>)- 136	(<i>R</i>)- 137
Lipozyme	99	96
Amano AK	97	96
Amano PS	81	98
Acylase from <i>Asp. melleus</i>	49	98
CALB	91	14
PPL	22	99
CRL	8	54

Lipases from *Geotrichum candidum*, *Rhizopus niveus*, *Penicillium* species, *Aspergillus usami*, *Mucor* species and *Pseudomonas cepacia* and porcine pancreatic lipase are used for stereoselective acetylation of racemic hydroxyphosphonates in toluene.^{172–181} Thus lipase from *Geotrichum candidum* catalyses the enantioselective acetylation of racemic hydroxy phosphonates to give the acetylated product in a 32%–34% yield and with optical an purity of 95%.¹⁷²

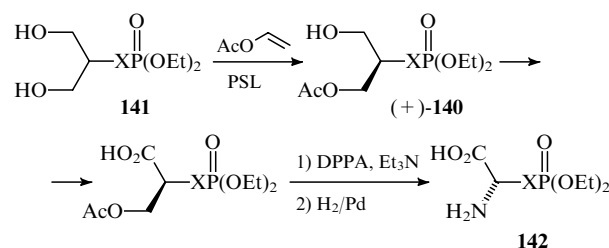
The optically pure monoacetate (*R*)-**138** is prepared from prochiral bis(hydroxymethyl)phenylphosphine oxide (**139**) by



Lipases Amano AK, PFK1 (from *Pseudomonas fluorescens*), Amano PS.

enzymatic acetylation with vinyl acetate in an organic solvent or enzymatic hydrolysis of bis(acetoxymethyl)phenylphosphine oxide.¹⁷³

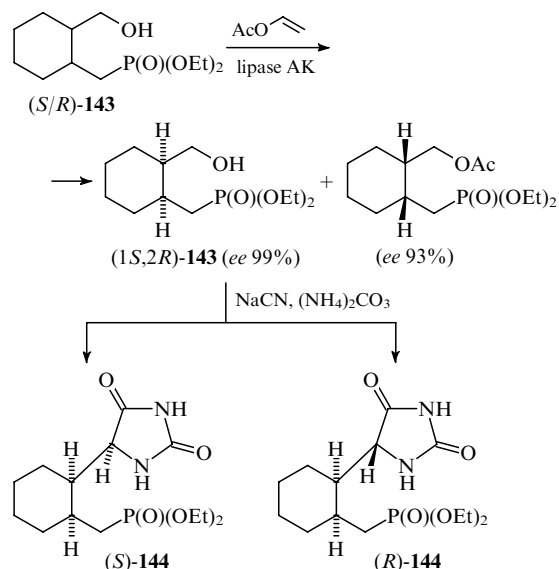
Shibuya and co-workers¹⁷⁴ prepared optically active alcohols **140** by enantioselective acylation of prochiral 2-(ω -phosphonoalkyl)propane-1,3-diols **141** with vinyl acetate in an organic solvent catalysed by lipase from *Pseudomonas cepacia* (PSL). Chiral alcohols (+)-**140** are formed in good yields and high enantiomeric excesses. Alcohols (+)-**140** are then converted into optically active α -amino- ω -phosphono acids **142**, which possess various biological activities and are intermediates in the synthesis of aminopentylphosphonic acid analogues.



X = CH₂, (CH₂)₂, CH₂CF₂; DPPA is diphenoldiphenoxyposphoryl azide.

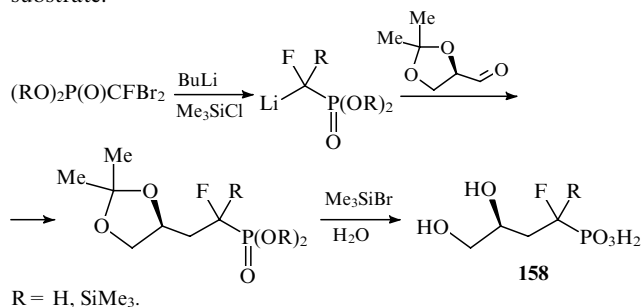
Solvent	The yield of 140 (%)	<i>ee</i> (%)
Pr ⁱ ₂ O	82	98
Pr ⁱ ₂ O (lipase AK)	98	70
THF	98	98
C ₆ H ₆	94	98
C ₆ H ₁₄	72	79

The same authors¹⁷⁵ carried out the kinetic resolution of racemic 1-diethoxyphosphorylmethyl-2-hydroxymethylcyclohexane (**143**) into enantiomers in good yields and high enantiomeric excesses by acetylation catalysed by lipases PSL or AK. Optically active alcohol (1*S*,2*R*)-**143** was converted into (*S*)- and (*R*)-hydantoin **144**.



PSL-catalysed hydrolysis of racemic or enantiomerically enriched acetates **145** gives enantiomerically pure α -hydroxy-alkylphosphinates (**146**) with *ee* 74%–99%.¹⁷⁶

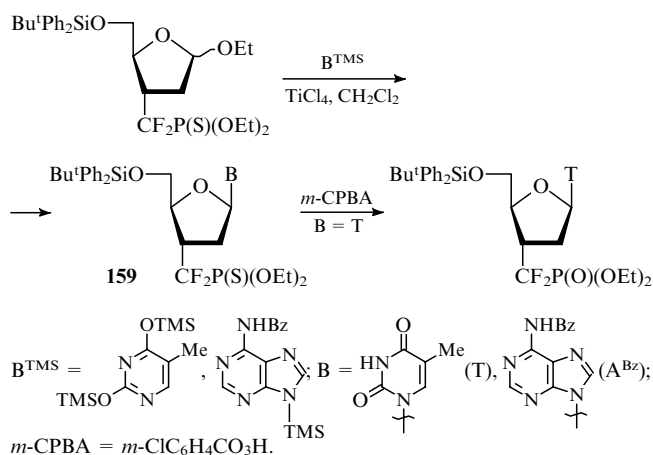
This method has been used¹⁸⁶ to prepare monofluorodi-hydroxybutylphosphonic acid **158**, which is an analogue of glycerol 3-phosphate, the glycerol 3-phosphate dehydrogenase substrate.



The CuBr-activated reaction of (diethylphosphonyl)difluoromethylzinc bromide with aryl iodides results in aryldifluoromethylphosphonates. Treatment of these compounds with trimethylsilyl bromide gives free acids, some of which being low-molecular-mass inhibitors of phosphatase.¹⁸⁷

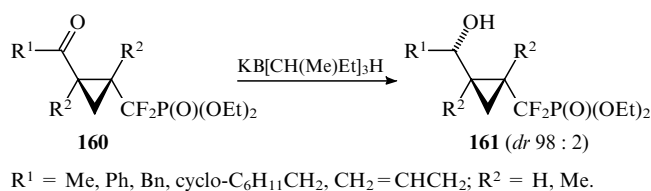
Berkowitz *et al.*¹⁸⁸ described a facile method for the synthesis of difluoroalkylphosphonates; this method was used to prepare difluoromethylphosphonic analogues of L-serine, L-allothreonine and L-threonine.

Shibuya and co-workers^{189,190} reported the synthesis of nucleotide analogues containing a phosphoryldifluoromethyl group. Titanium tetrachloride-catalysed glycosylation of the trimethylsilyl derivatives of heterocyclic bases with 2,3-dideoxy-ribofuranosides containing a thiophosphoryldifluoromethyl group at C(3) is a method for preparing pyrimidine β -nucleosides **159** with high stereoselectivity (*dr* 89 : 11). The oxidation of the thymine-containing nucleoside with *m*-chloroperbenzoic acid gives rise to the difluoromethylphosphonate analogue of thymidine 3'-phosphate.

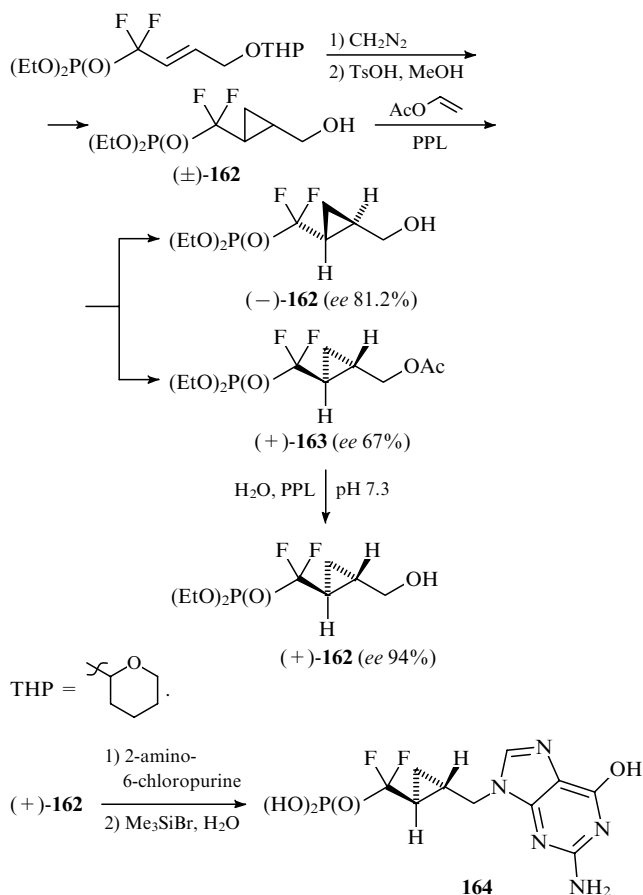


A solid-state method for the synthesis of fluorinated α -hydroxy phosphonates has been proposed.¹⁹¹ Keen interest is aroused by the fluorophosphonates containing a cyclopropyldifluoromethyl group, which has a pronounced effect on the biological properties of compounds.^{192–195} For example, {(1*S*,2*S*)-2-[(1*S*)-1-(6-oxo-1,6-dihydropurin-9-yl)ethyl]cyclopropyl}difluoromethylphosphonate is an efficient inhibitor of purine nucleoside phosphorylase.¹⁹⁴

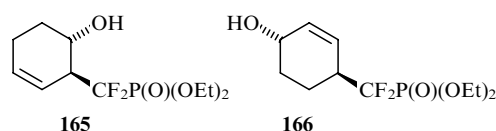
The reduction of [(1*S*,2*S*)-2-acetylcyclopropyl]difluoromethylphosphonates **160** with K-selectride occurs from the less hindered side of the carbonyl group (*si*-stereofacial) and gives cyclopropylethanols **161** with a high diastereoselectivity.



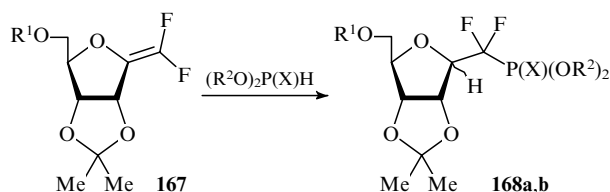
The synthesis of enantiomerically pure diethyl *trans*-4-hydroxy-1,1-difluoro-2,3-methanobutylphosphonate [(+)-**162**] by the reaction of diethyl 4-tetrahydropyranyloxy-1,1-difluorobut-2-enylphosphonate with diazomethane followed by enzymatic double resolution of the resulting racemic hydroxyphosphonates ($\pm$)-**162** has been reported.¹⁹⁵ By PPL-catalysed acetylation and hydrolysis of the enantiomerically enriched acetoxy phosphonate (+)-**163**, the optical purity of hydroxy phosphonate (+)-**162** was increased to *ee* 94%. Chiral hydroxy phosphonate (+)-**162**, the structure of which was confirmed by X-ray diffraction, was used for the synthesis of optically active 9-[(2*S*,3*S*)-4-phosphono-4,4-difluoro-2,3-methanobutyl]guanine (**164**), which is a purine nucleoside phosphorylase inhibitor.¹⁹⁵



Shibuya and co-workers¹⁹⁶ reported the synthesis of (hydroxycyclohexenyl)difluoromethylphosphonates **165** and **166** by the CuBr-catalysed reaction of (diethoxyphosphoryl)difluoromethylzinc bromide with hydroxycyclohex-2-en-1-yl phosphates. Compounds **165** and **166** are intermediates in the stereoselective synthesis of inositol phosphate analogues.

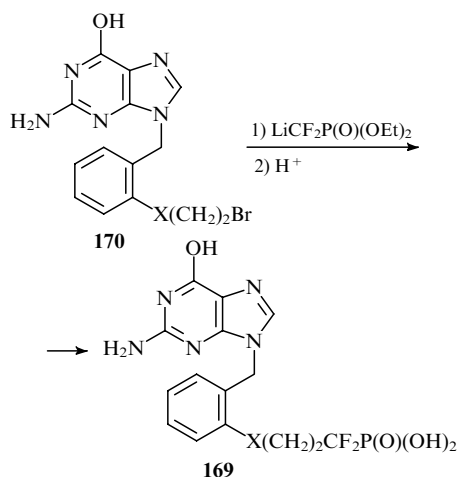


The reaction of dialkyl phosphites and thiophosphites with carbohydrate difluoromethylidene derivatives **167** yields anomeric mixtures of glycosyldifluoromethylphosphonates **168a** and -thiophosphonates **168b** with the isopropylidene protecting group.¹⁹⁷



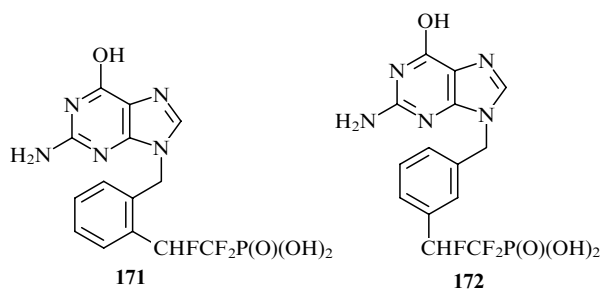
$R^1 = \text{H}$, $\text{Bu}^t\text{Me}_2\text{Si}$; $R^2 = \text{Et}$, Bn ; $X = \text{O}$ (a), S (b).

The synthesis of nucleotides **169**, containing a difluoromethylphosphonate group, which are reverse transcriptase inhibitors, has been reported.²⁰¹ Compounds **169** were prepared by the reaction of the lithium derivative of difluoromethylphosphonate with the bromo-containing nucleoside analogue **170** and subsequent hydrolysis of the resulting diester.



$X = \text{CH}_2\text{CF}_2$, CHFCH_2 , $(E)\text{-CH}=\text{CH}$, $(E)\text{-CH}=\text{CH}$, $\text{O}(\text{CH}_2)_2\text{CF}_2$.

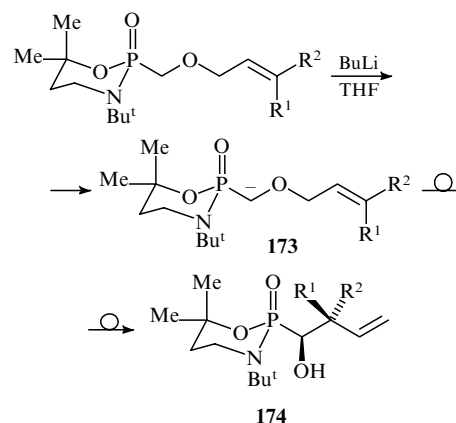
Fluorophosphonate derivatives of *N*⁹-benzylguanine **171** and **172**, functioning as purine nucleoside phosphorylase inhibitors, have been synthesised in a similar way.²⁰¹



8. Miscellaneous methods for the synthesis of hydroxy phosphonates

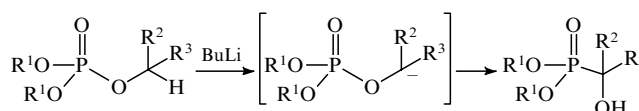
The asymmetric [2,3]-sigmatropic Wittig rearrangement of chiral phosphonate carbanions generated from allyloxymethyl and but-2-enyloxymethyl derivatives proceeds with high diastereo- and enantioselectivity.^{17,203} For example, deprotonation of allyl- and but-2-enyloxymethylphosphonamides under the action of butyllithium in THF at -70°C results in the formation of stable phosphonate carbanions **173**, which readily undergoes the

[2,3]-sigmatropic Wittig rearrangement to give hydroxy phosphonate **174** as the only diastereomer.¹⁷



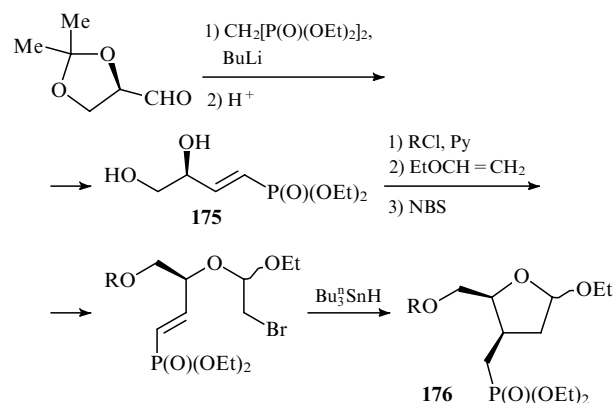
$R^1 = R^2 = \text{H}$; $R^1 = \text{Me}$, $R^2 = \text{H}$; $R^1 = \text{H}$, $R^2 = \text{Me}$.

Hammerschmidt²⁰⁴ described the phosphate-phosphate rearrangement, which gives rise to hydroxy phosphonates and is the model reaction for the biosynthesis of compounds with the $\text{P}-\text{C}$ bond.



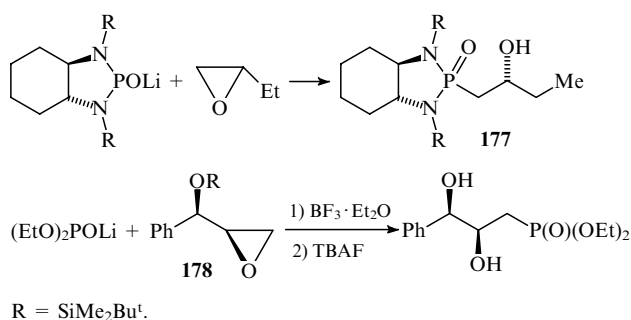
Hydroxy phosphonates are also obtained by the reaction of chiral epoxy chalcones with nucleophiles. In the presence of KF , diethyl phosphite adds preferentially to the *si*-face of the carbonyl group of epoxychalcones to give hydroxy phosphonates with *de* 50%.²⁰⁵

Shibuya and co-workers²⁰⁶ reported the synthesis of dihydroxy phosphonates **175** by the reaction of chiral isopropylidene-glyceraldehyde with bis(diethoxyphosphoryl)methane in the presence of butyllithium followed by deprotection of the hydroxy groups. The radical intramolecular cyclisation of the resulting dihydroxy phosphonates **175** yielded phosphonates **176**, which are analogues of 2-deoxyribose-3-phosphates, with the stereoselectivity (*de*) 76%–92%.

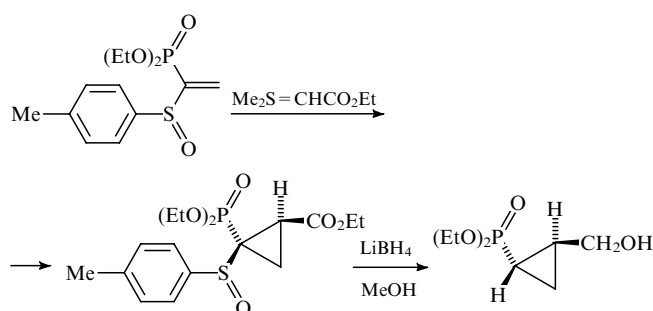


$R = \text{SiPh}_2\text{Bu}^t$, SiMe_2Bu^t ; NBS is *N*-bromosuccinimide.

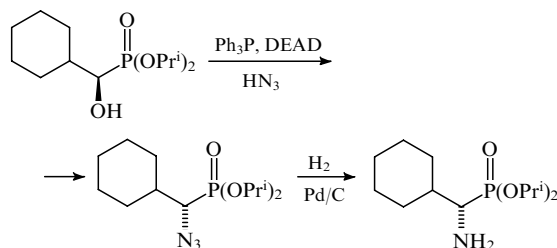
The reaction of optically active lithium *N,N,N',N'*-tetraalkylphosphorodiamidites with 1,2-epoxybutane leads to hydroxybutylphosphonamides **177** with a diastereoselectivity (*ee*) not exceeding 33%. The reaction of chiral epoxides **178** with achiral lithium diethyl phosphite also proceeds with a low stereoselectivity.¹¹⁸



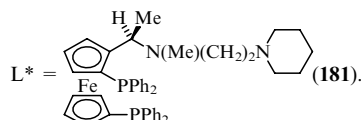
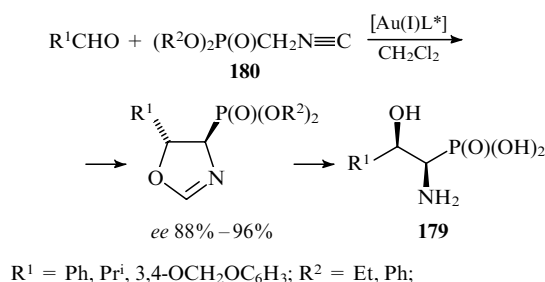
Considerable attention is paid to the synthesis of pharmacologically active hydroxyalkylphosphonates.²⁰⁷ For example, the Michaelis–Becker reaction of methanesulfonates with dialkyl phosphites furnished nucleoside analogues with a methylene-cyclopropylphosphonate fragment, some of which exhibited high antiviral activities.²⁰⁸ The reaction of [1-(diethoxyphosphoryl)-vinyl] *p*-tolyl sulfoxide with ethyl (dimethylsulfuranylidene)acetate yields (1*S*,2*S*)-1-diethoxyphosphoryl-2-ethoxycarbonylcyclopropyl *p*-tolyl sulfoxide, which is converted into optically pure 2-hydroxymethylcyclopropylphosphonate. This was coupled with adenin and chloropurine under conditions of the Mitsunobu reaction to give conformationally constrained analogues of the antiviral purine nucleotides.²⁰⁹



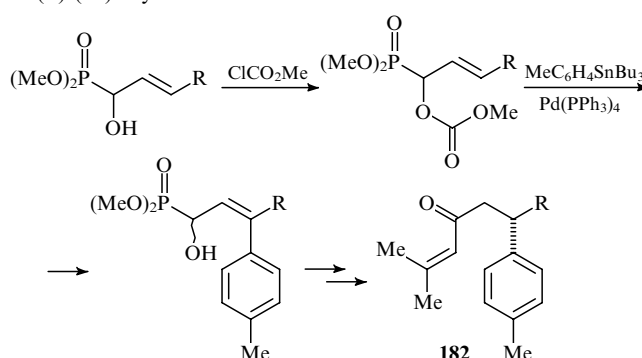
The hydroxy group in hydroxy phosphonates is replaced by the amino group using the Mitsunobu reaction.²¹⁰ Diisopropyl (*S*)-(+)- and (*R*)-(–)-hydroxy(cyclohexyl)methylphosphonates, prepared by the kinetic resolution of the racemic mixture using lipase AP 6, are converted by the Mitsunobu reaction, into optically active (*S*)-(+)- and (*R*)-(–)-amino(cyclohexyl)methylphosphonates with an optical purity of not less than 90%. The replacement of the hydroxy group by an amino group is accompanied by the inversion of configuration.



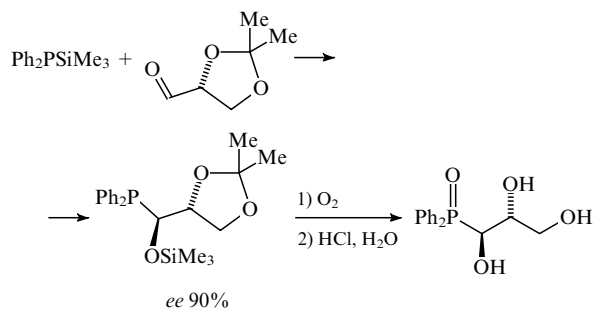
1-Amino-2-hydroxyalkylphosphonic acids **179**, which are isosteric analogues of biologically active and natural compounds, are synthesised by the asymmetric aldol condensation of aldehydes with isocyanomethylphosphonates **180**. The reaction is catalysed by the chiral complex of gold with the ferrocenylphosphine ligand **181**. The optical purity of the reaction products (*ee*) reaches 88%–96%.²¹¹



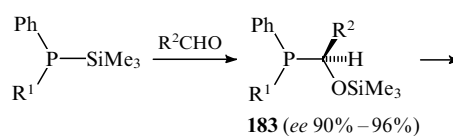
Rowe and Spilling²¹² described stereoselective arylation of hydroxyalkylphosphonates and used this reaction for the synthesis of (*S*)-(+)-aryl turmerone **182**.

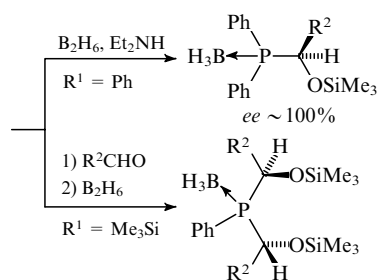


The asymmetric synthesis of (1*S*,2*R*)-(1,2,3-trihydroxypropyl-diphenyl)phosphine oxides, which are structural analogues of the open form of D-erythrose, has been developed.²¹³



Silylphosphines react with chiral aldehydes with high stereoselectivity to give optically active protected α -hydroxyalkylphosphines **183**. In some cases, the formation of borane complexes is used to increase the optical purity. Bis(hydroxyalkyl)phosphines were also obtained using this reaction and isolated as borane complexes.^{213–215}

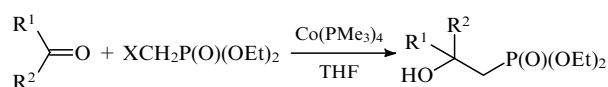




$R^1 = \text{Ph}, \text{Me}_3\text{Si};$

$R^2 = \text{H}_2\text{N}-\text{CH}(\text{CH}_2\text{Pr}^i)-, \text{H}_2\text{N}-\text{CH}(\text{CH}_2\text{Ph})-$

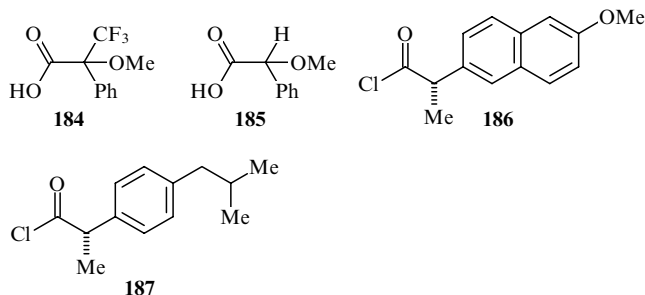
Cobalt complexes are used in the Reformatsky reaction of α -halo phosphonates with ketones or aldehydes to obtain diverse β -hydroxy phosphonates.²¹⁶



$R^1, R^2 = \text{H}, \text{Alk}, \text{Ar}; \text{X} = \text{Cl}, \text{Br}, \text{I}.$

III. Determination of the absolute configuration of hydroxy phosphonates

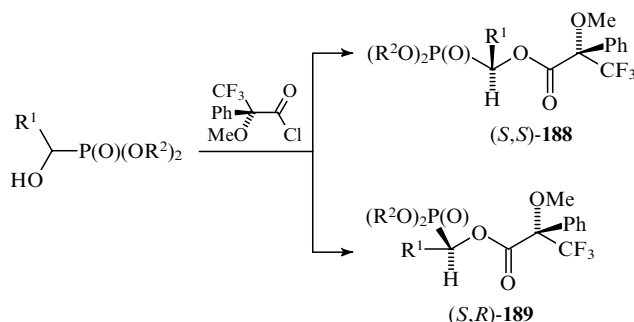
To determine the enantiomeric purity of dialkyl 1-hydroxyalkylphosphonates, modification by chiral reagents, resulting in the formation of diastereomeric derivatives, is used most often. In most studies, hydroxy phosphonates are modified by esterification with Mosher's acid **184**,^{217–219} camphoric acid²²⁰ and mandelic acid **185**,²²¹ amino acids^{222, 223} or with diazaphospholidine derivatives.²²⁴ (*S*)-Naproxen[®] (**186**) and (*S*)-Ibuprofen[®] (**187**) chlorides are convenient chiral reagents for determining the enantiomeric purity of 1-hydroxy- and 2-hydroxyalkylphosphonates by means of ³¹P NMR spectroscopy.²¹⁹ The ¹H NMR spectroscopy of chiral 1-(1-naphthyl)ethylammonium salts of hydroxy phosphonic acids,²²⁵ NMR in chiral media, GLC on capillary columns with chiral sorbents¹⁴⁶ and other methods^{226, 227} are also used.



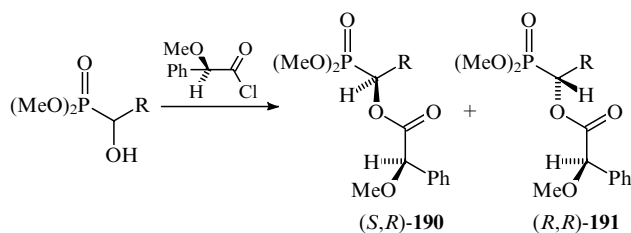
Esterification of hydroxy phosphonates with optically active Mosher's acid **184** is a convenient method for determining their optical purity and absolute configuration.^{217–219} The diastereomeric esters formed can be analysed by ¹H, ¹⁹F and ³¹P NMR spectroscopy. The signals of the P atoms in the ³¹P NMR spectra of (*S*)-hydroxy phosphonate esters **188** are usually located in a lower field than those of (*R*)-hydroxy phosphonates **189** (Table 1). This is due to shielding of the phosphorus atom in ester (*R*)-**189** by the phenyl group. The substantial difference between the chemical shifts ($\Delta\delta_P = 0.40 - 1.09$ ppm) allows reliable determination of the absolute configurations of hydroxy phosphonates.

Table 1. Chemical shifts (δ_P) in the ³¹P NMR spectra of Mosher's esters.^{217–219}

Mosher's ester		δ_P , in the spectrum of		$\Delta\delta = \delta(S) - \delta(R)$
R^1	R^2	<i>S</i> -isomer	<i>R</i> -isomer	
Et	Me	22.21	21.77	0.44
Pr ⁱ	Et	19.33	18.93	0.40
n-C ₅ H ₁₁	Et	19.90	19.43	0.47
BnCH ₂	Pr ⁱ	17.42	17.01	0.41

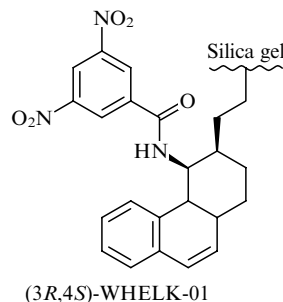


Kozłowski *et al.*²²¹ determined the enantiomeric purity and the absolute configuration of α -hydroxy phosphonates using esterification with mandelic acid. The upfield or downfield shifts of the signals for the methyl-group protons in the ¹H NMR spectra of compounds **190** and **191** depend on the arrangement of the phenyl group in the molecule and its shielding effect. The absolute configurations of compounds **190** and **191** were additionally proved by X-ray diffraction analysis.



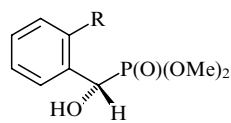
$R = \text{PhCH}=\text{CH}.$

Aryl(hydroxymethyl)phosphonates were separated by HPLC on chiral stationary phase.²²⁸ It was noted that (*R*)-(+)-hydroxyphosphonates are retained by the chiral stationary phase (3*R*,4*S*)-WHELK-01 more strongly than (*S*)-(–)-hydroxyphosphonates. This is due to the formation of a stronger hydrogen bond between the oxygen atom of the P=O group and the hydrogen atom of the amide NH group in the case of *R*-isomers than between the hydroxyl and NH groups in the case of (*S*)-hydroxyphosphonates.



The absolute configuration of hydroxy phosphonates is also determined by means of circular dichroism spectra.^{92, 114, 178} For example, Wynberg and co-workers⁹² used the CD spectra to

determine the absolute configuration of a number of chiral α -hydroxy phosphonates **192**. The enantiomers having *S*-configuration show a negative Cotton effect at 225 nm.

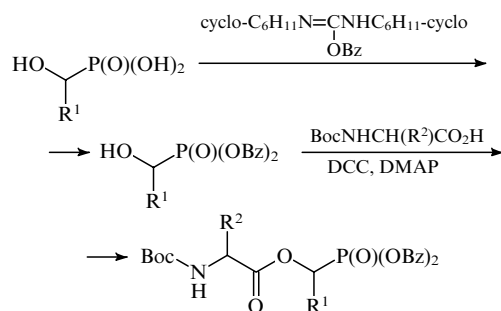
**192**

R = H, F, Cl, Br, NO₂, NH₂.

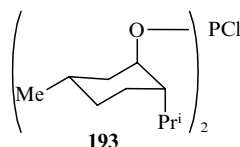
Yokomatsu *et al.*¹¹⁴ used the CD spectra to determine the absolute configuration of 1,2-dihydroxyphosphonates **91**. It was found that α,β -dihydroxy phosphonates having the (1*S*,2*S*)-configuration show a positive Cotton effect at 210–230 nm, whereas (1*R*,2*R*)-isomers show a negative Cotton effect at these wavelengths.

The enantiomeric composition of hydroxy phosphonates is determined using NMR spectroscopy in the presence of quinine, which is an efficient chiral solvating agent. The hydroxy phosphonate enantiomers are readily distinguished by ¹H and ³¹P NMR spectroscopy.^{227, 229, 230} No resolution of the enantiomer signals in the ³¹P NMR spectra of 1-hydroxy- and 2-hydroxy-alkylphosphonates was observed where quinine was replaced by brucine, cinchonine, ephedrine or 1-phenylethylamine.

Yet another method for determining the enantiomeric composition of chiral 1-hydroxyalkylphosphonic acids is the ³¹P NMR study of the diastereomeric derivatives obtained by the reaction of these acids with *N*-substituted L-amino acids.²²²



Dimethyl phosphorochloridite **193** is a convenient reagent for determination of the enantiomeric composition of hydroxy phosphonates (as well as amines, amino acids and alcohols).²³¹ The diastereomeric hydroxy phosphonate derivatives formed upon the reaction with this reagent differ appreciably in the chemical shifts δ_P ; therefore, the stereomer ratio can be easily determined by integrating the ³¹P NMR signal intensities.

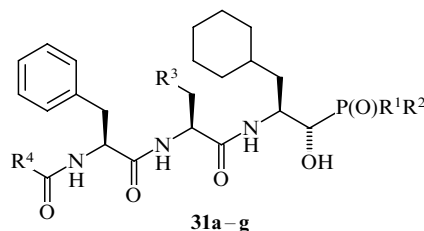
**193**

IV. Biological activities of hydroxy phosphonates

Being structural analogues of hydroxy carboxylic acids, in which the carboxy group has been replaced by the phosphonate group,² hydroxy phosphonic acids function as their substrates, as they compete with the carboxy-containing analogues for the active sites of the enzymes and cell receptors.^{232–236} The structural differences between the CO₂H and P(O)(OH)₂ groups do not prevent hydroxy phosphonic acids from serving as substrates for the enzymes that usually interact with hydroxycarboxylic acids. Thus, hydroxy phosphonic acids inhibit the enzymes involved in

the metabolism of hydroxy carboxylic acids, thus affecting various biological processes in the cell.²³⁷ They behave as antibacterial agents, neuroactive compounds, antitumour agents, and so on.^{71, 72, 238} Therefore, study of the biological activities of hydroxy phosphonates appears promising for the development of new bioregulators and drugs.^{238–246}

Patel *et al.*⁸ found that phosphonopeptides **31a–g**, containing a hydroxy group at the α -carbon atom, inhibit the proteolytic enzyme renin, which possesses an angiotensinogenic action (Table 2). Angiotensin is a powerful octapeptide bioregulator possessing vasoconstrictive properties and increasing blood pressure. It was found that for attaining high activities of compounds **31a–g**, the presence of at least one alkoxyl group at phosphorus is required.

**31a–g**

Dellaria *et al.*²⁴² reported renin inhibitors **194a–f** (see Table 2), which are phosphonate analogues of the natural substrate renin **195**. Pseudo-peptides **194a–e** (R³ = Im) contain both a fragment of the natural structure Phe⁸-His⁹ and a new phosphostatine fragment whose presence induces a 130-fold boost in the activities of compounds **194** as compared with the natural substrate **195**.

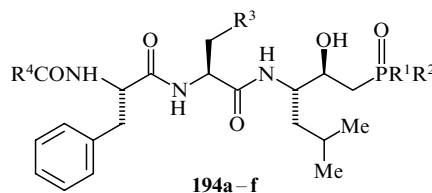
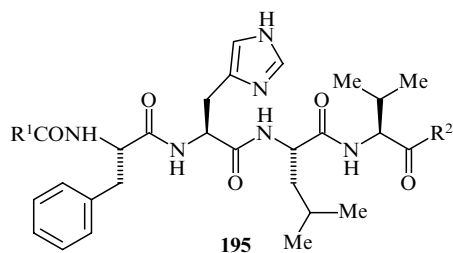
**194a–f**

Table 2. Effect of the substituent structure in the molecules of phosphonopeptides **31** and **194** on the 50% inhibition concentration (IC₅₀) of renin.^{8, 242}

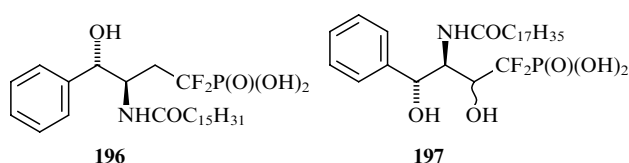
Compound ^a	R ¹	R ²	R ³	R ⁴	IC ₅₀ /nmol litre ^{−1}
31a	OEt	OEt	Pr ⁱ	Bu ^t O	28±3
31b	OEt	OEt	Pr ⁱ	cyclo-C ₅ H ₉	38±8
31c	OMe	OMe	Pr ⁱ	Bu ^t O	10±1
31d	OMe	OMe	Pr ⁱ	cyclo-C ₅ H ₉	16±1
31e	OMe	OMe	Pr ⁱ	H ₂ N(CH ₂) ₅	31±4
31f	OMe	OMe	Pr ⁱ		8.5±1.4
31g	OMe	OMe	Im ^b		41±14
194a (2 <i>R</i>)	OMe	OMe	Im	Bu ^t O	39
194a (2 <i>S</i>)	OMe	OMe	Im	Bu ^t O	90
194b	OEt	OEt	Im	Bu ^t O	72
194c	OMe	OMe	Im	Bu ^t CH ₂	47
194d	OMe	OMe	Im	EtO	50
194e	O(CH ₂) ₂ O		Im	Bu ^t O	80
194f	OMe	OMe	Pr ⁱ	Bu ^t O	20

^a Compounds **31a–g** have 2*S*-configuration; compounds **194b–f** have 2*R*-configuration; ^b Im is imidazolyl.



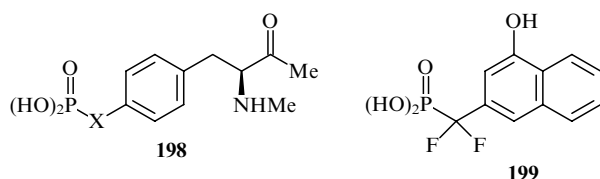
R^1 , R^2 are peptide residues.

N-Palmitoylsphingosine 1-phosphate analogue **196**, containing a hydrolytically stable difluoromethylphosphonic fragment, is a sphingomyelinase inhibitor ($IC_{50} = 3.3 \mu\text{mol litre}^{-1}$)²⁴⁰ with the same level of activity as schyphostatin, the most potent known low-molecular-mass inhibitor of this enzyme. Compound **197** inhibits non-competitively neutral sphingomyelinase in bovine brain microsomes, having $IC_{50} = 400 \mu\text{mol litre}^{-1}$ (Ref. 246). Phosphonic acid **197** prevents the action of the tumour necrosis factor TNF- α by inducing neuron PC 12 death at a concentration of $0.1 \mu\text{mol litre}^{-1}$.



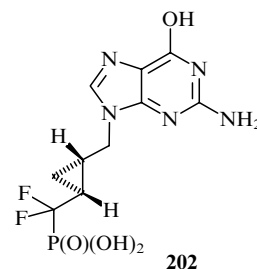
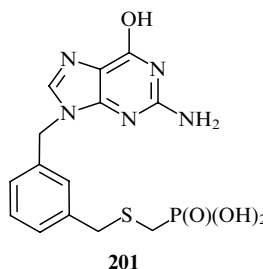
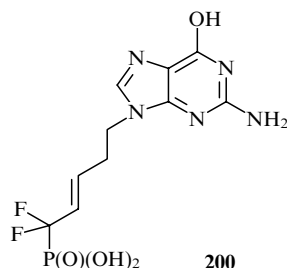
Non-competitive sphingomyelinase inhibitors have also been described in another study.²²⁸

Phosphonic acids **198** and **199** inhibit human phosphoprotein tyrosine phosphatase (PTP-1B) with IC_{50} in the range 57.9–718.1 nmol litre^{-1} (Refs 238, 244–246). Phosphoprotein tyrosine phosphatase catalyses the abstraction of the phosphate group from the tyrosine residue in the molecules of phosphorylated proteins and enzymes, thus inactivating them. Compounds **198** and **199**, which inhibit dephosphorylation of the VEGFR (vein endothelium growth factor), induce fast division of endothelial cells of human umbilical cord vein.²⁴⁴ The introduction of the second difluoromethylphosphonic fragment into the phosphonic acid molecule increases the inhibitory activity.²⁴⁷ The protein tyrosine phosphatase inhibitors exhibit a pharmacological action in the therapy of some diseases.^{108, 247}

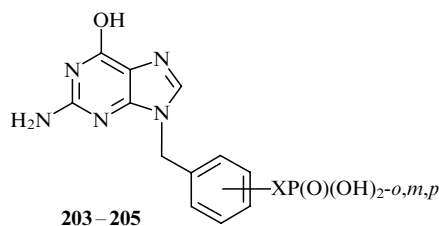


$X = \text{CF}_2, \text{CHF}, \text{CHOH}$.

Shibuya and co-workers¹⁹⁵ reported that purine-containing phosphonic acids **200**–**202** inhibit purine nucleoside phosphorylase (PNP). The PNP inhibitors are efficient in the therapy of proliferative diseases (T-cell leukemia, gout, some types of malaria). The introduction of a cyclopropane fragment, restricting the conformational mobility of the molecule, into the *N*-alkyl substituent enhances the inhibitory activity of compounds. For example, compound **202** has a 2400 times higher inhibitory activity with respect to PNP than compound **200**.¹⁹⁵ The replacement of the guanine residue by hypoxanthine also increases the inhibitory activity of hydroxy phosphonates.



Phosphonic acid derivatives **203**–**205** of the *N*⁹-benzylguanine series actively inhibit PNP isolated from calf spleen or human erythrocytes. Fluorine-containing compounds are more active than their non-fluorinated analogues.²⁰⁷

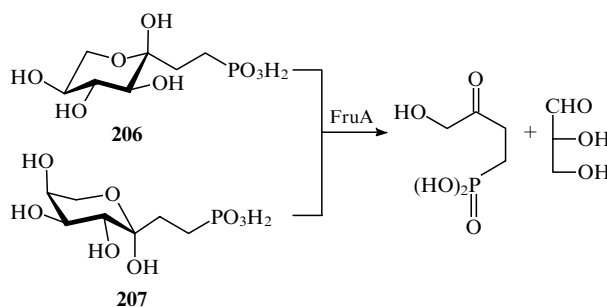


$X = \text{CH}_2\text{CF}_2, \text{CHFCH}_2, (E)\text{-CH}=\text{CF}, (E)\text{-CH}=\text{CH}, \text{O}(\text{CH}_2)_2\text{CF}_2, \text{O}(\text{CH}_2)_3$.

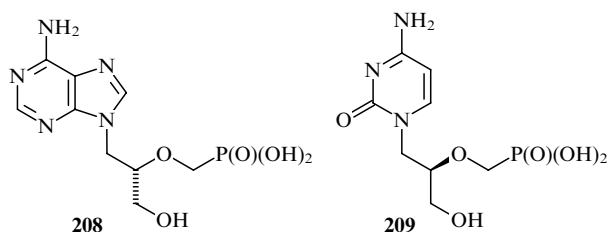
Difluoromethylphosphonates **158** behave as effective inhibitors of aspartate- β -semialdehyde dehydrogenase (ASA-DH) from *Escherichia coli*.²⁰²

Among the biologically active hydroxy phosphonates, interesting antibacterial and antiviral agents have been found;^{248–250} an example is (1*R*,2*S*)-(–)-1,2-epoxypropylphosphonic acid (phosphomycin, **42**), isolated from the culture medium of *Streptomyces fradiae* or *Pseudomonas syringae*.¹

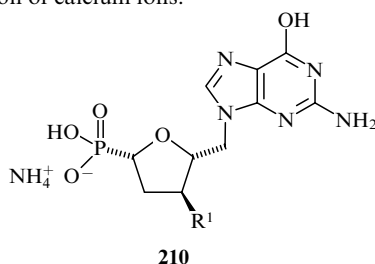
Phosphonic acids **206** and **207** are structural analogues of the aldolase substrate,²⁴⁹ the enzyme catalysing cleavage of fructosyl 1-phosphate into D-glyceraldehyde and dihydroxyacetone phosphate (DHAP) occurring in the liver.



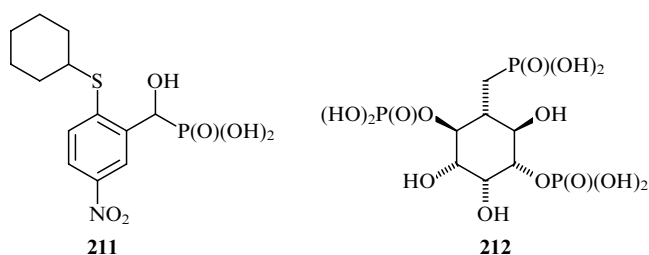
Hydroxy phosphonate derivatives containing residues of heterocyclic bases exhibit a high antiviral activity in the epithelial cells and organotypic cultures.²⁵⁰ The most active compounds of this type are 9-(*S*)-(3-hydroxy-2-phosphonomethoxypropyl)adenine [(*S*)-HPMPA, **208**], 9-(*S*)-(3-hydroxy-2-phosphonomethoxypropyl)-2,6-diaminopurine and 1-(*R*)-(3-hydroxy-2-phosphonomethoxypropyl)cytosine [(*R*)-HPMPC, **209**], known as cidofovir, efficient against human cytomegalovirus and the smallpox virus.



On the basis of hydroxy phosphonates, antitumour drugs have been developed.^{251–258} Nucleoside phosphate analogues **210** exhibit high antitumour activities in several lines of human malignant cells.²⁵³ Hydroxy phosphonic acids **211** have been proposed as inhibitors of phosphoprotein tyrosine phosphatase CD 45, which plays an important role in the inactivation of the protein growth factors and stabilisation of fast proliferation of the hematopoietic cells.²⁵⁴ The 5-methylenephosphonate analogue of D-*myo*-inositol-1,4,5-triphosphate **212** behaves as an intracellular messenger, favouring the opening of calcium channels and liberation of calcium ions.²⁵¹

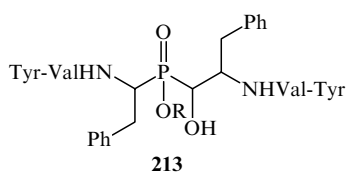


$R^1 = \text{OH, OMe}; R^2 = \text{OH, NH}_2$.

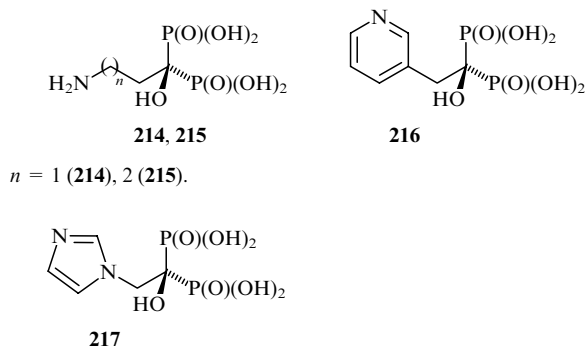


Hydroxy-[4-(5,6,7,8-tetrahydronaphthyl-1-oxy)phenyl]methylphosphonate is an inhibitor of *myo*-inositol monophosphatase, the activity of which with respect to the recombinant bovine brain enzyme corresponds to the inhibition constant $K_i = 20 \mu\text{mol litre}^{-1}$ (Ref. 252).

Compounds **213** inhibit HIV protease and are promising for AIDS therapy.²⁵⁵ The IC_{50} values of these compounds with respect to HIV protease are in the nanomolar range.



Hydroxyalkylbis(phosphonates) are used as pharmacological agents for the therapy of some diseases such as osteoporosis, hypercalcaemia and some kinds of malignant tumours.^{257–260} The most important among them are Pamidronate (**214**) (also retards bone resorption), Alendronate (**215**), Risedronate (**216**) and zoledronic acid (**217**).²⁵⁹



The bis-phosphonate derivative of 3-azido-3-deoxythymidine exhibits an antiviral activity in the therapy of AIDS²⁶⁰ and is registered as Zidovudine.

Some hydroxyalkylphosphonates are plant growth regulators. A number of unsaturated cyclic hydroxy phosphonates synthesised by the reaction of 4-aryl-5,5-dimethyl-1,3,2-dioxaphosphinanes with 2-epoxy-5-aryl-(2*E*,4*E*)-pentadienecarboxaldehydes function as wheat stem growth inhibitors.²⁶¹

Aminohydroxy phosphonates are promising as bidentate ligands for the formation of complexes with transition metals.^{262, 263} For example, copper(II) and zinc(II) complexes of alkyl- and aryl-substituted 2-amino 1-hydroxy phosphonates were studied in an aqueous solution by potentiometry and spectroscopy. A comparison of the stability constants shows that these ligands coordinate Cu^{2+} and Zn^{2+} more efficiently than amino phosphonates containing no hydroxy group.²⁶²

V. Conclusion

The present review considers various methods of asymmetric synthesis, enzymatic, kinetic and chromatographic separation, and some other ways of preparing enantiomers of hydroxy phosphonates with high optical purity. It is noteworthy that, despite the impressive progress attained in the synthesis and study of the properties of hydroxy phosphonates, the problems existing in the chemistry of these compounds are far from being completely solved. The search for enantioselective methods opening an easy route to optically active hydroxy phosphonates still remains topical. Therefore, the development of efficient catalysts for asymmetric phospho-aldol Abramov reaction and for the reduction of keto phosphonates appears especially important. The scope of chemical modification of hydroxy phosphonates aimed at introducing new, more complex, in particular, chiral groups to the carbon, oxygen and especially phosphorus atom is far from being exhausted. The separation of enantiomers and purification of hydroxy phosphonates remain topical tasks. Exact determination of the structure and the absolute configuration of these compounds can be successfully carried out only in some cases.

One can expect that hydroxy phosphonates will remain the subject of intensive research, especially in the field of biological activities and use of these compounds as drugs and bioregulators. In addition, hydroxy phosphonates, their derivatives and analogues can find practical use as synthetic receptors and chiral ligands in metal complexes and selective highly efficient complexes, extractants and analytical reagents.

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^a — *Russ. J. Gen. Chem. (Engl. Transl.)*

^b — *Russ. Chem. Bull., Int. Ed. (Engl. Transl.)*

Pyrocatechol Violet in spectrophotometric and novel optical methods

V M Ivanov, G A Kochelayeva

Contents

I. Introduction	255
II. Chemical and analytical characteristics of Pyrocatechol Violet	256
III. Pyrocatechol Violet as a complexometric indicator	258
IV. Pyrocatechol Violet as a reagent in optical methods	258
V. Conclusion	264

Abstract. The published data on chemical and analytical characteristics and the use of binary and ternary Pyrocatechol Violet complexes in spectrophotometric and novel optical methods of analysis are generalised. New promising trends are considered including studies of chromaticity characteristics of complexes of this reagent with various metal ions formed in the presence of cationic surfactants on the surface of anion-exchange resins or neutral sorbents aimed at increasing the sensitivity of determinations and developing new, more efficient test scales and optical sensors. The bibliography includes 105 references.

I. Introduction

The development of methods and techniques that combine high sensitivity and high selectivity with rapidity of analysis, availability of instruments and low cost is a topical task in analytical chemistry. This is achieved, in particular, through combination of preconcentration of tested compounds with new sampling techniques and most advanced methods of analysis. Mixed-origin specimens including environmental subjects supplement traditional analytical (inorganic or organic) subjects. By virtue of rapidity of analysis and possibility of direct visualisation of the tested subjects, spectroscopic molecular absorption methods are in continuous development resulting in appearance of new versions of the determination, novel or modified reagents and combination of several approaches (*e.g.*, hybrid and combinatory methods of analysis). To relatively new procedures one can relate diffuse reflectance spectroscopy, solid-phase spectrophotometry, chromaticity measurement and diverse test methods. The latter are worthy of note in view of simplicity, availability and relatively low cost at reasonably high precision. These methods are especially suitable for express analysis of a broad range of organic and inorganic substances. Chemical test methods are usually based on well-known reagents and analytical reactions where colour change plays the role of an analytical signal. The reagents for test methods should possess high selectivities and high sensitivities in determination of metal ions or various compounds, the abilities to form stable complexes or analytical forms, possibilities to be immobi-

lised on solid supports and ensure sufficiently high contrast of reactions.

Basic and polyhydroxytriphenylmethane dyes are the two main classes that are widely employed as analytical reagents. The reagents of the former class contain alkyl- or arylamino groups in the phenyl substituents and are usually employed in extractive-photometric procedures. An ionic pair of a negatively charged tested component and the protonated form of the reagent can be extracted by weakly polar organic solvents; however, the reagent itself is also partially extracted. The contrast range in such reactions does not usually exceed 10–20 nm; the reactions are carried out in acidic media with very strict acidity control (the range of optimum pH is very narrow), however the sensitivity of the determination is rather high [the molar extinction coefficient (ϵ) is of the order of 10^5].

The reagents of the latter class contain hydroxy groups in the phenyl substituents. Two hydroxy groups in the *ortho*-position (pyrocatechol) form a functional-analytical group in the reagent, which can be involved in complexation with the formation of chelate complexes. The contrast range of such reactions, especially with involvement of additional approaches, can exceed 200 nm; the values of molar extinction coefficients are of the order of 10^5 , the optimum acidity range is of the order of several units of pH, while the selectivity of the reaction can be changed upon introduction of masking substances. The reagents of the second class include Pyrocatechol Violet (3,3',4'-trihydroxyfuchsin-2''-sulfonic acid, pyrocatecholsulfonephthalein, PCV), a popular reagent for photometric determination of some metal ions and an indicator for complexometric studies. Its applications in novel optical methods, solid-phase spectrophotometry and chromaticity present certain interest. Complexes with PCV usually have bright colours; their formation results in marked bathochromic shifts and is often highly selective. Thus, this reagent is suitable for different test methods, since the latter often include preconcentration in the form of a coloured complex.

This review generalises the published data on chemical and analytical characteristics of Pyrocatechol Violet and its applications in analytical chemistry. Special attention is given to the use of this reagent in modern optical methods, such as diffuse reflectance spectroscopy, solid-phase spectrophotometry, chromaticity measurement, as well as in test methods. This type of a review is missing, while the information sources are either dispersed or hardly accessible.

V M Ivanov, G A Kochelayeva Department of Chemistry, M V Lomonosov Moscow State University, Leninskie Gory, 119992 Moscow, Russian Federation. Fax (7-495) 939 02 83, tel. (7-495) 939 22 77

Received 15 November 2005

Uspekhi Khimii 75 (3) 283–296 (2006); translated by R L Birnova

II. Chemical and analytical characteristics of Pyrocatechol Violet

1. Protolytic equilibria in solutions

The PCV molecule contains a pyrocatechol and an *o*-hydroxycarbonyl groups as well as a sulfo group in the third phenyl substituent and exists in different ionic forms depending on the acidity of the solution (Scheme 1).¹

The theoretical and experimental values of wavelengths of the absorption band maxima ($\lambda_{\max}$) of different forms of PCV are listed in Table 1. It is noteworthy that the band of the doubly ionised form could be identified only after the concentration of the reagent was increased to 8×10^{-4} mol litre⁻¹ (pH 13.0), while the analysis of alkaline solutions of PCV could be performed only after addition of 30 vol.% of acetone to suppress side reactions.¹

Table 1. Theoretical and experimental values of $\lambda_{\max}$ for different PCV forms.¹

Form of PCV	Existence conditions	$\lambda_{\max}$ /nm	
		theory	experiment
I (H_3R^-)	pH 1–6	450	450
II (H_2R^{2-})	pH > 7	591	600
III (HR^{3-})	pH > 9	646	650
IV (HR^{3-})	pH > 9	656	650
V (R^{4-})	0.5 mol litre ⁻¹ 40% NaOH	691	690
VI (H_5R^+)	0.5 mol litre ⁻¹ H_2SO_4 (conc.)	548	546

The hydroxy group of the Pyrocatechol fragment is ionised the first (ionisation of the SO_3H group is not taken into consideration), which results in a bathochromic shift of the long-wave absorption band. The appearance of the doubly ionised forms III and IV at pH > 9 with similar values of $\lambda_{\max}$ is equiprobable; however, with consideration of possible existence of an intramolecular hydrogen bond, the form IV is more likely. The triply ionised form V appears in strongly alkaline media.

Table 2. Dissociation constants of PCV ($c = 4 \times 10^{-5}$ mol litre⁻¹, $l = 1$ cm, $n = 5$, $P = 0.95$).¹

Dissociation step	$\lambda_{\max}$ /nm ^a	K	pK
$H_3R^- \rightleftharpoons H_2R^{2-}$	600	$(3.4 \pm 2.5) \times 10^{-10}$	9.48
$H_2R^{2-} \rightleftharpoons HR^{3-}$	650	$(3.7 \pm 2.2) \times 10^{-12}$	11.43
$HR^{3-} \rightleftharpoons R^{4-}$	690	$(2.9 \pm 2.1) \times 10^{-14}$	13.53

^a $\lambda_{\max}$ is related to more strongly ionised forms (right part of the equations).

The dissociation constants of the hydroxy groups are listed in Table 2. It has to be noted, however, that these data are not in full accord with those reported in Ref. 2 ($pK_{a1} = 7.82$, $pK_{a2} = 9.76$, $pK_{a3} = 11.73$).

Chelate-forming chromophoric organic reagents of the triphenylmethane series are Brønsted and Lewis bases. Therefore, studies of their complexation with metal ions should take into account the possible competition between the proton and the metal ion for the reagent. Partial protonation of analytically active groups of the polydentate ligand does not prevent its complexation with metal ions, but the protonation of the donor atom of the functional analytical group often makes this process impossible.

Hence, the reactivities of polydentate reagents of the triphenylmethane series with respect to metal ions in acidic media are largely determined by the formation of the protonated forms.

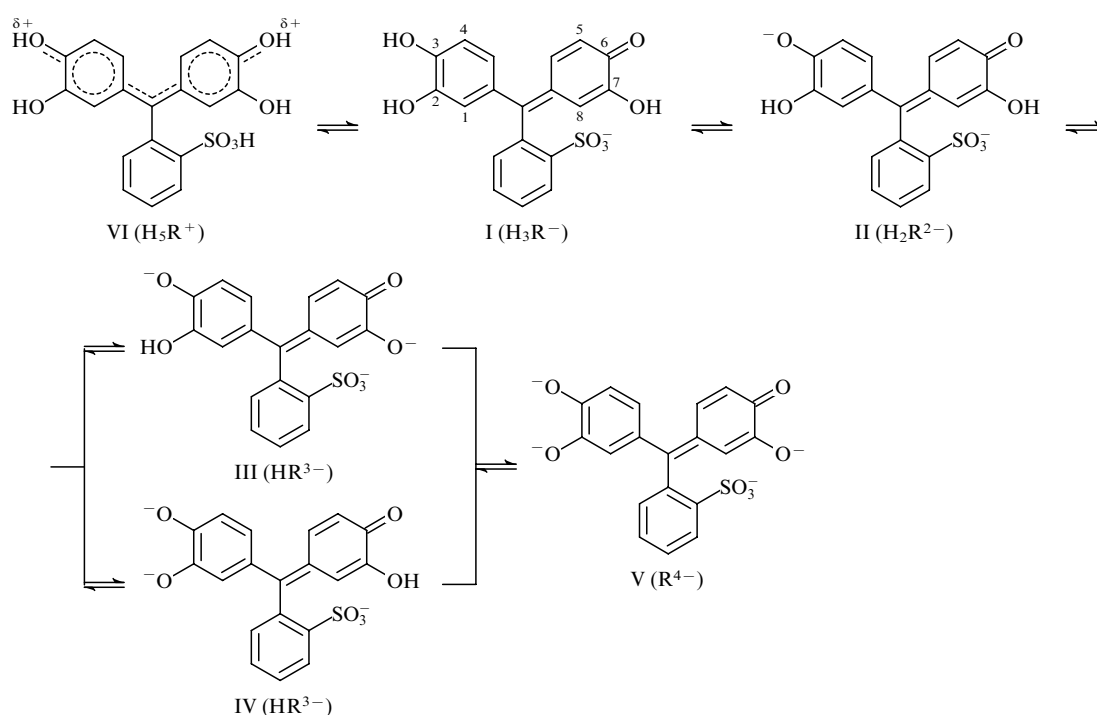


The attachment of the proton to the donor oxygen atom at pH 1 is a characteristic feature of PCV.

2. Effects of surfactants on acid-base properties of Pyrocatechol Violet

The acid-base properties of PCV are influenced by ionic strength, composition of the solution, the presence and the nature of organic co-solvents as well as the nature and concentration of surfactants. These factors determine also the optical characteristics of the reagents and complexes and stabilities of the latter.

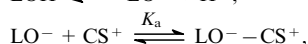
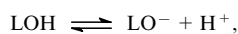
Three types of effects were found to be responsible for enhanced sensitivities and selectivities of reactions in metal ion –



Scheme 1

reagent–surfactant systems and protolytic properties of the triphenylmethane reagents,^{3,4} such as Phenol Red, Cresol Red, *m*-Cresol Purple, Xylenol Blue, Thymol Blue, Bromophenol Red, Chlorophenol Red, Bromophenol Blue, Bromochlorophenol Blue, Bromocresol Purple, Bromothymol Blue, Bromocresol Green and Pyrocatechol Violet, containing different *ortho*-substituents relative to the phenolic OH group.

One of the effects is related to the increase in the number of coordinated ligands in the analytical forms. The second is associated with the activation by a cationic surfactant (CS), which enables complexation in more acidic media due to deprotonation of the heteroatom and formation of stable associates:



where LOH is the reagent and K_a is the association constant. In the presence of CS, determination of the dissociation constant (K_{dis}) is impossible due to competitive formation of the ionic associate. The absorption spectra of the reagents, in the presence of CS, contain additional bands of associates, therefore it is the association constant that is determined photometrically. It is usually shifted to a more acidic region as compared with pK for the dissociation of the corresponding acid group that is involved in the formation of the associate. Therefore, the complexation of such associates takes place in more acidic media in comparison with the corresponding ionic forms of the reagents. This effect, *i.e.*, the apparent pH shift of the dissociation of acid groups, should be distinguished from true changes in the properties of acid groups of the reagents induced, as a rule, by non-ionic surfactants. The reasons for this phenomenon are as yet little understood.

The third effect is connected with multisite interactions of polydentate ligands involving both chelating and auxochromic groups in the presence of CS. For example, the number of CS cations [*e.g.*, cetylpyridinium (CP)] that add to PCV is increased in the presence of metal ions, which is only possible where a proton of one of the auxochromic groups of PCV (most probably, the OH group at position 3, see Scheme 1) is replaced by a CP cation with formation of a chelate associate.

The pronounced effect of deprotonation of the auxochromic group at position 3 on the π -electron system of the reagent⁵ underlies the increase in the contrast of reactions in the presence of surfactants.

The higher the solution acidity the less pronounced the effect of deprotonation of the donor heteroatoms of the reagents and the greater the amount of CS required for the shift of the reaction equilibrium (1) to the left.⁴ It is possible to determine the acidity threshold below which no deprotonation takes place even at maximum possible concentration of CP that is much above the critical micelle concentration (CMC). For PCV, this value was equal to 4.5 mol litre⁻¹ of H₂SO₄; in 1% H₂SO₄, the deprotonation pK shift was 0.8. Analysis of this effect at CP concentrations from 10⁻⁵ to 10⁻² mol litre⁻¹ showed that the deprotonation at CP concentrations far below CMC was typical of all reagents containing sulfo groups.

If the reagent contains no sulfo groups, deprotonation occurs at [CP] $\geq$ CMC. At concentrations below CMC, the deprotonation is related with the formation of ionic associates involving sulfo groups. The formation of neutral associates of ionised forms of the reagents and CP cations was established by amperometry. Such associates are much more hydrophobic than the hydrated reagent ions. Therefore, the protonation of hydrophobic associates with CS under the action of H₃O⁺ species is hindered. The formation of ionic associates diminishes with a decrease in the solution acidity and an increase in CS concentration up to CMC, since dissociation of sulfo groups is suppressed and sorption begins to predominate.

In the presence of charged CS micelles, deprotonation of polydentate organic reagents obeys the Hartley rule⁴ and is reduced to primary sorption of negatively charged ions or neutral

species on the surface of positively charged CS micelles. In this case, the deprotonation is of sorption character and is described by the Langmuir saturation isotherm. Similar to formation of hydrophobic associates, this process is accompanied by a shift of the equilibrium (1) to the left, which is consistent with the viewpoint commonly accepted in colloid chemistry. Therefore, the deprotonation of reagents in the presence of CS takes place in both aqueous and micellar phases. The pK values for the deprotonation of PCV in the presence of different concentrations of cetylpyridinium chloride are given below:⁴

c_{CP} /mol litre ⁻¹	0	2×10^{-5}	4×10^{-5}	4×10^{-4}	1.2×10^{-3}
pK	0.86	0.78	0.54	0.03	0.02

The addition of CS with the length of the hydrocarbon chain C₁₂–C₁₆ to reagents of the triphenylmethane series at concentrations far below CMC (10⁻⁶–10⁻⁴ mol litre⁻¹) in a pH range corresponding to complete dissociation results in a pronounced (by 5–20 nm) bathochromic shift of the absorption band of H₂R²⁻. The effect of CS on the absorption spectra of the reagents in which only the sulfo groups dissociated was less apparent and was accompanied by a small hypsochromic shift of the absorption band.

Electronic and ¹H NMR spectroscopic studies of the effect of CP or cetyltrimethylammonium (CTMA) revealed⁶ that the appearance of a new band was due to the formation of reaction products of PCV with surfactants in a 1 : 2 ratio. In more acidic media, where the sulfo group dissociated, the ratio of the components was 1 : 1, as followed from the results of elemental analysis of solid products. As the length of the non-polar radical increases, the associates become more stable, since counterions are bound by both electrostatic and hydrophobic interactions.

From the practical viewpoint, the shifts or redistribution of absorption band intensities in the spectra of triphenylmethane dyes upon interactions of their anionic forms with polymeric cationic flocculants [*e.g.*, poly(diallyldimethylammonium) chloride] with formation of non-extractable ionic associates can be employed in spectrophotometric determination of microgram quantities of flocculants in aqueous solutions; the use of the addition method is recommended to minimise the effects of admixtures.⁷

The concentration of a surfactant strongly affects the solubility of ionic associates. Its 1.5–3-fold increase in comparison with the stoichiometric ratio of the associate components prevents formation of a solid phase consisting of aggregated species of the associate. This results from dispersion of the associates upon attachment of several additional surfactant cations owing to hydrophobic interactions. The charged ionic associates containing overstoichiometric surfactant ions are sometimes referred to as mixed micelles. The effects of added inorganic salts on the ionic associates of sulfophthaleins and CS have been studied.⁶ The nature of a strong electrolyte anion is important. If the electrolyte anion interacts with CS to form its own ion pair CS⁺–An⁻ (An⁻ = NO₃⁻, Br⁻, I⁻ or ClO₄⁻), the CS–reagent associate is destroyed under the competitive action of An⁻. The addition of salts with anions that weakly react with CS brings about abnormal effects of ionic strength: at a concentration of anions in a solution as high as 0.1–0.5 mol litre⁻¹, the associates are either not destroyed at all or the decrease in their concentration is much less than is expected for compounds with an ionic type of bonds.

Two approaches to modification of organic reagents by surfactants can be noted, *viz.*, preparation of ionic associates and solubilisation in micelles. This allows conversion of common organic reagents into new in principle, more efficient compounds possessing quite different analytical properties. The first route is typical of ionogenic surfactants and reagents that dissociate in aqueous solutions. The formation of the corresponding ionic associates can be predicted. The second route is largely known for non-ionic surfactants; it is still little studied and is virtually unpredictable.

Despite such a complex behaviour of PCV in solutions with different pH, this reagent easily modifies organic or inorganic supports, which makes rather promising the application of its kinetically labile complexes in test methods. The absorption bands of aqueous solutions of H_3R^- , H_2R^{2-} and HR^{3-} correspond to the bands in the diffuse reflectance spectra of the same forms.⁸ However, the absorption band of H_3R^- adsorbed on the anion-exchange resin AV-17 in the diffuse reflectance spectrum of the PCV sorbate was shifted towards longer wavelengths by 20 nm in comparison with the band characteristic of aqueous solutions of this form. The sorption of the H_3R^- form on AV-17 occurs at pH 1–4; at higher pH values, dissociation of the hydroxy groups takes place. The spectral characteristics of the dissociated form H_2R^{2-} are changed thereupon. The $F = (1 - R)^2/2R$ vs pH curve (R is the diffuse reflectance coefficient) displayed a minimum at pH 6.5 due to the superposition of the absorption spectra of H_3R^- and H_2R^{2-} .^{8,9} The sorption of the doubly charged form of PCV is weaker in comparison with the singly charged form, apparently due to delocalisation of the charge generated upon deprotonation of the OH group. It is of note that PCV sorption is irreversible: the reagent is only partly desorbed in strongly acidic solutions and is not desorbed at all in strongly alkaline solutions.

III. Pyrocatechol Violet as a complexometric indicator

The use of PCV as a complexometric indicator was studied in the presence and in the absence of the cetyltrimethylammonium ion.¹⁰ It is commonly known that the sensitivity and the contrast of the colour reaction are crucial in the choice of an indicator for complexometric titration. Besides, the complexes formed must be highly stable with respect to exogenous substances (*e.g.*, buffer components), but less stable than the metal complex with EDTA. Titration should be carried out at the lowest possible values of pH where the logarithm of the conditional stability constant of the complexate is ≥ 7 to increase selectivity. In fairly acidic media (pH 1–2), PCV forms coloured complexes with some metal ions; however, its reactions with many metals proceed effectively only in weakly acidic media (pH 5–6). Only metal ions that do not form stable complexes with fluoride ions can be used as titrants for reverse titration in the presence of fluorides; thus, Sc, Th, Zr, Ti(IV), Al and REE salts cannot be used. Chelates of many metals that form unstable fluoride complexes possess fairly high conditional stability constants in the presence of fluorides; however, coloured PCV complexes with these metals are stable in the presence of fluorides not at all pH values. At high pH values where the metal–PCV complexes possess high conditional stability constants they are stable in the presence of fluorides, but are destroyed at low pH values where the conditional stability constants are low. As is known, pH has little effect on the stabilities of fluoride complexes but strongly affects the stabilities of metal complexes with triphenylmethane dyes (including PCV). In many cases, the use of an NH_4F – H_3BO_3 mixture instead of NH_4F enables efficient titration even at low pH values, since the concentration of free fluoride ions in the solution decreases drastically due to formation of the complex ion BF_4^- . The metals that can be determined by complexometric titration with PCV in the absence and in the presence of cetyltrimethylammonium¹⁰ are listed in Table 3; the use of ternary complexes makes the titration more sensitive in a broader range of contrast of colour change than with PCV alone.

At present, further development of complexometric titration with PCV takes place. It was proposed to fix the titration endpoint automatically by monitoring the changes in chromaticity characteristics, such as L , A and B (tristimulus coordinates in the *CIELAB* system), ΔE , W and G (total colour difference, whiteness and yellowness indices, respectively) and ΔS (colour saturation difference):

$$\Delta S = S_o - S_{rs},$$

Table 3. Conditions for complexometric titration of metals with PCV in the absence and in the presence of cetyltrimethylammonium.

Metal	In the absence of CTMA			In the presence of CTMA	
	pH	buffer solution, supplementary conditions	colour change	pH	colour change
Bi(III)	2–3	HNO_3	blue–yellow	2	blue–red–yellow
Cd(II)	10	ammonia	—	—	—
Co(II)	9.3	"	—	—	—
Ni(II)	8–9.3	"	greenish-blue–red-violet	—	—
Cu(II)	5–6.5	acetate	blue–yellow	6	blue–green–yellow
Fe(III)	5–6	pyridinium acetate	blue–red-violet	3	blue–red
Ga(III)	3–3.8	acetate	blue–yellow	3	blue–yellow
In(III)	5	hot acetate	blue–yellow	6	yellow–green
Mg(II)	10	ammonia	—	—	—
Zn(II)	10	"	—	—	—
Mn(II)	9.3	ammonia + NH_2OH	greenish-blue–red-violet	—	—
Sc(III)	—	—	—	6	blue–yellow
Pb(II)	5.5	urotropine	blue–yellow	6	yellow–green
Th(IV)	2.5–3.5	HNO_3 , 40 °C	red–yellow	—	—

where S_o and S_{rs} are the colour saturations of the tested and reference samples, respectively.¹¹ Methods have been developed for determination of Zr(IV) (Ref. 12) (where PCV is used together with other indicators), Cu(II) (Ref. 13) and Ni(II).¹⁴ A solution of the opposite problem, *i.e.*, determination of aminopolycarboxylic acids, such as nitrilotriacetic acid and EDTA, in natural waters, is also possible.¹⁵ These acids induce a bathochromic shift of the optical density maximum (580 nm) of a red coloured bismuth complex with PCV, which allows measurements of their concentrations in the range from 0.02 to 1.2 mmol litre^{−1}; other chelating reagents are masked with yttrium; the interference due to ions is suppressed by oxalic, citric and acetic acids.

IV. Pyrocatechol Violet as a reagent in optical methods

1. Binary Pyrocatechol Violet complexes with metal ions

PCV complexes with some metal ions have been investigated since the middle of the 20th century and described in numerous publications. However, in the majority of cases the complexation was studied in a narrow range of pH values. The spectrophotometric characteristics of these complexes are listed in Table 4.

As can be seen from Tables 1 and 4, the bathochromic shift of the absorption band in the complexation of PCV with the majority of metal ions listed exceeds 100 nm; the reason for the hypsochromic shift in a neutral medium for aluminium, gallium and indium remains obscure.²⁰ The molar extinction coefficients of copper, zinc, cadmium, scandium and vanadium complexes are small.

The complexation of PCV with aluminium was studied in most detail; this reagent was used for spectrophotometric determination of this metal in sea and underground waters as well as in industrial wastes (2–500 µg litre^{−1}, pH 6.1, urotropin buffer,

Table 4. Spectrophotometric characteristics of binary metal complexes with PCV.

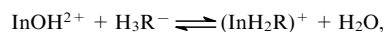
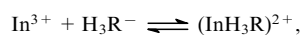
Metal	$\lambda_{\max}$ /nm	pH _{opt} (see ^a)	$10^{-4} \epsilon$ (log β)	Ref.
Cu(II)	580	6	0.54	10
	630	5	— (8.42)	16
Zn(II)	600 (pH 6.5–8.0)	7.5	0.61	17–19
Cd(II)	630 (pH 7.0–10.0)	9.5	0.77	17, 18
Ni(II)	—	—	—	18
Ag(I)	—	—	—	18
Al	580	6	7.75	10
	575–580	6.5–7.2	6.3 (13.81)	20
	610–620	5	2.5	20
Ga	580	5	3.95	10
	575–580	6.0–6.5	6.4 (17.11)	20
	615–620	4	2.6	20
In	580	6	2.46	10
	575–580	7.0–7.8	5.9 (7.54)	20
Sc	600	6	0.98	10
Ti(IV)	570 (without H ₂ O ₂)	6	1.88	10
	590 (with H ₂ O ₂)	6	1.48	10
Zr	550 (pH 1.5)	1.5	2.25	10, 21
	620 (pH 2–6)	5	—	10
Bi	550 (pH 1.5–2.5)	2	2.26	10
	600 (pH 5–6)	6	—	10
V(V)	550–555	6	0.54	10
V(IV)	555	6	1.0	10
Mo(VI)	555	1.3	1.39	10
Mo(V)	555	1.3	1.36	10
W(VI)	560	1	2.24	10
Fe(III)	605	6	6.27	10
Fe(II)	605	6	5.6	10
Pb(II)	570	6	1.0	10
	585	6	1.83	10

^a pH of the maximum complexation.

$\lambda_{\max}$ = 580 nm). It was shown²⁰ that PCV forms complexes with aluminium with the stoichiometry (*i.e.*, the metal : reagent ratio) from 3 : 1 to 1 : 5, gallium (from 2 : 1 to 1 : 5) and indium (from 3 : 1 to 1 : 1) as true solutions in several narrow intervals of pH values. In the case of indium, the formation of 2 : 3 complexes, which represent mixtures of 1 : 1 and 1 : 2 complexes, was possible with insufficiently pure PCV. The equilibrium in the reaction of Al(III) with PCV in aqueous solutions was studied.^{20, 22–24}

The coordination of PCV involves both quinonoid and *ortho*-dihydroxy fragments. At pH < 4.5, Al(III) ions, like Ga(OH)²⁺ ions,^{23, 24} displace one proton from each of two reagent molecules, since the metal : PCV ratio in the complexes is 1 : 2; higher pH values favour the formation of complexes with different ionic forms of PCV. In the intermediate range of pH, the coordination in the complexes involves both groups. The construction of the distribution diagram of complexes *vs* pH demonstrated that stoichiometric (1 : 2) complexes predominate at pH 5.6–6.5; this can be utilised in spectrophotometric determination of gallium and aluminium in natural waters. Computer simulation of conditions for the determination of aluminium ions revealed that in the given range of pH and in the presence of small excess of PCV the measurement error due to the formation of colloidal gibbsite species is minimum. A procedure for flow-injection spectrophotometric determination of total reactive aluminium in natural waters and other objects was developed.²⁵ It was found²⁶ that at pH 6.2 the rate of the reaction of aluminium with PCV strongly depended on the presence of competing ligands, such as oxalate, malonate, fluoride, salicylate, citrate and humic acids; the equilibration time was 10 min.

The mechanism and thermodynamic and kinetic characteristics of the reaction of indium with PCV were established by the temperature-jump method with the use of laser emitters.²⁷ Spectrophotometric measurements showed the predominant formation of (InH₃R)²⁺ and (InH₂R)⁺ species at [H⁺] > 0.015 mol litre^{−1} and of (In₂R)²⁺ species at [H⁺] < 0.015 mol litre^{−1}. Two relaxation effects were observed. Fast relaxation was associated with the reactions:

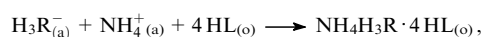


while slow relaxation was associated with the formation of (In₂R)²⁺. The electronic absorption spectra of gallium–PCV complexes in the absence and in the presence of electrolytes were studied.²⁸ It was found that the light absorption by a solution depends on the nature of the anion and the cation of the electrolyte.

On the whole, the utilisation of PCV–metal binary complex formation for analytical purposes is limited due to low reaction selectivity, narrow range of optimum pH values and, sometimes, by low molar extinction coefficients. Several approaches aimed at eliminating these drawbacks were proposed. One of them consists of a search for a third component of the complexes the introduction of which into the reaction system might significantly improve the spectrophotometric characteristics of the latter and increase the selectivity of the determination (see Section IV).

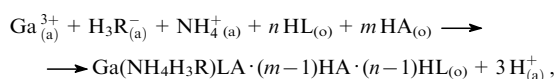
The second approach consists of preliminary separation of the tested element by extraction²⁹ or sorption^{30–32} on appropriate supports with subsequent re-extraction or desorption and determination in aqueous or organic phases using PCV. Alternatively, it is complexes with PCV that are extracted^{33, 34} or absorbed^{31, 32, 35–37} with subsequent determination of metals, as a rule, by spectrophotometric,^{29–31, 33, 34} atomic absorption^{32, 35–37} or atomic emission³² methods. Thus tin(IV) was extracted with tris(2-ethyl)hexyl phosphate in toluene;²⁹ the linearity range of the calibration curve (CC) was 10–100 $\mu\text{g ml}^{-1}$, the detection limit was 0.4 $\mu\text{g ml}^{-1}$. PCV complexes with Ga, Al, In³³ and Zr³⁴ were extracted with solutions of caproic (HL) and propionic (HA) acids in chloroform (Table 5). The linearity range of CC for gallium and aluminium determinations was 0.1–1.7 $\mu\text{g ml}^{-1}$; 100-fold concentrations of indium, 5-fold concentrations of bismuth and 10-fold concentrations of copper did not interfere with the determinations. It is noteworthy that PCV itself is extracted only by caproic acid, the extraction constant (K_{ex}) being equal to $(6.7 \pm 1.8) \times 10^3$.

The following schemes for the formation of extracted compounds were proposed [the subscripts (a) and (o) designate the aqueous and organic phases, respectively]: for PCV (H₃R[−])

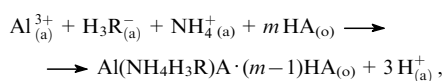
**Table 5.** Extraction of PCV–metal complexes.

Metal	$\lambda_{\max}$ /nm	pH _{opt}	$10^{-4} \epsilon$	K_{ex}	Extractant (M : PCV ratio within the complex)
Al(III)	585	6.5–7.2	3.7	$(1.8 \pm 0.1) \times 10^{11}$	propionic acid (1 : 2)
Ga(III)	585	6.2–6.5	2.5	$(1.4 \pm 0.3) \times 10^4$	caproic–propionic acid mixture (1 : 1)
Zr(IV)	600	6.2–6.5	2.6	4.3 ± 0.5	caproic–propionic acid mixture (1 : 1)

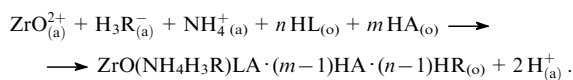
for Ga(III)



for Al(III)



for Zr(IV)



Preconcentration of lead in its determination in atmospheric air and construction materials was performed using Polyorgs VII as the sorbent;³⁰ the sorption time was 10 min and desorption was performed with 0.1 M acetic acid. Tin was determined in zinc ingots using the anion-exchange resin Dowex 2 × 4;^{31,32} this was combusted and the ash was dissolved in nitric acid.

Direct sorption of metal–PCV complexes was carried out on the anion-exchange resins Dowex 2 × 4^{31,32} or XAD-2 (for determination of Zn, Cd, Pb and Ni).³⁵ A procedure for preconcentration in the determination of trace amounts of Cu, Mn, Cd, Pb, Ni and Cr in potable water was developed,³⁶ which consisted of sorption of complexes with PCV on a column with an anion-exchange resin at pH 4–8 and elution with 1 M nitric acid in acetone; the detection limits for Cd and Cr were < 0.1 and 1 µg litre⁻¹, respectively. A possibility of preconcentration of Cu, Ni and Zn on a PCV-modified cation-exchange resin with subsequent regeneration of the resin at pH 12 or with 3 M KCl was investigated.³⁷

2. Interactions of Pyrocatechol Violet with anions

Reactions of this type are documented.^{38–40} Procedures were developed for spectrophotometric determination of anions based on oxidation of PCV with halogens. The latter oxidise PCV whereupon its colour fades. Thus for BrO₃⁻ the conditional $\varepsilon = 3.7 \times 10^4$, $\lambda_{\text{max}} = 557$ nm, the linearity range of CC is 0.1–1.3 µg ml⁻¹ (Ref. 38); the anion:PCV stoichiometric ratios for I⁻ and Br⁻ are 1:5 and 1:3, respectively; the detection limit for iodide ions is 0.0006 µg ml⁻¹ (Ref. 38); for ClO₂⁻, the ClO₂⁻:PCV ratio is 1:2; chloride, nitrate, sulfate, phosphate, carbonate, perchlorate and arsenate ions are not interfering, but the bromide ion interferes with the reaction course;³⁹ a method for determination of oxalic acid in food substances, which is based on enhancement of PCV oxidation by dichromate, has been described.⁴⁰

3. Mixed-ligand complexes and ionic associates

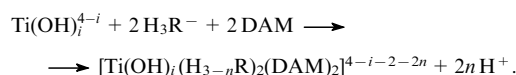
As mentioned above, the use of two-component complexes of PCV with metal ions for analytical purposes often faces problems. Mixed-ligand complexes and ionic associates hold more promise for spectrophotometric determinations, since they are more stable, better extracted and demonstrate larger bathochromic shifts; in some cases, the selectivities are higher. Thus a ternary zirconium complex with PCV and EDTA with a component ratio Zr:PCV:EDTA = 3:2:3 was described⁴¹ as early as 1968 and a method for determination of zirconium was developed. Since 1962, yttrium has been determined in the presence of some rare-earth elements (Pr, Nd, Ce, La)⁴² using a red coloured boron–pyrocatechol complex (BPCC) with a component ratio Y:BPCC = 1:1; the linearity range of CC is 0.9–4.5 µg ml⁻¹ for yttrium; $\varepsilon = 1.85 \times 10^4$ (590 nm) and 1.90×10^4 (607 nm). Ce(IV) and La(III) ions also react with BPCC, but the complexes formed are less stable. The interfering effect of lanthanum was eliminated by addition of boric acid, that of cerium, of hydrogen peroxide. Of substantial interest for further investigations are synergistic effects in the formation of ion–metal associates with PCV and Rhodamine 6G or Rhodamine B (Table 6).^{43–45}

Table 6. Some characteristics of metal complexes with PCV in the presence of Rhodamine 6G.

Metal	λ_{max} /nm	pH _{opt}	10 ⁻⁴ ε	Linearity range of CC /µg ml ⁻¹	Subject of analysis	Ref.
Al(III)	580	6.5	6.8	0–0.28	gramineal plants	43
Ti(IV)	560	5.0	7.6	0.08–0.48	alloys	45
Sn(II) ^a	560	5.0	11.8	0–0.6	canned fruits, steel samples	44

^a In this case, as a complex with PCV and Rhodamine B.

The complexation of PCV with titanium(IV) was studied in the presence of diantipyrylmethane (DAM).⁴⁶ It is known¹⁰ that aluminium and copper ions interfere with determination of titanium with PCV (see Table 4). The addition of DAM to the reaction system enables determination of titanium in the presence of a 300-fold (with respect to titanium) excess of aluminium and a 150-fold excess of copper. The formation of the Ti–PCV–DAM complex was characterised by a high range of contrast ($\lambda_{\text{max}} = 610$ nm, pH_{opt} 1.4–2.4, $\varepsilon = 2.00 \times 10^4$); the Ti:PCV:DAM ratio was 1:2:2; the linearity range of CC was 0.2–1.9 µg ml⁻¹; the stability constant of the complex was $(4.00 \pm 0.09) \times 10^{19}$. Titanium reacted with PCV and DAM according to the following scheme:

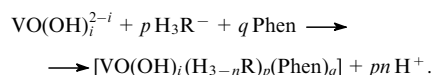


It was demonstrated that the role of a coordinating ion is played by Ti(OH)_i³⁺, which displaces one proton from each PCV molecule (*i.e.*, $i = 1$, $n = 1$). DAM is bound to two OH groups of PCV through the carbonyl oxygen. A tentative structure of the complex formed was proposed.⁴⁶

Heterocyclic bases (HetB), *e.g.*, quinine,⁴⁷ 2,2'-bipyridine⁴⁸ and 1,10-phenanthroline, were used as third components in mixed-ligand complexes of PCV with metals.^{49–51} Compounds formed were insoluble or poorly soluble in water; the addition of gelatin brought about their stabilisation. A gallium complex with PCV and quinine was formed in a very broad pH range ($5 < \text{pH}_{\text{opt}} < 10$); the component ratio for the Ga:PCV:quinine complex was 1:2:1, $\lambda_{\text{max}} = 680$ nm, the linearity range of CC was $(0.2–2.0) \times 10^{-5}$ mol litre⁻¹; this could be used for the determination of both gallium and quinine.⁴⁷ 2,2'-Bipyridine⁴⁸ (pH_{opt} 3–3.5, Ge:PCV:2,2'-bipyridine = 1:2:3, $\lambda_{\text{max}} = 610$ nm) was used as a third component in the germanium complex with PCV; the solubility product was $(1.04 \pm 0.02) \times 10^{-32}$; $\varepsilon = (3.08 \pm 0.25) \times 10^4$. In this case, amine-type compounds $[\text{Ge}(\text{OH})_i(\text{H}_3-n\text{R})_2 \cdot (\text{HetB})_3]^{4-i-2-2n}$ are formed characteristic of reactions with amines as bases.

In the presence of 1,10-phenanthroline (Phen), the aluminium–PCV complex is formed at pH_{opt} 6.15; $\lambda_{\text{max}} = 590$ nm; the detection limit for aluminium is 20 µg litre⁻¹. A procedure for determination of total concentrations of monomeric aluminium in natural waters and soil extracts has been developed.⁴⁹

Vanadyl complexes with PCV and 1,10-phenanthroline⁵⁰ or cetylpyridinium bromide (CP-Br)⁵¹ were investigated and the possibility of their extraction was examined. The main characteristics of the complexes formed in aqueous and organic media are listed in Table 7. EPR studies revealed that the complex contained V(IV). The following complexation equation was proposed:⁵⁰



It was found that the character of formation of ionic associates in the presence of CP-Br strongly depends on pH. In acidic media,

Table 7. Some characteristics of vanadium–PCV complexes.

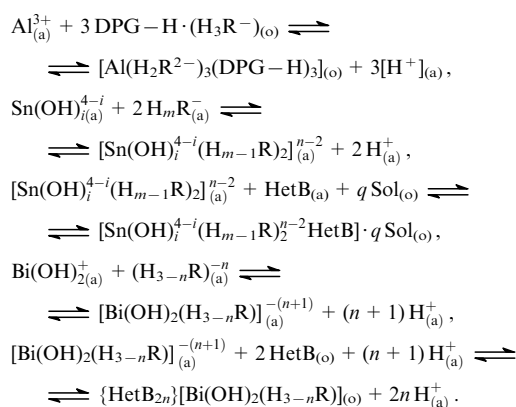
Compound	$\lambda_{\max}$ /nm	pH _{opt}	$10^{-4} \epsilon$	M : PCV : L ratio ^a	Additional information
PCV	450	2.8–3.6	—	—	aqueous medium
	450, 610	6.0	—	—	
V–PCV	550–560	—	—	—	the same
V–PCV–CP-Br	680	3.0–3.6	2.58	1 : 2 : 2	$\log \beta = 29.73$
	550, 680	5.0–6.4	2.41	1 : 2 : 2	$\log \beta = 28.36$
	550	6.0–6.4	2.48	1 : 2 : 4	aqueous medium $\log \beta = 33.97$
V–PCV–Phen	550–560	2.8–3.0	1.39	1 : 2 : 2 (see ^b) 1 : 1 : 1 (see ^c)	chloroform (extractant) aqueous medium non-extractable

^a L is CP-Br or Phen. ^b The V : PCV > 1 : 15 and V : Phen > 1 : 30 ratios in solution. ^c The V : PCV < 1 : 15 and V : Phen < 1 : 30 ratios in solution.

as with PCV–Phen associates, cetylpyridinium binds to the SO_3^- group of PCV, as can be judged from the similarity of their absorption spectra. In aqueous (pH 6.4) and organic media, PCV reacts with CP-Br differently. Although under the given conditions the PCV molecule exists in a singly ionised form (H_3R^-), the hydroxy group of the pyrocatechol residue is in a pre-ionisation state. Loosening of the O–H bond occurs under the action of cetylpyridinium, which enables substitution of the cetylpyridinium cation for the hydrogen of the hydroxy group. This group favours additional delocalisation of π -electrons of PCV, resulting in a pronounced bathochromic shift of the absorption band of PCV. In the organic phase, the second CP-Br molecule is bound to the sulfo group of the reagent, owing to which the extraction of the ionic associate PCV-CP is possible.

The extractability of the complexes can also be enhanced by addition of guanidine (GU) ⁵² or diphenylguanidine (DPG) ^{17, 39, 53–56} to the metal–PCV reaction system (Table 8). Spectrophotometric and IR-spectroscopic studies as well as quantum-chemical calculations revealed that metal ions displace one proton from each PCV molecule in the formation of ternary complexes with GU or DPG; the coordination of the metal occurs with the *o*-hydroxyquinone group of PCV. The PCV polyassociates are destroyed under the action of GU and DPG, which, acting as bases, block the free sulfo and hydroxy groups. It is noteworthy that GU is a more efficient partner for ions with smaller ionic radii, while DPG is more suitable for extraction of ions with larger ionic radii in reactions with the same triphenylmethane dye; the differences between the properties of individual elements are eliminated upon addition of surfactants. The follow-

ing complexation reactions have been proposed for aluminium, ⁵³ tin ⁵⁵ and bismuth ⁵⁶ (Sol is a solvent):



Mixed-ligand complexes of metals with triphenylmethane dyes (including PCV) and quarternary ammonium salts (QAS) hold a special place. Their advantages include high molecular mass, pronounced basic properties and the fact that they do not form complexes directly with metals. This determines their more unambiguous reactions and rules out competitive effects of other cations. Mixed-ligand complexes of PCV with iron ⁵⁷ or molybdenum ⁵⁸ and dialkylbenzylmethylammonium chloride were obtained as long ago as 1968–1970. The methods for determination of metals (Groups 3–14 of the Periodic Table) based on the use of heteroligand complexes with triphenylmethane dyes and QAS are known (Tables 9 and 10). The formation of these

Table 8. Extraction of metal–PCV complexes in the presence of guanidine and diphenylguanidine.

Metal	$\lambda_{\max}$ /nm	pH _{opt}	$10^{-4} \epsilon$	M : PCV : DPG ratio	Extractant, additional information	Ref.
Al(III) ^a	600	—	4.4	1 : 2 : 4	aqueous medium	52
	605	11.5	5.6	1 : 2	organic medium	52
	610	6.5	7.6	1 : 2		
Al(III)	590	5.3–5.5	5.6	1 : 3 : 3	isobutanol, lower threshold of tested concentrations 0.03 $\mu\text{g ml}^{-1}$ (for extract)	53
Ga(III) ^a	610	11.5	7.0	1 : 2	organic medium	52
Ga(III)	600	5.2	10.7	1 : 3 : 3 or 1 : 3 : 6	the same	52
Zn(II)	620	8.0	0.77	1 : 1 : 2	n-butanol	17
Cd(II)	580	9.0	0.9	1 : 1 : 2	"	17
Ti(IV)	560	6.0	6.6	1 : 4 : 4	chloroform, $\log \beta_4 = 10.38$	54
Sn(IV)	600	4–5	6.7	1 : 1 : 1	n-butanol and isobutanol, linearity range of CC 0.025–0.25 $\mu\text{g ml}^{-1}$ (for extract)	55
Bi(III)	630	4–8	2.6	1 : 1 : 2	n-butanol, linearity range of CC 0.5–5.0 $\mu\text{g ml}^{-1}$ (for extract)	56

^a In these cases, as complexes with guanidine; in other cases, as complexes with diphenylguanidine.

complexes is accompanied by pronounced bathochromic shifts; however, the absorption maxima are usually shifted hypsochromically with an increase in triphenylmethane dyes concentration. This accounts for different $\lambda_{\max}$ values for a mixed-ligand complex of the same element reported by different authors. Contrary to the common opinion that the formation of mixed-ligand complexes is maximum at lower pH values than that of homoligand complexes, the complexation with triphenylmethane dyes and QAS occurs at nearly the same pH values, the number of coordinated triphenylmethane dye molecules in mixed-ligand complexes being larger.⁶⁷

The number of coordinated QAS ions is often not given, only the metal:PCV ratios are determined. But even if this number is indicated, it is most likely approximate. The determination of the metal:QAS ratio requires preparation of a panel of solutions containing different concentrations of QAS, while solutions with low concentrations of QAS are usually turbid; therefore, experimental determination of the component ratios cannot be exact. It is known that physicochemical properties of compounds (including solubility) change upon formation of complexes with various ligands. For the compounds under consideration, in the formation of mixed-ligand complexes their solubilities first decrease and then increase. This can be explained by the stepwise complexation, *viz.*, the formation of a less soluble mixed-ligand complex with a smaller number of coordinated ions of the second ligand is

followed by the formation of a more soluble complex with a larger number of coordinated ions. One can draw an analogy between mixed-ligand metal complexes with triphenylmethane dyes and QAS, on the one hand, and some metal complexes with inorganic ligands (hydroxide, halide, cyanide ions, *etc.*), on the other hand, where the formation of metal hydroxide, halide or cyanide residues is followed by their dissolution with a further increase in the ligand concentration. The effect of micelle formation of QAS on the state of PCV, in particular, on the degree of its dissociation, was discussed above. The properties of mixed-ligand complexes depend, to a certain extent, on the nature of QAS as can be evidenced from the differences in the $\lambda_{\max}$ values and molar extinction coefficients (see Tables 9 and 10); this can also be explained by different effects of QAS on the dissociation of triphenylmethane dyes. Physicochemical analysis showed⁶⁷ that mixed-ligand complexes have permanent compositions due to formation of ionic associates. A positively charged ion or a QAS micelle is bound to a negatively charged metal–PCV complex by electrostatic forces, which brings about changes in the conjugation chains and absorption spectra. Then the ammonium salt of the anionic complex is dispersed in the excess of the surfactant and, contrary to binary PCV–metal complexes, can be extracted by organic solvents. However, virtually no increase in the sensitivity occurs, although the selectivity of metal determination can some-

Table 9. Spectrophotometric characteristics of metal–PCV complexes in the presence of various quarternary ammonium salts.

Metal	$\lambda_{\max}$ /nm	pH _{opt}	$10^{-4} \epsilon$	Ratio M : PCV : QAS	QAS, additional information	Ref.
Fe(III)	—	—	—	1 : 2 or 1 : 3 (see ^a)	benzyltetradecyldimethylammonium chloride	57
Mo(VI)	560	0.25–0.6 M HCl	—	1 : 2 (see ^a)	dialkylbenzylmethylammonium chloride, extraction with CHCl ₃ ; interfering Sn(IV), W, not interfering Zr, Zn, Co, Ni, Cu, Al, Fe(III), Cr(III), Th, Ti, V(V), U(VI)	58
	590	—	18	1 : 1 : 1	dodecylpyridine, room temperature, slow reaction; interfering Al, Th, Zr, Bi	59
	718	—	120	1 : 1 : 1 : 2 (HA)	dodecylpyridine–hydroxylamine (HA), not interfering 5-fold excesses of Al, Th, Zr	
	718	—	120	1 : 1 : 1 : 2 (HA)	dodecylpyridine–HA, linearity range of CC 0.8–100 $\mu\text{g ml}^{-1}$	60
Sn(IV)	591	3.6 (aqueous phase)	7.3	1 : 2 : 2	tridodecylethylammonium bromide; extraction with benzene, xylene, CCl ₄ , CHCl ₃ , n-butyl acetate, isobutyl methyl ketone, n-butanol	61
	—	—	—	—	triethylenediamino-bis(<i>N,N'</i> -decyloxycarbonylmethyl ammonium) diiodide; ethylene-1,2-bis(piperidinoyl- <i>N</i> -decyloxycarbonylmethylammonium) dibromide	62
Zr(IV)	610	1.6–3.6	—	1 : 1 : 4	triethylenediamino-bis(<i>N,N'</i> -decyloxycarbonylmethylammonium) diiodide, extraction with CHCl ₃	63
	620	1.5	—	1 : 2 : 4	ethylene-1,2-bis(piperidinoyl- <i>N</i> -decyloxy carbonyl methyl-ammonium) dibromide, aqueous solution	
Al(III) ^b	585	6.3–7.8	4.5	1 : 2 : 3	benzyltrimethylphenylammonium chloride	64
	587	6.3–7.4	6.2	1 : 2 : 5	decylpyridinium iodide	
	592	6.4–7.8	6.0	1 : 2 : 3	pentadecylpyridinium iodide	

^a The M : PCV ratios are indicated for these cases; ^b data from n-butanol extraction.

Table 10. Spectrophotometric characteristics of metal–PCV complexes in the presence of cetyltrimethylammonium or cetylpyridinium halides.

Metal	In the presence of cetyltrimethylammonium halide				In the presence of cetylpyridinium halide				
	$\lambda_{\max}$ /nm	pH _{opt}	$10^{-4} \epsilon$	ref.	$\lambda_{\max}$ /nm	pH _{opt}	$10^{-4} \epsilon$ (log β)	M : PCV : QAS ratio	ref.
Be(II)	—	—	—	—	680	8.0	1.5	1 : 1 : 5	65
Co(II)	—	—	—	—	720	10.0	1.1	1 : 1 : 5	65
Cu(II)	650	6	—	10	720	7.0	1.8	1 : 1 : 5	65
	720	—	2.83	10					
	660	6–7	5.0	66					

Table 10 (continued).

Metal	In the presence of cetyltrimethylammonium halide				In the presence of cetylpyridinium halide				
	$\lambda_{\max}$ /nm	pH _{opt}	$10^{-4} \varepsilon$	ref.	$\lambda_{\max}$ /nm	pH _{opt}	$10^{-4} \varepsilon$ (log β)	M : PCV : QAS ratio	ref.
Zn(II)	—	—	—	—	690	9.0	1.3	1 : 1 : 5	65
Cd(II)	—	—	—	—	710	10.0	1.2	1 : 1 : 5	65
Fe(II)	620	5	4.3	10	—	—	—	—	—
	640	6	—	10					
Fe(III)	630	5	4.37	10	—	—	—	—	—
	630	5.0–6.0	5.3	66					
Pd(II)	760	6	6.1	10	700	8.0	1.7	1 : 1 : 5	65
	540	4	—	10					
	580	5	—	10					
	650	6	3.43	10					
	675	5.0–6.2	2.4	66					
Al(III)	570	9.7–10.2	5.3	67	700	5.0	1.7	1 : 1 : 5	65
	685	6	4.8	10	595	7.4–10.0	6.5	1 : 2 : 5	64
	670	6.0–7.3	7.3	68				(n-butanol)	
	670	9.7–10.2	5.3	52	590	7.5–8.0	6.5	1 : 2 : 5	69
								(n-butanol)	
Ga(III)	545	2.4–3.2	—	10	680	6.0–6.5	5.30	1 : 2 : 2	70
	625	4–6	—	10			(31.83)	(aqueous medium)	
	680	—	2.3	10	595	6.8–7.8	7.10	1 : 2 : 4	70
	675	7.0–7.5	6.2	68			(43.62)	(n-butanol)	
In(III)	675	6	3.65	10	680	6.0–6.5	4.75	1 : 2 : 2	70
	680	5.6–7.2	7.6	68				(aqueous medium)	
					595	6.8–7.8	5.60	1 : 2 : 4	70
							(43.64)	(n-butanol)	
Sc(III)	600	6	0.98	10	—	—	—	—	—
	665	6.8–7.1	6.9	68					
La(III)	—	—	—	—	673	8.27	4.3	1 : 2 : 3	71
Th(IV)	665	7.0–7.4	4.6	68	—	—	—	—	—
U(VI)	660	5.5–6.0	3.5	67	—	—	—	—	—
Cr(III)	650	—	6.2	72	—	—	—	—	—
Bi(III)	550	2	—	10	680	5.0	1.0	1 : 1 : 5	65
	600	6	2.42	10					
	600	4.3–5.4	2.9	66					
Ti(IV)	580	6	2.30	10	745	2.0	7.5	1 : 1 : 4	65
	730	3.2	7.4	73	730	—	7.8	1 : 2 : 3	74
					569	6.2	5.5	1 : 3 : 2 : 2 (EDTA)	75
Zr(IV)	540	1.5	1.09	10	700	6.0	1.3	1 : 1 : 5	65
Ge(IV)	—	—	—	—	680	1 M HCl	7.0	1 : 1 : 4	65
Sn(IV)	660	2.5	9.6	67	670	4.0	7.8	1 : 1 : 2	65
	662	2.2	9.5	76					
	660	see ^a	9.54	77					
V(IV)	680	6	—	10	—	—	—	—	—
	690	5	—	10					
	750	4	2.6	10					
	680	4.8–5.5	3.7	66					
V(V)	685	4	2.33	10	—	—	—	—	—
	660	6	—	10					
Nb(V)	—	—	—	—	570	0.8–1.6	5.3	1 : 4	67
Ta(V)	—	—	—	—	610	—	—	—	67
Mo(VI)	660	4.0–6.0	4.7	66	—	—	—	1 : 2 : 2	78
	680	see ^b	4	79					
	638	—	—	80					
Mo(V)	590	1	—	10	—	—	—	—	—
	680	5–6	4.2	10					
Mo(VI)	590	1.1	—	10	670	2.0	8.2	1 : 1 : 5	65
	680	5	4.3	10					
	670	6	—	10					
	640	3.0–4.0	1.8	9					
W(VI)	635	1	—	10	670	1.0	6.4	1 : 1 : 2	65
	650	5	4.0	10	670	1–1.5	—	1 : 1 : 2	67
	640	6	—	10	—	—	—	1 : 1 : 2	81
	650	2.7–4.6	4.4	66					

^a 0.75 M HCl; ^b acetate buffer.

times be slightly increased through the adequate choice of a solvent.

4. The use of mixed-ligand Pyrocatechol Violet – metal complexes in the analysis of miscellaneous objects

Methods for determination of tungsten,^{65,81} chromium,⁷² titanium^{65,73,74} and molybdenum⁸⁰ in steels, of lanthanum in silver alloys,⁷¹ of gallium in GaAs–GaSb films,⁷⁰ of tin in bronzes⁶⁵ and aluminium ingots⁷⁹ as well as in metals and various biological objects⁸² are developed. The use of PCV complexes in the analysis of pharmaceutical substances is promising as well, *e.g.*, for determination of fluoxetine and fluvoxamine,⁸³ imipramine⁸⁴ and chlorpromazine hydrochloride.⁸⁵ Aminoglycoside antibiotics⁸⁶ react with PCV and aluminium at pH 3.0 to yield mixed-ligand complexes with the stoichiometry Al:PCV:antibiotic = 1:1:3 (monomycin and canamycin) and 1:1:4 (streptomycin and gentamycin); the linearity range of CC is 0.02–50 µg per ml of a biological fluid. These determinations can be carried out in the presence of 10⁴-fold excesses of tetracyclines, penicillins, amino acids, novocaine and nitrates. Of particular interest are methods for determination of proteins based on their interactions with PCV in the presence of Triton X-100 (pH 1.4–2.0)⁸⁷ (the linearity range of CC for bovine serum albumin or human blood serum content is up to 8.0 and 9.0 mg litre⁻¹, respectively) or in the presence of tin(IV);⁸⁸ the latter allows determination of down to 200 µg of albumin in 10 ml of biological fluids.

5. Novel optical methods

The concentration of a tested element or a compound in natural and biological objects is usually insufficient for its spectrophotometric measurement. As stated above, the introduction of a third component and preparation of a mixed-ligand complex is a way to enhance their chemical and analytical characteristics. An alternative approach to the increase in sensitivity of determinations is a search for novel methods of analysis and their optimisation. Rapid analyses performed under field conditions demand elaboration of easy-to-use novel versions of optical methods based on solid-phase spectrophotometry, which combines preconcentration of a complex on an appropriate sorbent with spectrophotometric determinations.

Sorption of PCV–gallium complexes in the presence of quinine on the cation-exchange resin KU-2 with subsequent solid-phase spectrophotometric analysis was studied as long ago as 1973;⁴⁷ sorption of 14 metals except for alkali metals and calcium complexes on silica gel impregnated with a PCV–Aliquat 336 mixture was demonstrated in 1994.⁸⁹ It is possible to determine metals by solid-phase spectrophotometry, which includes sorption of binary aluminium PCV complexes⁹⁰ on AV-17 or Amberlite IRA-458-Cl (pH 3–7) and of tungsten⁹¹ and molybdenum⁹² PCV complexes on Sephadex QAE-A-25 (the detection limit was 2–8 ng ml⁻¹).

Other promising methods for the solution of this problem include diffuse reflectance spectroscopy (DRS)⁹³ and chromaticity measurement.^{9,11,94} The latter can be regarded as a next stage in the development of DRS (particularly, with regard to colour characteristics). This opens up new opportunities for improvement of the sensitivity of determination and development of simple rapid test methods.^{95,96} Of special interest are procedures and techniques, which combine detection of an element owing to formation of coloured compounds, their preconcentration on various supports and determination in the sorbent phase without desorption, *e.g.*, by DRS, or semi-quantitative colorimetric determinations based on special scales built with the use of reference samples. Both methods are complementary: DRS allows investigation of chemical and analytical properties of sorbates, while colorimetry ensures rapid and inexpensive semi-quantitative production tests.

Thus a DRS procedure for determination of molybdenum(VI) (pH 1.5–3.5) and tungsten(VI) (pH 1–3) was developed, which includes sorption on a chemically modified silica S-80 containing

propionamidoxime and propionhydroxamic acid⁹⁷ or propylamine⁹⁸ residues with subsequent treatment with PCV.^{97,98} Complexation in aqueous solutions and on the surface of adsorbents occurred under identical conditions, but the spectral characteristics of the complexes differed considerably. As it was mentioned, the complexation mechanism and chemical and analytical characteristics of the complexes can change depending on the chemical nature of surfactants, whereas the properties of the ‘metal–chromophoric reagent–sorbent’ system were very similar to those of metal–chromophoric reagent–CS complexes. The complexation can thus be represented as follows. In the sorption step, MoO₄²⁻ and WO₄²⁻ form ionic associates with the protonated amino groups of the sorbent. Subsequent treatment of the latter with PCV yields PCV complexes with metal ions, which bind to the sorbent surface. The formation of ionic-associative bonds between the functional groups of PCV that are not involved in the coordination to the metal ion and the protonated amino groups of the sorbent results in more rigid structures of complexes. This brings about delocalisation of π -electrons and a shift of the absorption maximum towards the longer wavelength region [*e.g.*, $\lambda_{\max}$ for aqueous solutions of PCV at pH 1–5 is 480 nm, $\lambda_{\max}$ for aqueous solutions of molybdenum–PCV complexes at pH 2–5 is 560 nm, $\lambda_{\max}$ for the sorbent was 660 (Ref. 97) or 610 nm,⁹⁸ *i.e.* the bathochromic shift was 130–180 nm]. A similar effect was observed in the sorption of the molybdenum(VI)–PCV complex on the anion-exchange resin AV-17.⁸ Assuming that the effect of anion-exchange resins is similar to that of CS, it was expected⁹ that the sorptive effect would be enhanced after addition of a surfactant (CTMA). However, because of the competition⁹ between the anion-exchange resin and CTMA, the AV-17 resin had to be replaced by a neutral sorbent (Silochrome S-120). The bathochromic shift thereupon amounted to 230 nm, while the sensitivity of the determination increased owing to the use of chromaticity characteristics. These results were used for the development of novel test methods⁹ and fibre-optical sensors based on PCV. In a recently developed iron-specific fibre-optical sensor in which Sephadex DEAE is used as a sorbent and PCV, as an immobilised indicator,⁹⁹ the formation of a metal complex is accompanied by changes in the diffuse reflectance spectra at 460 nm.

V. Conclusion

As can be seen from the literature data, Pyrocatechol Violet is a valuable analytical tool and a popular reagent for classical (as a metal indicator in complexometry) and physicochemical (optical) methods of analysis. High reactivity of PCV is determined by its functional and analytical groups. The complexation of PCV involving these groups yields mixed-ligand compounds; this process can be controlled by introducing additional reagents or changing the solution acidity. The presence of a sulfo group favours the formation of ionic associates with cationogenic surfactants, whereas the non-compensated charge of binary complexes favours the formation of mixed-ligand complexes some of which are extracted by organic solvents.

Chromaticity offers new opportunities, especially in combination with sorption (sorption chromaticity) and diffuse reflectance spectroscopy. Being a representative of the triphenylmethane group and a close analogue of Pyrogallol Red (PGR), Pyrocatechol Violet is a conformationally active compound. Large molar extinction coefficients of ionic forms of both reagents and very high molar coefficients of chromaticity functions of PGR^{100,101} suggest high perspectiveness of PCV chromaticity, especially of its sorption chromaticity version. As regards specific characteristics, PCV complexes share many common features with PGR complexes with molybdenum,¹⁰² copper and titanium,¹⁰³ tungsten and vanadium(V),¹⁰⁴ tin(IV) and aluminium¹⁰⁵ as well as other metal ions. Determination of chromaticity characteristics of molecular and ionic forms of PCV will permit one to rationalise the choice of complexation conditions aimed at

the development of new optical methods for determination of various ions. Taking into account the discrepancy between literature data, it seems interesting to specify the values of dissociation constants of PCV using the chromaticity method. An objective confirmation of high practical utility of PCV as an analytical tool for advanced optical measurements can be derived from the values of molar coefficients of chromaticity functions of soluble complexes and sorbates.

Studies of chromaticity characteristics of PCV–metal complexes on the surface of anion-exchange resins and neutral sorbents in the presence of CS aimed at increasing the sensitivity of determinations and development of new, more efficient test scales and optical sensors is the most promising approach to their further application.

This review has been written with the financial support of the Russian Foundation for Basic Research (Project No. 05-03-32337).

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Analytical chemistry and chemical analysis

Analytical chemistry is often identified with chemical analysis. Nevertheless, the relationship between the analytical chemistry and chemical analysis is much the same as that between medical science and medical practice.

Modern analytical chemistry can be defined as a science concerned with the development of general approaches, methods and tools for the study of chemical compositions of substances and analysis of objects; chemical analysis is restricted to acquisition of information about chemical compositions of substances.

Chemical analysis is an essential tool for qualitative estimation of miscellaneous products and control over environmental objects and technological processes; besides, it is a valuable diagnostic tool in medicine. It is used in routine criminalistic studies and military practice. The conclusions in many sciences, such as molecular biology, geochemistry, chemical kinetics, *etc.*, are based, to a great extent, on the results of chemical analysis.

On the global scale, the number of analyses can be indirectly estimated, if one recalls at least some wide spread analyses, *e.g.*, measurements of carbon, phosphorus and sulfur in melted steels; of aromatic hydrocarbons and sulfur in natural oils and petroleum products; of carbon monoxide and hydrocarbons in motor car exhausts; of chlorine in swimming pool water; of pH levels in soils; of moisture content in grains and of fat content in milk, and, finally, analyses of blood and urine samples in clinical laboratories.

The range and complexity of problems facing chemical analysis and, as a consequence, analytical chemistry as a science, are steadily increasing with an increase in the number of subjects to be analysed. Who, in the middle of the 20th century, might surmise that the objects for investigation in molecular biology, biochemistry, biotechnology and, perhaps, contemporary medicine would occupy an important place among objects for analytical investigations; that the necessity of analysing complex oxides would emerge in connection with the discovery, in the 1980's, of high-temperature superconductivity; that rapid development of electronic engineering would place high-purity elements into the group of most important and most difficult objects of chemical analysis?

The number of problems facing chemical analysis and control over 'classical' objects and the new ones that constantly appear is also increasing. One of them, related to the increase in the number of components to be identified and characterised, demanded novel analytical methods for its solution. Thus inductively coupled plasma atomic emission spectroscopy (ICP-AES) made simultaneous measurement of 30–40 elements a routine practice, while the use of ICP-mass spectrometry made possible simultaneous determination of 60 elements at a sufficiently high level of sensitivity. Gas chromatography on capillary columns enables detection and, to some extent, quantitation of several hundred components of tested objects (*e.g.*, over 400 components were identified in coffee aroma). This list is far from being complete, and the problems continue to emerge over and over again.

In recent years, a demand arose for local (distribution) analysis as an alternative to bulk analysis, since in many objects the analysed components are characterised by non-homogeneous or non-uniform distribution over the thickness of the sample. The necessity to solve this task led to the development of complex and

expensive instrumental methods, such as electronic probe, X-ray electron and Auger spectroscopy, sophisticated versions of mass spectrometry, *etc.* It can be expected that the range of problems to be solved by distribution analysis will continue to expand in the future.

Problems demanding non-destructive analysis of specimens (*e.g.*, material exhibits, archeological finds, medieval paintings, *etc.*) arise regularly in some other fields, *e.g.*, technology, criminalistics, archeology, fine arts, science, *etc.*, aimed at prolongation of their functioning where required. Today, these problems are solved with either the help of X-ray fluorescence analysis, radioactivation method (in the case of short-lived radioisotopes) and IR spectroscopy or techniques producing minute destruction (electron probes, atomic emission analysis, *etc.*). There is no end to work here, and novel simple and inexpensive original procedures are required.

As time goes on, the need for continuous analysis (*e.g.*, on-line downstream analysis of sea water or express analysis of ore on a conveyor belt) as well as remote analysis (*e.g.*, control over technological processes involving radioactive or highly toxic substances or examination of extraterrestrial objects) is increasing. This is the scope of spectroscopic and electrochemical methods. However, challenging (or altogether intractable) problems of remote analysis still exist and tomorrow they will be even more numerous.

Throughout its history, analytical chemistry was trying to solve problems connected with increasing the sensitivity, accuracy, selectivity and rapidity of analysis and not without advantage. Today, there is seemingly no need in ultraprecise methods; the level of precision attained is usually very high. However, with consideration that practical requirements are changing continuously, the analysts must be ahead of time while developing ultraprecise methods for analysis.

On the other hand, it is not always necessary to perform multicomponent determinations. Sometimes, it is sufficient to establish a common parameter (the so-called integral index), which represents a cumulative effect of the whole gamut of the components. For instance, natural potable water can contain phenols, which are disagreeable by themselves, but especially hazardous are the toxic organochlorine compounds formed upon chlorination of water with participation of phenols. The detection of diverse phenolic species (nitrophenols, cresols, *etc.*) and, particularly, quantitation of each of them is a labour- and time-consuming process, at the least. However, their presence and total content can be established with the help of a single group reaction that is common for all phenols. This parameter is usually referred to as the 'phenol index' and provides a very simple example of the integral index. The degree of water pollution with oxidisable substances can be established with the help of an integral index called chemical oxygen demand (COD), which is determined from the consumption of an oxidant (as a rule, dichromate) and is proportional to the degree of contamination of water with organic compounds. Other determined parameters include total concentrations of heavy metals and polynuclear aromatic hydrocarbons. If such assays give positive results, individual analyses of compounds have to be performed where necessary.

Screening (two-step analysis) is usually employed in wide spread analyses in order to reduce labour, time and reagent consumption; in its first step, samples containing no components that are looked for are rejected. The negative result (*i.e.*, lack of the component) is considered to be final and the corresponding samples are excluded from subsequent analysis. The 'positive' samples are analysed more carefully. In this approach, the first step may include simplified and relatively inexpensive procedures, *e.g.*, test methods.

The mass character of analyses is provided by unification of experimental procedures. Carefully selected, repeatedly approved, well-developed techniques facilitate test operations. Standardisation is the highest grade of unification: while the use of unified protocols can only be recommended, the use of standardised protocols is often compulsory.

The productivity of analyses can be increased through automation and computerisation of analytical procedures. Thus the number of samples tested in agrochemical laboratories increased sharply after reorientation to analytical conveyors and the so-called continuous flow analysis.

The need for laboratory analyses is reduced with the advent of novel analytical methods and tools for their realisation: the instruments become more compact and portable and the methods are gradually becoming reagent-free as is the case with X-ray fluorescence analysis. Moreover, some analytical investigations, *e.g.*, remote analyses of extraterrestrial objects, cannot either be realisable in principle or impractical under laboratory conditions (*e.g.*, measurements of CO content in motor car exhausts or of methane content in coal mines).

The recently developed chemometric technique is yet another novel approach towards analysis. This area of research is intermediate between chemistry (analytical chemistry, in the first place), mathematics and information theory. For instance, the chemometric approach named image recognition has proved to be efficient in the analysis of complex mixtures. Here, the very paradigm of chemical analysis is changed and we renounce the idea of a 'one-after-another-component analysis'.

Since the middle of the 20th century, classical chemical methods of analysis have been continuously replaced by instrumental methods based on the use of physical phenomena, physicochemical regularities and most recent achievements in electronics, mathematics and informatics as well as in biochemistry, immunology and other biological sciences. Today, the absolute majority of practical analyses are carried out using these methods. Whereas in 1951 gravimetric, titrimetric and colorimetric methods were used as the major analytical procedures for certification of the most popular and universally employed standard geological samples, X-ray fluorescence and mass-spectrometric methods came to the foreground in 2004–2005.

The significance and abundance of one or another method change with time and space [*i.e.*, the place (country) where the analysis is carried out]. Its choice relies not only on its analytical potential and practicability for the solution of specific tasks, but also on extraneous (sometimes, critical) circumstances, such as financial situation, availability of experts, working areas, just traditions and even prejudices.

Hybrid methods became especially popular in the past decade; this refers primarily to a combination of separation and measuring techniques, *e.g.*, capillary electrophoresis and virtually all modern chromatographic techniques that combine chromatographic columns with detectors for continuous determinations. Flow-injection analysis is also related to hybrid methods, except that in this case the role of a column is played by a sampling unit, which includes an injector, chemical reactors and often a preconcentration device.

The recent trend is towards miniaturisation of analysis and analytical systems. Generally speaking, the transition from macroanalysis ('wet' chemical analysis) to semimicro- and microanalyses occurred very rapidly in due time; microscopic methods and techniques for ultramicrochemical inorganic analysis and

electrochemical analyses of biological objects including isolated cells were devised in the middle of the past century. An attempt to accommodate multifunctional devices on a microelectronic chip is the most promising recent trend; this concerns, in particular, capillary electrophoresis and, to some extent, flow-injection analysis. Many problems remain to be solved, especially in the design of mini-detectors, but the future is more than exciting. Pocket-size mini-analysers for determining a single substance (less frequently, several substances), *e.g.*, gas analysers, already appeared on the market. As a rule, the methodology for their operation is built-in, no calibration is also necessary. The instrument control is very simple: a single touch of a key and the result is displayed on the screen. The first devices of this type were, most probably, pH-metres.

However, an opposite trend, *i.e.*, the design and manufacture of sophisticated multifunctional instruments able to perform not one, but two or several related analytical procedures, also exists. The devices for surface analysis can serve as examples. These bulky and very expensive instruments combine X-ray emission microanalysis (electronic probe) with X-ray (photo)electronic and Auger spectroscopy and even secondary-ion mass spectrometry. It is noteworthy that the commercial production of analytical instruments is among the most dynamically developing branches of industry all over the world.

The formulation of adequate policy with regard to laboratory facilities still presents a problem. In case of difficult financial situations and high production cost of complex, often multifunctional instruments, their collective purchase and maintenance are of vital importance.

In conclusion, let us note once again the main trends in the development of modern analytical chemistry:

- miniaturisation of analysis including development of general-purpose analytical instruments and simple analysers based on microelectronic chips with microfluid and other systems;
- explosive development of methods and tools for extralaboratory ('field') chemical analyses including design of efficient easy-to-use tools for on-site detection of explosives and drugs;
- use of the most recent advances in mathematics and information theory (chemometrics) for effecting the transition from conventional ('one-after-another-component') analyses to estimation of integral indices and image recognition; design of expert systems; design of an 'electronic nose' and an 'electronic tongue'; development of approaches to multiparametric calibration;
- further improvement of methods and tools for distribution (local), continuous (flow-type), remote and non-destructive analyses;
- design of novel, in principle, tools for chemical analysis based on the use of nanotechnologies including development of continuously operating chemical sensors;
- expansion of studies aimed at perfection of analyses of biomedical objects;
- search for novel principles of generation of analytical signals, *e.g.*, the use of solid chemical (semiconductor, acoustic, *etc.*) sensors;
- further development and improvement of the existing spectroscopic, mass-spectrometric, chromatographic, electrochemical, *etc.* methods of analysis including surface analyses.

The past decade was marked by a departure from the conventional term 'analytical chemistry' to the term 'analytics'. This tendency is not random, of course. The matter of analytical chemistry underwent significant transformations. Today, it is far from being a mere chemistry, but rather an interdisciplinary science, which belongs partly to chemistry and partly to physics. To a considerable degree, the science of chemical analysis rests upon mathematics, information theory and biological sciences. Among analysts (especially those who are concerned with spectroscopic and nuclear-physical methods of analysis), physicists and engineers constitute rather a large group. They are analysts, but not chemists.

The present issue of the *Russian Chemical Reviews* is devoted to the state-of-the-art in individual methods of chemical analysis, since the description of all existing procedures cannot be published in one issue. Chemometric problems are considered in the review by O Ye Rodionova and A L Pomerantsev 'Chemometrics: achievements and prospects'. Spectrometric methods of analysis are described in the reviews by A A Bol'shakov *et al.* 'Prospects in analytical atomic spectrometry' and by A Kh Gilmutdinov *et al.* 'Spatially resolved atomic absorption spectrometry'. The prospects for Mössbauer spectroscopy in chemical analysis are discussed in the review by V G Semenov *et al.* The review by Ya I Yashin and A Ya Yashin 'Analytical chromatography. Methods, instrumentation and applications' is devoted to the state-of-the-art in chromatographic methods of analysis. And, finally, the review by S B Savvin *et al.* deals with the description of various methods for modification of organic reagents used in spectrophotometric assays.

Academician Yu A Zolotov

Chemometrics: achievements and prospects

O Ye Rodionova, A L Pomerantsev

Contents

I. Introduction	271
II. Data and models used in chemical analysis	274
III. Qualitative analysis methods. Exploration, classification and discrimination	276
IV. Quantitative analysis methods. Calibration	280
V. Data preprocessing and signal processing	282
VI. Conclusion	283

Abstract. The key chemometric methods and models used to solve the problems of qualitative and quantitative analysis and for process analytical technology are considered. The achievements in the field of chemometrics made in the last 20 years are surveyed. The trends and prospects for its development are discussed. The bibliography includes 228 references.

I. Introduction

1. The history of chemometrics and its position in the system of knowledge

Twenty years have passed since the publication of the Russian translation of the only (until recently) book on chemometrics;¹ much has changed during this period. Currently, chemometric methods are used in various fields of science and engineering. This review is mainly devoted to analytical chemistry where three fields of application of chemometrics can be distinguished: qualitative and quantitative analysis, process analytical chemistry and design of experiments.² The attention is focused on the first application, the second one receives less attention and the third is barely considered. This choice of key points is due to the fact that the awareness of Russian chemists of the chemometric methods increases in exactly this order. Numerous papers dealing with design of experiments³ and metrology⁴ are published in Russian scientific journals.

The number of publications dealing with chemometrics rapidly grows: 15 years ago ~100 papers per year were published, while now their number is more than 5000 a year. Therefore, when preparing the review we reasonably restricted its scope. Analysis of chemical data is the most important direction in chemometrics. In recent years, it has been rapidly and fruitfully developing; analytical chemists have proposed not only new methods for data processing, but also new approaches to experiment setting.

Chemometrics is a synthetic discipline at the boundary of chemistry[†] and mathematics. As is often the case with boundary

disciplines, it still lacks a generally recognised definition. The most popular definition was proposed by Massart,⁶ namely, ‘Chemometrics is the chemical discipline that uses mathematical, statistical and other methods employing formal logic to design or select optimal measurement procedures and experiments, and to provide maximum relevant chemical information by analyzing chemical data’. Probably, many people would accept this definition. However, the scope of science should be determined by the objects and goals it pursues rather than by the methods and instruments used. Certainly, the problem of information retrieval from source data is very important for both practice and the development of the theory; however, the experiment setup that would give results containing the required information is equally important. These two equivalent aspects, *i.e.*, retrieval of information from the data and collection of data that contain the desired information, have been reflected in the modern definition of chemometrics proposed by Wold.⁷ Chemometrics solve the following problems in chemistry:

- how to get chemically relevant information out of measured chemical data;
- how to represent and display this information;
- how to get such information into data.

The vigorous development of chemometrics in the late 1970s is correlated with the advent, in the same period, of high-speed computer facilities, which have become universally available to scientists and engineers. This allowed implementation of many complicated algorithms, especially for analysis of data obtained in multiresponse and multivariate experiments. As a consequence, more complex equipment capable of performing a much higher number of measurements appeared. However, it turned out that a large amount of data does not necessarily mean that there is enough information. Therefore, analytical chemists have started to use chemometric methods to retrieve this information and to confirm that the conclusions drawn are reliable. This led to the first obvious success. It was found that traditional labour-consuming analytical methods that require unique equipment and expensive chemicals can be replaced by much faster and less expensive indirect methods. This trend is manifested most clearly in the use of IR spectroscopy, especially in the near region, which has previously considered to be of low utility due to high noise level difficult to eliminate, caused by intense absorption of water

O Ye Rodionova, A L Pomerantsev N N Semenov Institute of Chemical Physics, Russian Academy of Sciences, ul. Kosygina 4, 119991 Moscow, Russian Federation. Fax (7-495) 939 74 83, tel. (7-495) 939 74 83, e-mail: oksana@chph.ras.ru (O Ye Rodionova), forecast@chph.ras.ru (A L Pomerantsev)

Received 23 August 2005

Uspekhi Khimii 75 (4) 302–321 (2006); translated by Z P Bobkova

[†] Chemometrics appeared as a separate subdiscipline within analytical chemistry in 1974.⁵ B Kowalski (USA) and S Wold (Sweden) can be considered its founders.

and by the scattering effect in reflectance spectra.⁸ Therefore, the first works in chemometrics were devoted to methods of analysis of spectroscopic data,^{9–11} construction of calibration models (calibrations) by the principal component analysis¹² and projections to latent structures.¹³

When speaking about the history of chemometrics, one cannot but mention the scientists who laid the grounds of the chemometric approach well before the 1970. Apparently, K Gauss, who proposed the least-squares method in 1795, is the first to be mentioned. Gosset (known under the name Student),¹⁴ who worked as the analyst at a brewer and used methods for analysis of chemical data back in the late 19th century, should also be regarded a first chemometrician. In the early 20th century, Pearson's study was published¹⁵ in which he proposed the principal component analysis; the works of Fisher,¹⁶ the author of numerous statistical methods such as the maximum likelihood method and factor analysis, and the pioneering studies on experiment planning¹⁷ were published somewhat later. Among Russian scientists, one should mention, first of all, Nalimov,¹⁸ who greatly contributed to the theory of design of chemical experiment.

The chemometrics appeared and has developed for a long period within the framework of analytical chemistry; specialists in this field still remain the main users of chemometric methods. However, a tendency appeared with time regarded by some researchers as the departure of chemometrics from 'under the wing' of analytical chemistry to become an independent discipline. Two circumstances provided grounds for this conclusion. The first one is complication of the mathematical tools used in chemometrics. Ten years ago analytical chemists could learn and accept the multivariate approach to data analysis, *i.e.*, methods such as the projection to latent structures¹⁹ or singular value decomposition.²⁰ However, subsequently, in the period of general enthusiasm of chemometricians about new methods of data analysis (multiway approach,²¹ wavelet analysis,²² support vector machines,²³ and so on), some gap between chemists and chemometricians started to form: chemists did not understand what and why chemometricians did, while the latter in turn did not realise why their new methods are not in demand in analytical chemistry. Second, numerous applications appeared in which the chemometric approach was successfully used in the fields far from analytical chemistry, for example in multivariate statistical process control,²⁴ image analysis²⁵ and in biology.²⁶ This lack of understanding is also obvious from the fact that at the last conference 'Chemometrics in Analytical Chemistry' (CAC-2004, Lisbon),²⁷ many participants argued whether chemometrics is still a part of analytical chemistry.

It can be seen from the foregoing that chemometrics is closely related to mathematics, especially mathematical statistics. Most analytical chemists understand the necessity of using statistical methods in chemical analysis and apply them to calculate average values, deviations or detection limits, to verify hypotheses and so on. They believe that these simple operations form the basis of chemometric approach in analytical chemistry. However, only some of researchers realise that this is not true and can use all diversity of chemometric methods for the analysis of chemical data.

It should be noted that for efficient application of chemometrics, it is not necessary to know, for example, the statistical theory of the principal component analysis; understanding of the fundamentals and basic ideas of this approach is sufficient. However, one should indeed know the methods of data preprocessing and variable selection principles, and, what is most important, know how to interpret correctly the data projections (loadings and scores) in the principal component space. As shown by long-term experience, this skill can be applied without in-depth mathematical knowledge. The idea of this review is to describe the main principles, methods and achievements of chemometrics using as little mathematics as possible and with geometric interpretation prevailing over the algebraic one.

Mathematicians²⁸ consider with every reason that many methods and algorithms used in chemometrics are poorly substantiated. Chemometric specialists regard their activity as a compromise between the possibility and necessity, believing that a practical result is more important than a theoretical substantiation of its impossibility. Being faced with practical problems of interpretation of very large and intricately organised data,²⁹ they create new methods of analysis so quickly that mathematicians, according to American statistician Friedman,[‡] have no time not only to criticise them, but even to merely understand what happens in chemometrics. This approach is in contrast with the situation existing in biometrics,³⁰ which can be figuratively called the 'elder sister' of chemometrics. Since Fisher's time, only approved classical methods of mathematical statistics such as factor analysis or linear discriminant analysis have been traditionally used in biometrics. Meanwhile, specialists engaged in another closely related field, psychometrics,³¹ are actively developing new approaches to data analysis. For example, the method of projection to latent structures, most popular in chemometrics, has been developed by Wold³² for application in this field.[§]

Owing to this vigorous approach to data analysis, chemometrics has found numerous applications in various fields of chemical science (for example, to study kinetics in physical chemistry,³⁴ to predict the activity of compounds from their structure (QSAR) in organic chemistry,³⁵ in polymer chemistry,³⁶ and in theoretical and quantum chemistry³⁷) and in related and other fields (for example, in brewing,³⁸ astronomy,³⁹ in forensic science⁴⁰ and quality control of the manufacture of superconductors⁴¹).

Some directions of chemometrics were developed in the USSR and later in Russia. Back in the 1950s, studies dealing with mathematical description of equilibria were carried out under Komar's⁴³ direction at the Kharkov State University. More recent relevant publications include the studies by Gribov⁴⁴ and Elyashberg⁴⁵ on spectroscopic methods, Mar'yanov⁴⁶ on titrimetric analysis, Derendyaev and Vershinin⁴⁷ on computer identification of organic compounds and Zenkevich⁴⁸ on chromatography. The active use of the chemometric approach is characteristic⁴⁹ of the scientific school of Academician Zolotov.² QSAR studies related to chemometrics headed by Academician Zefirov are underway.⁵⁰ The metrological aspects and control of the quality of chemical analysis are investigated in Dvorkin's works.⁵¹ A research group headed by Vlasov⁵² at the St Petersburg State University is working on sensor systems known as the 'electronic tongue', and analogous systems called 'electronic nose' are developed at the Voronezh Technological Academy.⁵³ All of these fields actively utilise chemometric methods. Razumov^{54,55} and his colleagues from the Institute of Chemical Physics of the RAS (Chernogolovka) employ multivariate methods of data analysis to solve problems of chemical kinetics. In recent years, new research groups that develop and utilise chemometric methods appeared in Russia, namely, the groups of Rodionova,⁵⁶ Pomerantsev,⁵⁷ Bogomolov^{58,59} (in Moscow); Kucheryavski,⁶⁰ Zhilin⁶¹ (in Barnaul); Romanenko⁶² (in Tomsk) and Shabanova and Vasil'ev⁶³ (in Irkutsk).

2. Information and software provision

We have already noted the monograph well-known in Russia,¹ which reflects the state-of-the-art in the chemometrics by the mid-

‡ J Friedman *Boosting and Bagging*. Available at <http://www.amstat.org/sections/spes/GRC2001.htm>

§ It is of interest that in the early 1970s the prevailing opinion was that 'the method seems to have few applications in the physical, engineering and biological sciences. It can sometimes be useful in the social sciences as a way of finding effective combination variables' (see Ref. 33).

¶ Detailed analysis of the use of chemometric methods in various fields is given in the monograph by Brereton,⁴² to which an interested reader can refer.

1980s. At present, the chemometric methods are described most comprehensively in a two-volume edition^{64,65} written by a group of authors headed by Massart. Apart from the detailed description of the key chemometric methods and techniques, this edition gives numerous examples of their practical application. In addition, there are lots of editions meant for different types of readers. The students and specialists in analytical chemistry who start to become familiar with chemometrics are advised to resort to the monograph by Brereton;⁴² other books^{66,67} would be useful for the researchers engaged in spectral analysis. A lot of useful information can be found in the publication by Beebe *et al.*⁶⁸ One cannot but mention the monograph by Malinowski,⁶⁹ which is still considered to be the best relevant handbook by many analytical chemists. The theoretical grounds of chemometrics can be found in other studies.^{70,71} Recently, a handbook⁷² containing a brief description of chemometric techniques has been translated into Russian. An interesting introduction to chemometrics was written by Maryanov.⁷³ An abridged translation of the handbook written by Esbensen⁷⁴ was published in Russia in a short run (for the participants of three scientific schools in chemometrics).

Two specialised journals, *Journal of Chemometrics* and *Chemometrics and Intelligent Laboratory Systems*, are devoted to the problems of chemometrics. Papers describing the results of application of chemometric methods for solving applied problems are routinely published by more than 50 scientific journals, for example, *Analytical Chemistry*, *Analytica Chimica Acta*, *Analyst*, *Talanta*, *Trends in Analytical Chemistry*, *Journal of Chromatography*, *Computers and Chemical Engineering*, *Vibrational Spectroscopy*, etc. The number of publications the authors of which use chemometric methods as the main tool for analysis and processing of experimental data increases every year (Fig. 1).

Problems of chemometrics are considered at both small regional conferences and seminars and at regular international conferences. The conference 'Chemometrics in Analytical Chemistry'²⁷ and 'The Scandinavian Symposium on Chemometrics' are most prestigious.[†] In Russia, international workshops symposia 'Modern Methods of Multivariate Data Analysis' are held annually starting from 2002.^{75–77} The theoretical and applied aspects of chemometrics are widely represented as Internet resources, mainly, English-language ones;[‡] however, some Russian resources are also available.

The software used in chemometrics includes specialised program packages,[¶] which allow fast and vivid data processing in the interactive mode. General-purpose statistical packages are also widely used.^{††} Often, researchers compose the procedures themselves, for example, in MATLAB codes,^{‡‡} and publish them for free access on the Internet or in books.⁷⁸

3. Designations and terms

The following designations are used in the review. The scalar variables are marked by italic, for example, *s*. The vectors

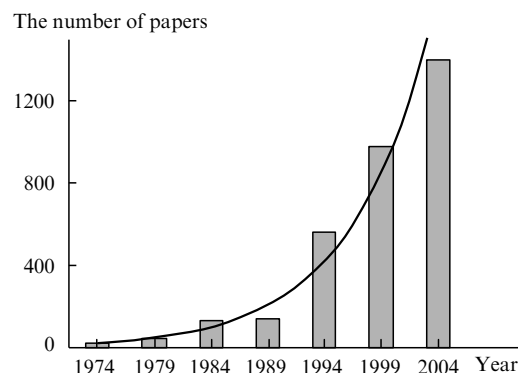


Figure 1. Diagram illustrating the growth of the number of papers in chemometrics among the publications in Elsevier periodicals.

(columns) are designated by Roman bold lower-case letters, for example, **x**, while matrices are shown by upper-case letters, for example, **W**; the multiway matrices are marked by italic, for example, *G*. The array elements are designated by the same but lower-case letter. For example, w_{ij} stands for an element of matrix **W**, the subscript *i* indicating the matrix row and varies from 1 to *I*; the subscript *j* corresponds to the column number and varies from 1 to *J*. Similar designations have been used for other subscripts, for example, $a = 1, \dots, A$. The transposition operation is denoted by superscript *t*, for example, **X**^{*t*}.

No generally accepted set of chemometric terms has been formed in the Russian literature as yet. Some concepts were translated incorrectly or inaccurately. In many cases, translators simply avoided giving Russian names to key concepts of chemometrics, such as scores and loadings and used complex euphemisms instead. In our opinion, chemometrics cannot do without such notions or their analogues.

As in any other field of knowledge, specialists in chemometrics, often use abbreviations, *i.e.*, abridged names of methods, algorithms and special terms. Below we present the list of the abbreviations used.

ALS, Alternating Least-Squares; ANN, Artificial Neural Network; DASCO, Discriminant Analysis with Shrunk COvariance matrices; EFA, Evolving Factor Analysis; GA, Genetic Algorithm; IA, Immune Algorithm; INLR, Implicit Non-linear Latent Variable Regression; ITTFA, Iterative Target Transformation Factor Analysis; KNN, *K*-Nearest Neighbours; LOO, Leave One Out; MIA, Multivariate Image Analysis; MSC, Multiplicative Signal Correction or Multiplicative Scatter Correction; MSPC, Multivariate Statistical Process Control; NAS, Net Analyte Signal; NIPALS, Non-linear Iterative Projections by Alternating Least-Squares; OSC, Orthogonal Signal Correction; PARAFAC, PARAllel FACtor Analysis; PAT, Process Analytical Technology; PC, Principal Component; PCA, Principal Component Analysis; PCR, Principal Component Regression; PLS, Projection on Latent Structures; PLS-DA, PLS Discriminant Analysis; PMN, Penalized Minimum Norm projection; QPLS, Quadratic PLS; QSAR, Quantitative Structure-Activity Relationship; RMSEC, Root-Mean Square Error of Calibration; RMSEP, Root-Mean Square Error of Prediction; SIMCA, Soft Independent Modeling of Class Analogy; SIMPLISMA, SIMPLEx-to-use Interactive Self-modeling Mixture Analysis; SIMPLS, SIMple Partial Least Squares regression; SMCR, Self-Modeling Curve Resolution; SPC, Statistical Process Control; SVD, Singular Value Decomposition; SVM, Support Vector Machine; WFA, Window Factor Analysis.

[†] The 9th Scandinavian Symposium on Chemometrics (SSC9). Available at <http://www.conference.is/ssc9>

[‡] Home of Chemometry Consultancy. Available at <http://www.chemometry.com>; *Chemometrics Literature Database*. Available at <http://www.models.kvl.dk/ris/risweb.isa> (May 1, 2005); *Chemometrics World*. Available at <http://www.wiley.co.uk/wileychi/chemometrics/Home.html>; *The Alchemist*. Available at <http://www.chemweb.com/alchemist>

[§] Russian Chemometric Society. Available at <http://rcs.chph.ras.ru>; *Chemometrics in Russia*. Available at <http://www.chemometrics.ru>

[¶] The Unscrambler. Available at <http://www.camo.no>; *Eigenvector Research Inc.* Available at <http://www.eigenvector.com>; *Umetrics*. Available at <http://www.umetrics.com>

^{††} SPSS. Available at <http://www.spss.com>; STATISTICA. Available at <http://www.statsoftinc.com>

^{‡‡} MATLAB. Available at <http://www.mathworks.com>

stances A and B was to be determined in the above experiment, then substance C would be an undesirable impurity and its contribution would be regarded as noise. What is to be attributed to noise and what should be considered information? This question is always solved with allowance for the goal and the methods used to attain the goal. This is the second principle of the chemometric approach to data analysis.

The noise and data redundancy are manifested through the correlation relationships between variables. Turning back to the idealised example, one can notice that in the matrix of 'pure' spectra $\mathbf{S}$ with the dimension 3×30 [3 rows (samples) by 30 columns (wavelengths)], only three columns would be linearly independent. Having fixed this triple, any fourth column can be represented as their linear combination. Naturally, the number equal to three is not occasional, as the system contains exactly three components. This number is called the rank of the matrix $\mathbf{S}$ and plays an important role in the chemometric analysis. When considering the same example in a more realistic version (with allowance for the errors), additional correlations between the data can be noted. This would be the case, for example, if the concentration of the third substance C is much lower than the error (noise). The data are now inadequate for reliable determination of all three concentrations and the effective rank of the matrix is equal to two. Thus, the errors in the data may give rise to random rather than systematic relationships between variables. Evidently, the former case deals with correlation relationship, while the latter case is a causal relationship.[¶]

The notion of effective (chemical) rank and hidden (latent) variables the number of which is equal to this rank underlies the third most important principle of chemometrics.⁶⁹ We shall illustrate this by the following example. Let there be several (I) mixtures of substances A, B and C, their pure spectra $s_A(\lambda)$, $s_B(\lambda)$, $s_C(\lambda)$ being unknown. One can obtain the spectra of these samples as two-way data and to construct matrix $\mathbf{X}$ with the dimension $I \times 30$. By usual mathematical analysis, one can determine the rank of this matrix. This number gives information of how many components are present in the system or, at least, how many components can be distinguished.

Thus, chemical data involve most often inner latent relationships between the variables, resulting in numerous correlations, *i.e.*, multicollinearity. This feature can be manifested as data redundancy, which increases the quality of estimates. However, in the case of a faulty method for data processing, the multicollinearity can have an adverse effect on the quality of analysis. For example, multiple linear regression cannot be used with multicollinearity.⁷⁴ For regression analysis of this sort of data, special methods are required, for example, ridge regression⁸⁶ or projection approaches.⁷¹

Sampling can be an essential source of noise. The sampling theory, a substantial contribution to which was made by Jy,⁸⁷ has become very popular in recent years.⁸⁸ Its numerous applications can be found in a publication⁸⁹ completely devoted to this subject. Yet another problem that may be faced by an analytical chemist is the gaps in the data,⁹⁰ caused by various reasons such as instrument failure, going beyond the detection limits, sample deficiency and so on. Most of chemometric methods do not work with missing data; therefore, special methods are used to fill the gaps, a method based on an iteration algorithm being used most often. Each iteration consists of two steps. In the first step, the model parameters are estimated as if the data were known completely. To this end, the gaps are filled by some *a priori* permissible values, for

example, average over the surrounding elements of the data array. In the second step, the model obtained is used to find the most probable values for the missing data, and the next iteration is carried out. An approach based on the likelihood maximum is also used to fill the gaps.⁹¹ Details of these algorithms largely depend on the data description model used.

2. General strategy of data analysis. Models and methods

The chemometric methods of data analysis can be divided into two groups corresponding to two principal tasks: (i) exploration of the data, for example, classification and discrimination; (ii) prediction of new values, for example for calibration. The first-group methods usually operate with one block of data, while the second one, with at least two blocks (predictors and responses). Depending on the goals, the methods can be directed to prediction either within the range of experimental conditions (interpolation) or beyond this range (extrapolation). The methods are classified into soft also called 'black' and hard or 'white'. When formal models are used,⁹² the data are described by an empirical dependence (most often, linear), which is valid in a limited range of conditions. In this case, one need not know the mechanism of the process under study. However, this method does not allow solving extrapolation problems. The parameters of soft models are devoid of a physical meaning and are to be interpreted using appropriate mathematical methods. The hard modelling⁹³ is based on physicochemical principles and permits extrapolating the system behaviour under new conditions. The parameters of a 'white' model have a physical meaning, and their values can help in interpretation of the elucidated dependence. However, this method is applicable only in the case where the model is known *a priori*. Each of the approaches has both advantages and drawbacks,³⁶ and both adherents and opponents. Historically, the hard method was intensively developed in Russia, while the soft method was developed more actively in other countries. The authors of many recent publications consider so-called 'grey' models,⁹⁴ which combine the advantages of both methods. Below we illustrate different approaches to modelling by examples from analytical chemistry.

Titrimetric processes, distinguished by a diversity of chemical reactions and signals registered, often serve as objects of mathematical modelling in analytical chemistry. The equations for titration curves are often fairly sophisticated and cannot be written in an explicit form with respect to the signal registered. This hampers the use of hard models for solving the inverse problem, namely, estimation of the parameters from the measured points of the curve. Nevertheless, by using modern computing systems, this problem can still be solved within the framework of the 'white' modelling.⁹⁵ It has been noted⁹⁶ that titration curves resemble in their shape the plots for reciprocal hyperbolic and trigonometric functions. Therefore, it has been proposed to use soft ('black') dependences composed of trigonometric functions $\arcsin$, $\arccos$, *etc.* According to the trade-off ('grey') approach proposed by Mar'yanov *et al.*,⁴⁶ a change in variables can transform a hard model into a piecewise-linear one. Subsequently, the parameters are estimated by the ALS method,⁹⁷ which implies progressive approximation of the model to the data: first, linear parameters are estimated by linear regression methods with non-linear parameters being fixed, and after that, non-linear parameters are estimated in a quickest descent procedure with the fixed linear parameters found previously. The procedures alternate until the results converge.

The interest in 'black' and 'grey' modelling methods is due to the difficulty of the selection and validation of a hard model. In many cases, this is reduced to mere enumeration of a small number of competing dependences, as a result of which a simple model with the smallest discrepancy is chosen. However, this does not validate the chosen method and may give rise to gross errors. Researchers often use models that have been reasonably called 'pink' [†] based on idealised dependences which poorly comply with artifacts present in real data such as baseline drifts, anomalous

[¶]The difference between the causality and correlation is amusingly illustrated in a book,⁸⁵ which cites an example of high positive correlation between the numbers of citizens and storks in Oldenburg (Germany) in the period from 1930 to 1936. Of course, these two variables are related by a correlation dependence caused by the fact that the system includes a third latent variable to which they are both related by a causal relationship.

errors, *etc.* The formal multivariate linear models and appropriate methods for their analysis are much better 'adapted' to handling artifacts. These models operate in those cases where the hard physicochemical approach is by no means applicable. The grounds for using linear models are provided by the fact that any, even a very complicated but continuous dependence in a rather narrow range can be represented as a linear function. In this case, a fundamental question is what range can be considered acceptable, in other words, the question of the scope of applicability of the constructed soft model. This question can be answered by using model validation techniques.

When the model has been properly constructed, the initial data consist of two rather representative sets obtained independently of each other. The first set, called training set, is used for model identification, *i.e.*, for estimation of its parameters. The second set, called test set, serves only for model validation. The constructed model is applied to the test set, and the results obtained are compared with the test data. The results of the comparison are considered to make decision about the model validity and accuracy. In some cases, the data array is too small for such validation. In this case, cross-validation is used.⁹⁸ According to this method, the test values are computed by the following procedure. Some invariable fraction (for example, the first 10%) of samples are excluded from the initial set of data. Then the model is constructed using only the remaining 90% of the data and then applied to the excluded set. In the next cycle, the excluded data are returned and another part of the data (the next 10%) are removed. A model is constructed once again and applied to the excluded data. This procedure is repeated until all data have functioned as excluded (in our cases, this requires 10 cycles). The leave-one-out (LOO) cross-validation procedure is used most often (without reason). Validation by the leverage correction algorithm is also employed in the regression analysis.⁷⁴ It is noteworthy that one or another validation procedure should be applied not only in quantitative, but also in qualitative analysis in solving discrimination and classification problems.

The results obtained in the analysis and modelling of experimental data always involve an uncertainty. The quantitative estimate or qualitative judgement may be changed after a repeated experiment as a result of diverse random or systematic errors either present in the initial data from the very beginning or introduced during the modelling.⁹⁹ The uncertainty in the quantitative analysis is described by either a value, *i.e.*, standard deviation,¹⁰⁰ or an interval, *i.e.*, a confidence¹⁰¹ or prediction interval.⁵⁶ In qualitative analysis, verification of statistical hypotheses is used¹⁰² in which the uncertainty is characterised by the probability of making a wrong decision.¹⁰³ The methods for estimation of the uncertainty during modelling of multivariate¹⁰⁴ and multiway¹⁰⁵ data arouse considerable interest in chemometricians. Various aspects of reliability of an analytical method are described using special characteristics: specificity, selectivity, detection limit, signal-to-noise ratio.⁷³ A topical method for their determination is the approach based on the NAS concept.¹⁰⁶ A multivariate NAS vector is defined as a part of the full signal (spectrum), which is used for modelling and prediction.¹⁰⁷ The remaining part of the signal, which includes errors and contributions from foreign components, is considered as noise. The NAS concept was applied to the problem of determining the detection limit in the analysis of two¹⁰⁸ and three-way¹⁰⁹ data. The obtained results have found numerous practical applications, one being considered below.

The reliability of an analytical method largely depends on the data that have been used to construct and validate the model. The presence of outliers¹¹⁰ or spurious data decreases the accuracy of the model and, conversely, the presence of representative (significant) samples in the experiment¹¹¹ substantially improves the model quality. The data significance can be estimated by classical regression methods¹¹² or by non-statistical procedures.⁵⁶ When the constructed model is used to determine desired parameters, similar problems arise. The method may prove inapplicable to some samples (an outlier in the prediction¹¹³) or give inaccurate results. Estimation of the method uncertainty for particular samples rather than on average¹¹⁴ is a complicated task, which is tackled by a number of research groups.¹¹⁵ Their effort determines the successful solution of practical problems such as calibration transfer,¹¹⁶ variable selection¹¹⁷ and the construction of robust models for data analysis.¹¹⁸

III. Qualitative analysis methods. Exploration, classification and discrimination

1. Principal component analysis

Modern instruments easily do a multitude of measurements per unit time. For example, if a spectroscopic sensor is used *in situ* to measure a spectrum at 300 wavelengths every 15 s, then after 1 h it will produce a 240×300 matrix of data, *i.e.*, 72 000 values. However, due to the multicollinearity, the fraction of useful information in this array may be relatively low. To isolate useful information, data compression methods are used in chemometrics (unlike the traditional approach in which only the results of some, especially significant measurements are selected from the data). For representing the initial data, new latent variables are used in these methods. Two conditions must be fulfilled. First, the number of new variables (chemical rank) should be much lower than the number of the initial variables, and, second, the loss caused by data compression should be commensurable with the noise. Data compression allows one to represent useful information in a more compact form convenient for visualisation and interpretation.

Data are compressed most often using the PCA technique,¹⁹ which underlies other similar chemometric methods including EFA,¹¹⁹ WFA,¹²⁰ ITTFA¹²¹ and numerous classification methods, for example, SIMCA.¹²² The principal component analysis implies decomposition of the original 2D matrix $\mathbf{X}$, *i.e.*, representing it as a product of two 2D matrices $\mathbf{T}$ and $\mathbf{P}$,⁷⁴

$$\mathbf{X} = \mathbf{TP}^t + \mathbf{E} = \sum_{a=1}^A \mathbf{t}_a \mathbf{p}_a^t + \mathbf{E} \quad (1)$$

In this equation, $\mathbf{T}$ is called the matrix of scores, $\mathbf{P}$ is the matrix of loadings and $\mathbf{E}$ is the matrix of residuals (Fig. 3). The numbers of columns, $\mathbf{t}_a$ in the matrix $\mathbf{T}$ and $\mathbf{p}_a$ in the matrix $\mathbf{P}$, are equal to the effective (chemical) rank of the matrix $\mathbf{X}$. This value is designated by A and is called the number of principal components; naturally, it is smaller than the number of columns in the matrix $\mathbf{X}$.

To illustrate the PCA method, let us turn back to the example considered in Section II.1. The matrix of the mixture spectra $\mathbf{X}$ can be represented as the product of the concentration matrix $\mathbf{C}$ and the spectrum matrix of pure components $\mathbf{S}$

Figure 3. Graphical view of the principal component analysis.

† See O N Karpukhin *Global (strategic) problems of the practical use of complex mathematical statistics methods (chemometrics)* Report at the fourth International Symposium 'Modern Methods of Analysis of Multivariate Data' (WSC-4). Chernoholovka, February 14–18, 2005. Available at <http://www.chemometrics.ru/articles/karpukhin>

$$\mathbf{X} = \mathbf{C}\mathbf{S}^t + \mathbf{E}. \quad (2)$$

The number of rows in matrix $\mathbf{X}$ is equal to the number of samples (I), each row corresponding to the spectrum of a single sample recorded for J wavelengths. The number of rows in matrix $\mathbf{C}$ is also equal to I and the number of columns corresponds to the number of components in the mixture ($A = 3$). The matrix of pure spectra is present in expansion (2) in the transposed form, as the number of its rows is equal to the number of wavelengths (J), while the number of columns is equal to A . As noted above, in the analysis of real data complicated by errors represented by matrix $\mathbf{E}$, the effective rank A does not necessarily coincide with the real number of components in the mixture. More often, it is greater due to the influence of non-concentration factors, for example, temperature.

The problem of resolution of the experimental matrix $\mathbf{X}$ into 'pure' components corresponding to the concentrations $\mathbf{C}$ and spectra $\mathbf{S}$ (understood in the generalised sense) is a special field in chemometrics called curve resolution.¹²³ Two directions can be distinguished in this field. The first one uses self-model curve resolution (SMCR)¹²⁴ and is mainly applied as a supplement to hyphenated chromatography.¹²⁵ The self-model approach is implemented using soft modelling method, for example, PCA or EFA, which do not utilise the conceptual knowledge about the system. Within the framework of this approach, the SIMPLISMA method can be distinguished,¹²⁶ which makes use of a simple but fairly effective procedure based on variable selection.¹²⁷ Conversely, the second direction employs *a priori* information about the processes and utilise 'grey' models.¹²⁸ This direction is applied in the studies of kinetics³⁴ and thermodynamics.¹²⁹ The key point in these problems is determining the chemical rank of the system, *i.e.*, the number of principal components A .¹³⁰ In the ideal case, the predicted spectra $\mathbf{S}$ and concentrations $\mathbf{C}$ should be close to the true values, although they cannot be exactly recovered. The reason is not only the experimental error, but also the fact that the spectra can partially overlap. When PCA is used to resolve the data into the chemically meaningful components, as in Eqn (2), it is also called factor analysis, unlike the formal principal component analysis.¹³¹

The principal component analysis is efficient not only in the problems of resolution. It is used to analyse any chemical data. In this case, the score $\mathbf{T}$ and loading $\mathbf{P}$ matrices can no longer be interpreted as the spectra and the concentrations, and the number of principal components A , as the number of chemical components present in the system. Nevertheless, even formal analysis of the scores and loadings is very useful for understanding the data structure. Below we present a simple two-dimensional illustration of PCA.

Data consisting only of two highly correlated variables x_1 and x_2 are presented in Fig. 4a. The same data in new coordinates are shown in Fig. 4b. Loading vector $\mathbf{p}_1$ of the first principal component (PC1) determines the direction of the new axis along which the data change more appreciably. The projections of all initial points on this axis form vector $\mathbf{t}_1$. The second principal component $\mathbf{p}_2$ is orthogonal to the first one, its direction (PC2) corresponding to the largest variation in the residuals (shown by segments perpendicular to the axis $\mathbf{p}_1$).

This trivial example shows that principal component analysis is executed successively, step by step. In each step, the residuals $\mathbf{E}_a$ are studied, the direction of the most pronounced change is chosen among them, the data are projected onto this axis, new residuals are calculated and so on (NIPALS algorithm).⁷⁴ According to another popular data compression algorithm, SVD,¹³² the same decomposition (1) is constructed without iterations. The number of principal components A is chosen (in other words, the iteration procedure is terminated) based on criteria that show the accuracy of the decomposition attained. Assume that matrix $\mathbf{X}$ has I rows

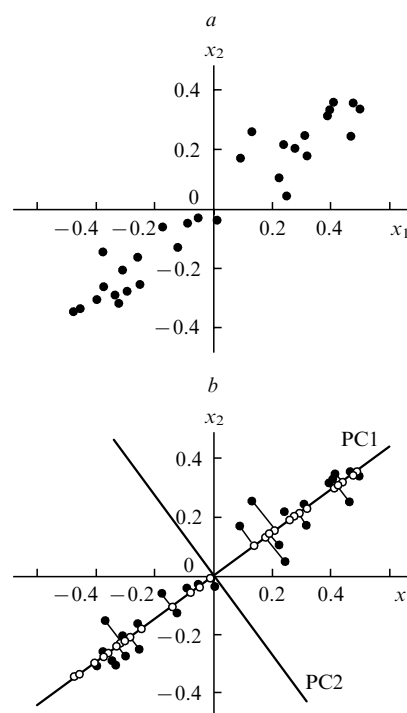


Figure 4. Graphical illustration of the principal component analysis. (a) data in the initial coordinates, (b) data in the principal component coordinates.

and J columns and A principal components participate in expansion (1). The values

$$\mu_a = 100 \sum_{i=1}^I t_{ia}^2 / \sum_{i=1}^I \sum_{j=1}^J x_{ij}^2, \quad (3)$$

$$E_a = 100 \left(1 - \sum_{i=1}^I \sum_{j=1}^J e_{ij}^2 / \sum_{i=1}^I \sum_{j=1}^J x_{ij}^2 \right), a = 1, \dots, A$$

are called the normalised eigenvalue and explained variance, respectively. They are usually plotted vs. value a . A sharp change in these values attests to the required number of principal components. For a correct choice of A , test-validation or cross-validation is required.

Equations (1) contain no absolute term; therefore, prior to data decomposition, data centring (*i.e.*, subtraction of the average over the column) is often required.

The principal component analysis can be interpreted as data projection onto a subspace with a lower dimensionality. The residuals $\mathbf{E}$ thus arising are regarded as noise containing no significant chemical information. In this subspace, one can introduce a sample dissimilarity measure called Mahalanobis distance,¹³³ which helps to solve many problems of qualitative analysis. Yet another potent method for data analysis in a projection subspace is the Procrustean rotation method.¹³⁴

When exploring the data by PCA, the attention is focused on score and loading plots. They bear information on the data structure. In the score plot, each sample is depicted in the $(\mathbf{t}_i, \mathbf{t}_j)$ coordinates, most often, $(\mathbf{t}_1, \mathbf{t}_2)$. The proximity of two points implies their similarity, *i.e.*, positive correlation. The points located at a right angle are uncorrelated, while those located in the opposite positions have a negative correlation. By using this approach in chromatographic analysis,⁴² one can find out, for example, that the linear section in the score plot corresponds to the

regions of pure components in the chromatogram, the curved sections are regions of peak overlap, and the number of such sections corresponds to the number of components in the system. Whereas the score plot is used for analysis of sample relationships, the loading plot is used to study the role of variables. In the loading plot, each variable is reflected by a point in the $(\mathbf{p}_i, \mathbf{p}_j)$ coordinates, for example, $(\mathbf{p}_1, \mathbf{p}_2)$. By analysing this plot similarly to the scope plot, one can understand which variables are interconnected and which are independent. A joint investigation of pair score and loading plots also helps to retrieve useful information from the data.⁷⁴

Consider an example of practical use of PCA in chemical analysis. The possibility of using near-IR spectroscopy for detection of counterfeit drugs has been considered.¹³⁵ Samples of true (N1, 10 items) and fake (N2, 10 items) tablets of a popular antispasmodic agent have been studied. Twenty diffuse reflectance spectra $R(\lambda)$ were recorded on a Bomem MB160 instrument with a Powder Sampler attachment in the 3800–10 000 cm^{-1} range (1069 wavelengths) without special sample preparation. The initial data were converted to $-\log R$, centred and prepared by the MSC procedure (Fig. 5).⁷⁴ The negative values of the signal are due to the use of different gain settings for the background and the sample spectra.

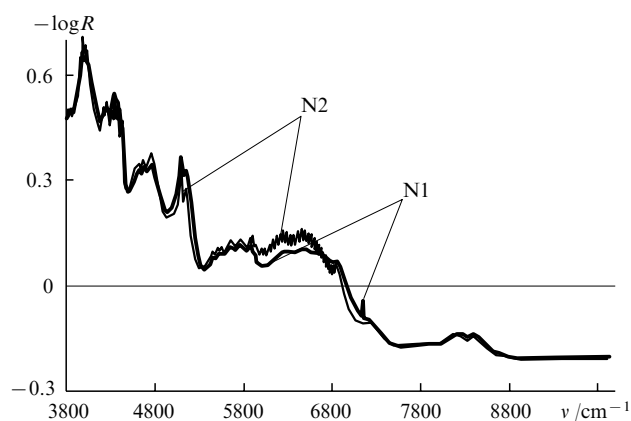


Figure 5. Spectra transformed by the MSC procedure.¹³⁵ Here and in Fig. 6 the following designations are used: N1 are true tablets, N2 are fake tablets.

In the PCA score plot (t_1, t_2) for these spectra (Fig. 6a), one can clearly see two groups of points corresponding to the true and counterfeit tablets. The scatter of points in group N2 (counterfeit) is much greater than in group N1 (original). This may be attributed to a better quality control in the legal production. In this example, it is sufficient to use only two principal components for which $\mu_1 = 94\%$, $\mu_2 = 4.9\%$, $E_2 = 99\%$.

2. Classification and discrimination

The example considered above refers to classification problems. This is a rather extensive class of problems of qualitative chemical analysis with the goal of attributing a sample to a particular class. Classification problems can be subdivided into two groups. One group includes so-called unsupervised problems that use no training set; they can be regarded as a sort of explorative analysis. This approach has been used in the above example with counterfeit tablets. The problems of the second group referred to as supervised classification are also called discrimination problems. They are solved using a training set of samples, which are known *a priori* to belong to particular classes. The methods for unsupervised classification are mainly based on PCA decomposition followed by analysis of distances between classes,¹³⁶ construction of dendrograms, the use of the fuzzy set,¹³⁷ etc. Procrustean rotation¹³⁸ and Mahalanobis distance^{139–141} have been used for

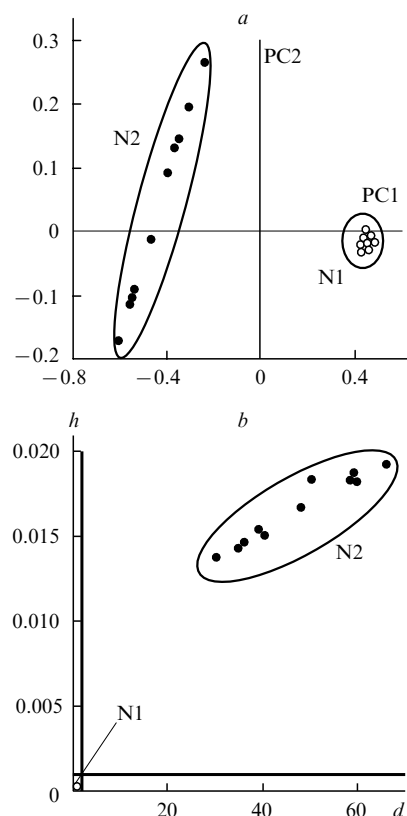


Figure 6. Determination of counterfeit drugs using PCA scores (a) and SIMCA (b).

these purposes. However, if discrimination is possible, these methods should be preferred.

A training set of samples is used to construct a classification, *i.e.*, a set of rules that can be used to assign a new sample to one or another class. When the model (or models) has been constructed, it has to be test- or cross-validated to determine the degree of its precision. If the validation is successful, the model is ready for practical use. In analytical chemistry, multicollinear data (spectra, chromatograms) are usually classified; therefore, the discrimination model is nearly always multivariate and is based on projection approaches, PCA and PLS. Note the use of linear discriminant analysis in the near-IR spectroscopy¹⁴² and canonical discriminant analysis.¹⁴³ The SIMCA method¹⁴⁴ developed by Wold¹²² is very popular.

The SIMCA method is underlain by the assumption that all objects that belong to the same class have both similar and distinctive features. When constructing a discrimination model, one should take into account only the similarity, while the distinctive features should be rejected as noise. To this end, every class from the training set is modelled independently using PCA with different numbers of principal components A . After that, distances between the classes and the distances between each class and the new object are calculated. Two values are used as distance functions. The distance from the object to a class (d) is found as the root-mean-square value of the residuals $\mathbf{e}$ arising upon projecting an object onto the class

$$d = \sqrt{\frac{1}{J-A} \sum_{j=1}^J e_j^2}.$$

This value is compared with the root-mean-square residue within the class

$$d_0 = \sqrt{\frac{1}{(I-A-1)(J-A)} \sum_{ij} e_{ij}^2}.$$

The second value, the distance from the object to the centre of the class (h), is found as the leverage (the squared Mahalanobis distance)

$$h = \frac{1}{I} + \sum_{a=1}^A \frac{\tau_a^2}{\mathbf{t}_a^T \mathbf{t}_a},$$

where τ_a is the projection of a new sample (score) on the principal component a , and $\mathbf{t}_a$ is the vector containing scores for all training samples in the class.

The use of the SIMCA method for tablet discrimination is illustrated in Fig. 6b. As the class, true tablets were used; the plot shows the distances d and h from counterfeit samples. The vertical and horizontal lines dictate the rules that can be applied to assign a new item to the class of true tablets. It can be seen that all samples of fake tablets are located far away from the true class; therefore, they can be readily discriminated. On the given scale, the points that correspond to true samples converge into one point, which almost coincides with the origin of coordinates.

Apart from SIMCA, a similar DASCO method,¹⁴⁵ as well as KNN,¹⁴⁶ SVM^{147,148} and many other methods are used for discrimination of chemical data. The PLS-DA method is a powerful tool.¹⁴⁹ The basic idea is that the discrimination rules for K classes are specified by linear regression of the form

$$\mathbf{X}\mathbf{B} = \mathbf{D},$$

where $\mathbf{X}$ is the full matrix of all initial data ($I \times J$), $\mathbf{B}$ is the matrix of unknown coefficients ($J \times K$), and $\mathbf{D}$ is a special matrix ($I \times K$) composed of zeros and ones. During the construction of matrix $\mathbf{D}$, ones should be placed only in those rows (samples) that belong to the class corresponding to the number of the column. The regression problem is solved by the PLS method (see below), which allows one to use subsequently the constructed regression to predict the assignment of new samples. For this purpose, the response of a new sample is predicted and the result is compared with zero or one.

3. Three-way methods

Principal component analysis has been developed for the analysis of data that can be represented as a two-way 2D matrix. However, in recent years analytical chemists deal more and more often with three (and higher) way data with a more complex structure. These data are gained, for example, by using hyphenated^{150,151} and evolution methods.¹⁵² The data are compressed using special approaches three of which (used most often) are briefly considered in this Section. The most comprehensive and systematic description of these methods with numerous examples of their application to chemical analysis can be found in a monograph.⁸⁰ A brief review of methods and algorithms used for analysis of three-way data has been reported.¹⁵³ The same algorithms are used to process the data obtained by hyperspectral measurements⁸³ and for image analysis.²¹

The unfolding method¹⁵⁴ is the simplest method of analysis of three-way data used to unfold 3D matrix $\mathbf{X}$ with dimension $I \times J \times K$ into a usual 2D matrix ${}^u\mathbf{X}$ with the dimension $I \times JK$ (Fig. 7). The value I is called the basic mode. After unfolding, the principal component analysis can be applied (see Section III.1). This approach is often efficient (see, for example, a study³⁶),

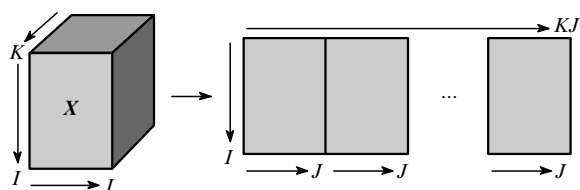


Figure 7. Graphical view of the unfolding method into a 2D matrix.

although it suffers from a number of drawbacks; first, any of three directions can be chosen as the basic mode, *i.e.*, unfolding involves uncertainty; second, the connection between neighbouring points is lost, since on passing from a 3D to a 2D matrix, it is no longer taken into account that the measurements x_{ikj} and $x_{ik+l,j}$ are neighbouring, which may be important.

The Tucker3 algorithm¹⁵⁵ allows processing three-way data, while maintaining their initial structure and, hence, the sequence of measurements, for example, the order of wavelengths in the spectrum or the time sequence of points in a chromatogram. The initial 3D data $\mathbf{X}$ are presented as three conventional 2D loading matrices ($\mathbf{A}$, $\mathbf{B}$, $\mathbf{C}$) and a three-way core array $\mathbf{G}$. The pattern of such data expansion is shown in Fig. 8. Each element of the initial 3D matrix $\mathbf{X}$ can be written as the sum

$$x_{ijk} = \sum_{p=1}^P \sum_{q=1}^Q \sum_{r=1}^R a_{ip} b_{jq} c_{kr} g_{pqr} + e_{ijk}, \quad (4)$$

where a , b and c are elements of the loading matrices, each of them corresponding to a particular way; g are elements of the core array $\mathbf{G}$. The number of principal components along each direction (P , Q , R) can be different.

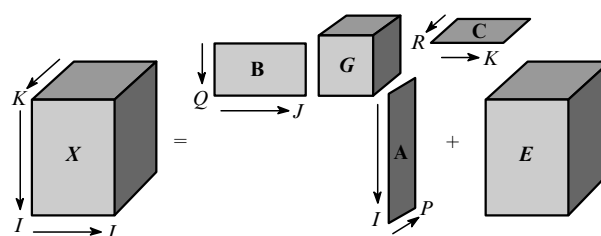


Figure 8. Graphical view of the Tucker3 model.

The PARAFAC method¹⁵³ differs from the Tucker3 model in the fact that each way is represented by the same number of principal components R . The expansion is constructed to minimise the sum of squares of the residuals e_{ijk}

$$x_{ijk} = \sum_{r=1}^R a_{ir} b_{jr} c_{kr} + e_{ijk}. \quad (5)$$

The major advantage of this method is the uniqueness of expansion. If a mixture of several chemical substances was studied, then with a correct choice of the number of principal components, the loading matrices are pure spectra of the initial compounds. The graphical scheme of the PARAFAC method is shown in Fig. 9.

The MATLAB codes of the PARAFAC algorithm can be found in a publication.¹⁵⁰ Since the loading matrices in expansion (5) are determined by an iteration procedure, this method requires a very large amount of computation. Studies aimed at acceleration of computation procedures are now in progress. A critical analysis of the most recent achievements in this field has been reported.¹⁵⁵ The algorithms of all the considered methods for decomposition of three-way data are documented.¹⁵⁶

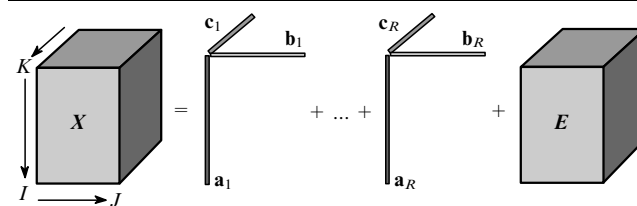


Figure 9. Graphical view of the PARAFAC model with R components.

IV. Quantitative analysis methods. Calibration

1. Linear calibration

Two blocks of data are used to solve problems of quantitative analysis.² The first block **X** is the matrix of analytical signals (for example, spectra, chromatograms and so on); the second block **Y** is the matrix of chemical parameters (for example, concentrations). The number of rows (*I*) in these matrices is equal to the number of samples, the number of columns (*J*) in the matrix **X** corresponds to the number of channels (wavelengths) in which the signal is recorded, and the number of columns (*K*) in matrix **Y** is equal to the number of chemical parameters, *i.e.*, responses. The purpose of calibration is to construct a mathematical model that would relate blocks **X** and **Y** and could be subsequently used to predict parameters **y** over a new row of analytical signals **x**.¹³

A simplest calibration model is one-dimensional regression ($J = 1, K = 1$)¹⁵⁷

$$y = a + bx,$$

which corresponds to a single channel of the analytical signal. Using classical regression analysis, it is possible to construct a more complex multiple regression ($I > J, K = 1$) involving several channels,³³

$$\mathbf{y} = \mathbf{Xb}.$$

Using these models normally implies that factors x_{ij} are known exactly, errors being present only in block **y**. Therefore, two approaches to the model construction can be distinguished: the first is called direct calibration and the other is inverse calibration.¹⁵⁸ In the first approach, chemical parameters (**X** = **C**) are used as independent parameters, while spectral measurements (**Y** = **S**) are used as responses. Previously, it has been believed that the direct model fits better to the assumption of the lack of errors in block **X** and, in addition, it is in agreement with the Bouguer–Lambert–Beer law.⁷² In the second approach, **Y** = **C**, **X** = **S**. This approach currently prevails in chemometrics, because it is more practically convenient, as it directly predicts the required analytical parameter (for example, the concentration **C**) from the measured signal (spectrum **S**). In addition, modern regression methods (PCR, PLS) make it possible to handle data with errors present in both blocks.

To illustrate various calibration methods, let us turn back to the example considered in Section II.1. Now we fill this with a particular content by simulating data **X** and **Y**. Let there be a mixture of two substances A and B ($K = 2$) and an instrument that measures an analytical signal *s* (spectrum) at 101 channels ($J = 101$). The spectra of ‘neat’ substances ($c_A = 1, c_B = 1$) are presented in Fig. 10*a* (curves *A* and *B*). The spectra significantly overlap; therefore, it is impossible to distinguish ‘selective’ channels for estimating the concentrations. Figure 10*b* shows nine simulated spectra ($I = 9$) of various mixtures of substances A and B in which a random error has been introduced with a standard deviation of 0.05. They will be used as the training set.

To construct a one-dimensional calibration, we took the intensities $s(\lambda_{50})$ of nine signals for channel 50 and plotted them in Fig. 10*c* as functions of concentrations c_A and c_B of A (points 1) and B (points 2). The calibration dependence $s = bc$ is shown by a straight line.

The calibration accuracy is usually characterised by the RMSEC value

$$\text{RMSEC} = \sqrt{\sum_{i=1}^I (y_i - \hat{y}_i)^2 / F}, \quad (6)$$

where y_i and $\hat{y}_i$ are the measured and predicted values of a chemical parameter (concentration) for the training samples $i = 1, \dots, I$; F is the number of degrees of freedom:⁴² $F = I - 1$ for one-dimensional regression without an absolute term. Evidently, the lower the RMSEC, the more accurate the description of the training data. In addition, the quality of calibration is

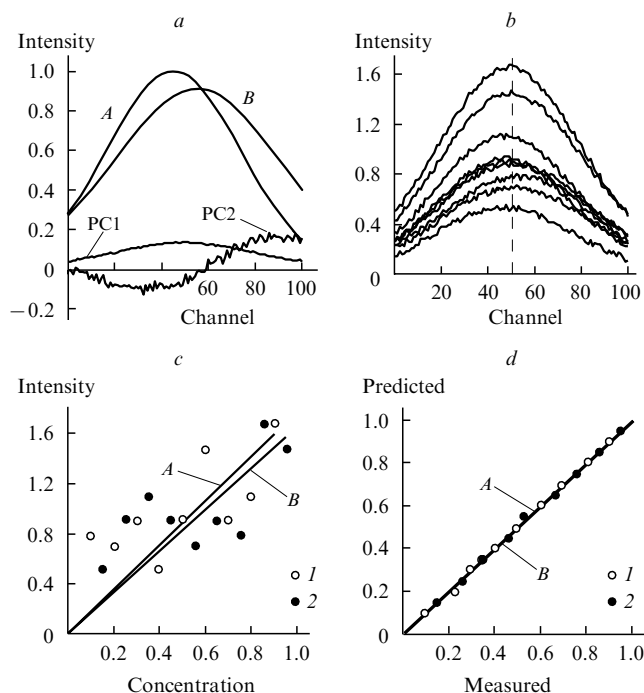


Figure 10. Examples of the construction of various calibrations.

(*a*) spectra of pure (curves *A*, *B*) and principal components (curves PC1, PC2); (*b*) model spectral data; (*c*) one-dimensional calibration, $R_A^2 = 0.50$, $\text{RMSEC} = 0.26$, $R_B^2 = 0.46$, $\text{RMSEC} = 0.219$; (*d*) PCR calibration, $R_A^2 = 0.999$, $\text{RMSEC} = 0.011$, $R_B^2 = 0.998$, $\text{RMSEC} = 0.012$.

characterised by correlation coefficient R^2 between values **y** and $\hat{\mathbf{y}}$: the closer this to unity, the higher the calibration quality. The corresponding values are given in the caption to Fig. 10*c*. The graphical dependences show that due to low instrument selectivity, the one-dimensional calibration is unsatisfactory. The calibration using multiple regression is considered below.

Consider the application of a multivariate model constructed by the PCR method.⁸⁶ The PCR method uses inverse calibration, so that **Y** = **C**, **X** = **S**. In terms of the PCA method, the matrix **X** can be expanded using formula (1); in our example, $A = 2$. Loading vectors **p**₁ and **p**₂ thus found are shown in Fig. 10*a* (curves PC1 and PC2). By comparing the plots presented in Fig. 10*a,b*, one can see that the first principal component describes a smooth trend in the data, whereas the second component shows the noised deviations from this trend. The obtained score matrix **T** is used as the block of independent variables (predictors) in the regression to the response block **Y**, *i.e.*, **Y** = **Tb**. The results of PCR calibration are presented in Fig. 10*d*, which shows the predicted concentrations $\hat{\mathbf{y}}$ as functions of the measured values **y** (points 1 for substance A and points 2 for substance B) and the regression lines, which coincide. The RMSEC and R^2 values demonstrate that PCR provides high ‘mathematical’ selectivity and gives estimates for the concentrations of A and B with much higher accuracy than the one-channel calibration. In the PCR method, the number of degrees of freedom appearing in Eqn (6) equals

$$F = I - A.$$

It has been noted above that each chemometric model requires a proper validation. In our example, the validation was carried out using a test set (test validation) comprising five samples (mixtures of A and B). The validation results for substance B are shown in Fig. 11*a*. The data for nine samples participating in calibration and five test samples are given in the ‘measured–predicted’ coordinates. The RMSEC and RMSEP values and the correlation coefficients for the training (R_C^2) and test (R_T^2) sets are also given.

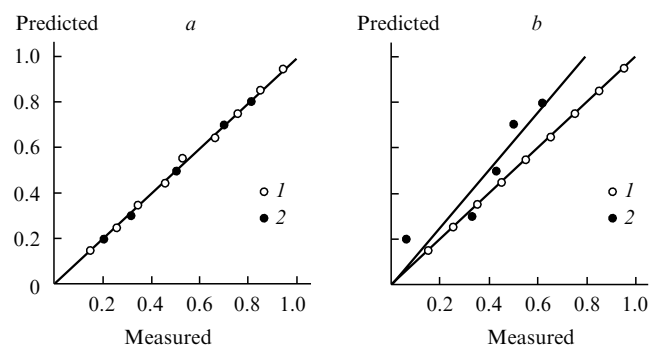


Figure 11. Validation of the calibrations in the model example using the principal component regression (a) and multiple regression (b). (a) $R^2 = 0.999$, RMSEC = 0.008, $R^2_c = 0.998$, RMSEC = 0.12; (b) $R^2 = 0.86$, RMSEC = 0.14, $R^2_c = 1.0$, RMSEC = 0; (1) training set, (2) test set.

The RMSEP values are calculated similarly to RMSEC [see Eqn (6)] but only for test samples. The number of degrees of freedom F is equal to the number of these samples. It can be seen that the principal component analysis passed the validation: the calibration and validation lines coincide.

Let us consider in this context the calibration by means of multiple regression. The training set consists of nine samples; therefore, not more than eight channels can be used for model construction ($I > J$); for example, the first, fourteenth, twenty-seventh, etc. The calibration and validation results for multiple regression are presented in Fig. 11 b. Since the number of samples is greater than the number of the channels only by one, the calibration line passes exactly through all points of the training set (points 1); therefore, RMSEC = 0 and $R^2_c = 1$. However, validation showed an unsatisfactory quality of this calibration: the accuracy is ten times worse than the accuracy in the PCR method, and the validation straight line does not coincide with the calibration line. This is a typical example of model overfitting:⁷¹ the accuracy of calibration is much higher than the accuracy of prediction.

The problem of balancing of data calibration is considered in many publications by Höskuldsson,¹⁵⁹ which introduced a new modelling concept, the so-called H-principle. According to this principle, the accuracy of modelling evaluated by the RMSEC parameter and the prediction accuracy evaluated by RMSEP are interrelated. A better RMSEC entails a poorer RMSEP; hence, they must be considered together. For this reason, the multiple linear regression, which always involves a redundant number of parameters, yields unstable models unfit for practical use.

Currently, PLS is the most widely used method for multivariate calibration in chemometrics. It resembles the PCR method; however, an important distinction is that PLS implies simultaneous decomposition of matrices $\mathbf{X}$ and $\mathbf{Y}$

$$\begin{aligned}\mathbf{X} &= \mathbf{TP}^t + \mathbf{E}, \\ \mathbf{Y} &= \mathbf{UQ}^t + \mathbf{F}.\end{aligned}\quad (7)$$

The projections are constructed in coordination, in such a way as to maximise the correlation between the X-score ($\mathbf{t}_a$) and Y-score ($\mathbf{u}_a$) vectors. Therefore, the PLS regression describes much better the complex relationships using a smaller number of principal component. The PLS method has been considered in detail in a book.⁷⁴ This approach has served as the basis for numerous calibration methods used in chemometrics, for example, SIMPLS,¹⁶⁰ PMN,¹⁶¹ robust PLS,¹⁶² ridge-PLS¹⁶³ and other.¹⁶⁴

However, all these methods give predictions as point estimates, whereas in practice, an interval estimate including the prediction uncertainty is often required. The construction of

confidence intervals by traditional statistical methods is impossible due to the problem complexity,¹¹⁴ while the use of simulation methods⁹⁸ is hampered due to the long computation time.¹⁰¹ Kantorovich¹⁶⁵ proposed to replace minimisation of the sum of squared deviations by a set of inequalities, which is solved by linear programming. In this case, the prediction gives an interval; therefore, this method was called 'simple interval calculation'.^{36, 56} Several works in analytical chemistry have been performed using this method.¹⁶⁶

2. N-Way regression

The multivariate calibration methods are naturally extended to the case where blocks $\mathbf{X}$ and $\mathbf{Y}$ are represented by N -way matrices.⁸⁰ The regression can be constructed in different ways. Using PARAFAC and Tucker3, the predictor block $\mathbf{X}$ is represented as a product of 2D loading matrices, which are used to estimate the parameters. These methods can be regarded as extension of PCR to multiway data. An extension of PLS is the Tri-PLS decomposition of the 3D matrix $\mathbf{X}$, which can be represented as follows:¹⁶⁷

$${}^u\mathbf{X} \approx \mathbf{T} {}^u\mathbf{P}.$$

Here ${}^u\mathbf{X}$ is a 2D matrix (with the dimension $I \times KJ$) obtained by unfolding of the 3D matrix $\mathbf{X}$ (with the dimension $I \times K \times J$) (see Fig. 7); $\mathbf{T}$ is the 2D score matrix (with the dimension $I \times A$); ${}^u\mathbf{P}$ is the 2D weight matrix (with the dimension $A \times KJ$), which in turn represents the unfolding for the 3D matrix $\mathbf{P}$, represented as the tensor product of two 2D matrices

$$\mathbf{P} = {}^J\mathbf{P} \otimes {}^K\mathbf{P}.$$

The decomposition of block $\mathbf{Y}$ is carried out in a similar way

$${}^u\mathbf{Y} \approx \mathbf{U} {}^u\mathbf{Q}.$$

Here, as in the usual PLS method, the scores $\mathbf{T}$ are chosen in such a way as to maximise the correlation between vectors $\mathbf{t}_a$ and $\mathbf{u}_a$. The regression problem $\mathbf{U} = \mathbf{TB}$ is solved by the conventional procedure.

The mathematical tool used in the multiway calibration is rather complex. However, the currently existing software[‡] allows chemists to overcome mathematical difficulties. Numerous examples of using multiway calibration in chemical analysis have been documented. For example, this method is used in spectrophotometry to determine pesticides,¹⁶⁸ in high performance liquid chromatography with diode matrix detection for peak resolution,¹⁶⁹ to determine trace concentrations of metals,¹⁷⁰ etc.

The use of gas chromatography – mass spectrometry to determine traces of clenbuterol in biological samples has been described.¹⁷¹ In recent years, this method has been widely used to analyse traces of organic compounds. However, due to the complexity of biological products and low content of the analyte, the estimated detection limit depends appreciably on the method of mathematical processing of experimental data. In the study cited, seven standard samples with known clenbuterol concentrations were prepared. The mass-spectrometric detection was carried out both in the full-scanning mode (210 ions) and for eight particular ions. The obtained data are three-way, the first way being the samples, the second, the mass spectra and the third, chromatograms. The full-scanning mode gave a 3D predictor matrix $\mathbf{X}$ with the dimension $7 \times 210 \times 37$; the separate ion detection mode gave a $7 \times 8 \times 22$ matrix. The response block is a 1D vector $\mathbf{y}$, which includes seven concentrations.

The calibration was constructed using various three-way algorithms: PARAFAC, PARAFAC2, Tucker3 and Tri-PLS. The Tri-PLS method proved to be the method of choice as this gave the lowest detection limit. A comparison of the results obtained by this method and a standard univariate procedure

[‡] See R Bro, C A Andersson *The N-Way Toolbox for MATLAB*. Version 2.02 (2003). Available at <http://www.models.kvl.dk/source>

showed a pronounced decrease in the detection limit, in particular, from 283 to 20.91 mg kg⁻¹ in the full-scanning mode and from 73.95 to 26.32 mg kg⁻¹ for scanning of particular ions. The detection limits were calculated in terms of the NAS concept.¹²⁴

3. Non-linear calibration

In some cases, for example, in the titration problems considered above, it is impossible to build a linear calibration. In addition, the linear technique requires a large number of data, which are not always available. Two alternative approaches are possible. One implies multiple non-linear regression, while the other, multi-variate non-linear calibration. Both approaches are considered below.

The non-linear regression analysis¹⁷² can be successfully used to solve problems of quantitative analysis if the variables are few in number. In addition, a conceptual model relating the blocks **X** and **Y** is required. Apparently, the scope of such problems is not wide, including mainly kinetic (in particular, titration) problems.⁹⁵ This approach was employed, for example, in the analysis of the activity of antioxidants,³⁶ in solving the inverse kinetic problem^{34, 94} and for the above-mentioned titration.^{173, 174} A detailed analysis of the problems faced by a researcher who uses this approach has been reported.⁵⁷

An alternative to the classical regression is the soft approach, which does not require the knowledge of a hard model but implies the presence of a large number of data.⁷⁸ To take into account non-linear effects, the INLR,¹⁷⁵ GIF-PLS¹⁷⁶ and QPLS¹⁷⁷ methods representing the upgraded PLS method have been proposed.⁸¹ In addition to non-linear PLS, the ANN method^{178, 179} simulating signal propagation in the cerebral brain cortex is used in chemometrics. This method is used successfully for function interpolation. About 10 years ago the neural network method attracted attention of chemists, which started to use it for classification,¹⁸⁰ discrimination⁵³ and calibration.^{181, 182} However, more recently, the interest somewhat attenuated and the use of ANN in chemometrics became more seldom. The reason is the above-noted model overfitting. When using neural networks, it is very difficult to evaluate correctly the degree of complexity of the model, which results in an unstable and unreliable prediction. Yet another interesting version of non-linear modelling that simulates biological processes is the GA method.^{183, 184} This method and its modification, the IA method, are useful in those cases where the chemical analysis problem fails to be formalised in terms of the usual objection functions, for example, for resolution of overlapping multicomponent chromatograms.¹⁸⁵ Examples of practical application of non-linear approaches in chemiluminescent analysis have been reported.¹⁸⁶

V. Data preprocessing and signal processing

1. Data preprocessing

An important condition for correct modelling and, hence, successful chemical analysis is the preliminary data preprocessing, which includes various transformations of the initial ('raw') experimental values. The simplest transformations include centring and scaling.¹⁸⁷ Centring is subtraction of some matrix **M** from the initial matrix **X**

$$\tilde{\mathbf{X}} = \mathbf{X} - \mathbf{M}.$$

Usually, centring is carried out by columns: for each vector **x_j** the average values are calculated

$$m_j = \frac{x_{1j} + \dots + x_{Ij}}{I}.$$

Then

$$\mathbf{M} = (m_1 \mathbf{l}, \dots, m_J \mathbf{l}),$$

where **l** is a vector of ones with the length *I*. In some cases, centring by rows is also carried out: the average values for the rows are

calculated and these values are subtracted from the corresponding rows **x_i^t**. In the case of multiway data, centring can be carried out separately for each way. Centring is required if the model is uniform, *i.e.*, has no absolute term, as in Eqns (1) and (7). After this operation, the chemical rank of the model decreases by unity and the accuracy of description may increase. Centring may be considered as projecting onto a zero principal component,¹³ hence, it is always used in the PCA and PLS methods. However, centring should not be employed if there are gaps in the data.

The second simplest transformation of data is scaling. Unlike centring, this transformation does not change the structure of the data but only the weight of their parts on processing. Scaling can be carried out for each mode. Scaling by columns is multiplication of the initial matrix **X** by matrix **W** on the left

$$\tilde{\mathbf{X}} = \mathbf{W}\mathbf{X},$$

where **W** is a diagonal matrix with the dimension *J* × *J*. Usually, diagonal elements *w_{jj}* are equal to the reciprocal of the standard deviation

$$d_j = \sqrt{\sum_{i=1}^I (x_{ij} - m_j)^2 / I}$$

along column **x_j**. Normalisation by rows is multiplication of matrix **X** by diagonal matrix **W** on the right

$$\tilde{\mathbf{X}} = \mathbf{X}\mathbf{W}.$$

The dimension of **W** is *I* × *I*, while its elements *w_{ii}* are the reciprocal values of the standard deviations of the rows **x_i^t**. A combination of centring and scaling by columns

$$\tilde{x}_{ij} = \frac{x_{ij} - m_j}{d_j}$$

is called autoscaling.

Data scaling is often used in order to equalise the contribution of variables to the model (for example, in the liquid chromatography–mass spectrometry hyphenated method), to take into account the heteroscedastic errors, or for combined processing of different blocks of data. Scaling can also be considered as a method that allows one to stabilise the computation algorithms.⁷¹ However, this type of transformation should be used with caution, because it can distort the results of qualitative analysis.⁴²

Apart from linear transformations, non-linear transformations of experimental results are also used. For example, in analysis of the data of near-IR spectroscopy, the Kubelka–Munck transformation is often employed.¹⁸⁸ The purpose of this and other transformations, for example, the Box–Cox transformation,³³ is model linearisation. Simple operations with the data such as taking the logarithm⁵⁶ or extraction of the root³⁶ can often markedly improve the model.

Almost in all cases, the initial data contain errors both random and systematic. In order to reduce the influence of random noise, various methods of data smoothing are used, for example, moving average, the Savitzky–Golay method.^{42, 189} Reducing the effect of systematic errors, *i.e.*, removal of the systematic shift of the data, is more difficult. If this shift is invariable, it can be removed using centring. In the case of linear or square dependence on the variable (for example, wavelength), numerical differentiation may prove useful. In the case of more complex dependences, special methods are used; two of these are considered below.

The multiple signal correction method, called also multiplicative scattering correction (MSC),⁷⁰ was first developed¹⁹⁰ for near-IR spectroscopy and was based on ideas stated by Kubelka and Munck.¹⁸⁸ The MSC transformation procedure is simple. First, the 'basic spectrum' is determined as the average over all rows of matrix **X**.

$$\mathbf{m}^t = \frac{\mathbf{x}_1^t + \dots + \mathbf{x}_I^t}{I}$$

Then a regression is constructed for each row $\mathbf{x}_i^t$

$$\mathbf{x}_i^t = a_i + b_i \mathbf{m}^t + \mathbf{e}_i^t$$

and the coefficients a_i and b_i are determined. The transformed data are obtained from the equation

$$\tilde{\mathbf{x}}_i^t = \frac{\mathbf{x}_i^t - a_i}{b_i}.$$

The MSC parameters a_i and b_i can be found only for some (floating) window rather than for all variables.¹⁹¹

The second method (more precisely, a group of methods), OSC¹⁹² differs in the fact that the predictor matrix $\mathbf{X}$ is transformed using the response block $\mathbf{Y}$. This method is applied for data preprocessing in solving problems of quantitative analysis. The idea of OSC is to remove, from block $\mathbf{X}$, all the systematic dependences not related to the modelled response, *i.e.*, the part of matrix $\mathbf{X}$ that is orthogonal to matrix $\mathbf{Y}$. This should result in an increase in the correlation coefficient R^2 and decrease the number of PLS components A needed for data modelling. There are many versions of this method, which was first proposed by Wold *et al.*¹⁹³ and developed by other researchers.^{194,195} The OSC procedure, like the PLS procedure, is accomplished successively by steps. In each step, a part of matrix $\mathbf{X}$ related to one OSC component is removed. The part of the matrix

$$\mathbf{X} = \mathbf{X}_1 + \mathbf{X}_2,$$

orthogonal to $\mathbf{Y}$, *i.e.*, such that

$$\mathbf{Z} = \mathbf{Y}^t \mathbf{X}_2 = 0,$$

is determined using an algorithm similar to PLS. The OSC method and MATLAB codes have been described in detail in a publication.¹⁹⁵

An approach that improves the model quality by selection of variables is an alternative to the MSC and OSC methods. The utility of selection, *i.e.*, elimination of some columns $\mathbf{x}_j$ from the initial data $\mathbf{X}$, was confirmed by both theoretical investigations and experimental results. This approach is used in both qualitative¹⁹⁶ and quantitative analysis.¹⁹⁷ The variable selection is performed using a number of methods, in particular,¹⁹⁸ Pareto optimisation¹⁹⁹ and 'jack knife'.¹¹⁷ Of special importance is variable selection in those cases where the analytical signal continuously depends on the channel, for example, in the analysis of spectrometric data.²⁰⁰ In this case, variables are selected by blocks, as in methods considered in Refs 195, 201. Apart from variable selection, the selection of samples, *i.e.*, rows $\mathbf{x}_i^t$ in matrix $\mathbf{X}$ (together with the corresponding values in the response matrix $\mathbf{Y}$), is also used. The sample selection may also improve the model quality, but it is especially important for detection of outliers,¹¹³ for calibration transfer from one instrument to another.^{116,202,203} The new approach to sample classification and selection has been reported.⁵⁶

2. Signal processing

The processing of analytical signals using various transformations and filters plays an important role in chemical analysis.^{204,205} The Fourier transform has actually revolutionised NMR, IR and X-ray spectroscopy during the last 20 years. The initial data are not recorded as primary spectra but as temporal series in which all the spectroscopic information is mixed, and recovery of the spectra requires a mathematical processing. A main reason for using Fourier spectrometry is increasing the signal-to-noise ratio; in addition, the experiment can be carried out about 100 times faster than with a conventional spectrometer. For example, this allowed ¹³C NMR spectroscopy to become a routine analytical method, despite the low sensitivity of the ¹³C nuclei to an external magnetic field. Using pulse NMR spectroscopy, one can accumulate and sum up signals for a large number of pulses. Simultaneously with Fourier transform spectroscopy, numerous methods appeared for improving the quality of data. These methods

include the so-called Fourier deconvolution (signal separation), some operations with the initial data in the temporal domain and the subsequent use of the Fourier transform.

Yet another modern method for signal processing is wavelet analysis.²⁰⁶ This allows encoding, compression and modelling of large data containing thousands of variables. This analysis is a natural development and continuation of the Fourier method. A drawback of the Fourier method is that its basis functions depend continuously on time; therefore, they cannot be used to present time-dependent data. Wavelet analysis employs basis functions with a limited range of variation of the argument, which satisfy special requirements of a scaled range. These functions shift along the signal axis and the spectra obtained upon verification provide a time-and-frequency representation with different resolutions depending on the range width. If wavelet analysis precedes the PCA or PLS method, these methods can be applied to analyse very large data without loss of information.²⁰⁷ Wavelet analysis is also used for compression and smoothing of mono- and two-way IR spectra and NMR spectra.²⁰⁸

In some cases, it is necessary to perform a fast signal smoothing in real-time. The Kalman filter is a method developed for this purpose. It can be used, for example, to model the variation of the kinetics during a process. The general idea of the Kalman filter is correction of the model following the process development. As soon as new data become available, the model is supplemented and improved. With the advent of fast and powerful computers, the Kalman filter has become of virtually no use, although some works performed with this tool still appear (see, for example, Ref. 209).

VI. Conclusion

1. Process analytical technology

We have considered the key achievements of chemometrics during the last 15–20 years and their applications in analytical chemistry. Many topical issues and applications both related to and far from analytical chemistry remained beyond the scope of the review. One issue deserves special attention, as it reflects most vividly the trends and prospects of the development of chemometrics and analytical chemistry, in particular, we are speaking about methods for the process analytical technology.

In the 1930s, the American statistician Shewhart²¹⁰ proposed to use statistical methods for the control of industrial processes. His idea is very simple: if data on a normally operating industrial process over a long period are collected and statistically processed, then for a controlled operating parameter x , a range can be established, $[x_{\min}, x_{\max}]$, in which the process operates normally. The departure of the parameter x beyond these limits gives warning about some emergency that requires immediate intervention. This method was called statistical process control. It has been successfully used in practice (Shewhart charts). However, subsequently, as the process technology became more complicated, it turned out that each parameter x_i cannot be monitored separately independently of other parameters. This often resulted in faulty decisions such as false alarms, off-spec products, *etc.* The point is that the measured operating parameters $x_1, x_2, \dots$, are usually interrelated (correlated) with each other and they should be considered together. The situation largely resembles analysis of multichannel chemical data (*e.g.*, spectra). Taking into account this analogy, MacGregor²¹¹ developed a new approach to the solution of this problem, MSPC.²¹² He proposed to use the PCA method for the analysis of multivariate data and to construct control limits in the score space by means of the Mahalanobis distance. The idea proved highly fruitful and found numerous supporters. Chemometric specialists developed methods for the multivariate control of batch (for example, biochemical) processes based on the three-way calibration;²⁴ hierarchical,²¹³ block²¹⁴ and path⁸² methods have been developed for the analysis of complex processes. The authors of some studies proposed not only to monitor but also to optimise the processes.²¹⁵ These theoretical

results have been used in practice, first of all, in the food²¹⁶ and pharmaceutical²¹⁷ industries. Systems for the quality control in the production of polymers,²¹⁸ non-ferrous metals²¹⁹ and semi-conductors⁴¹ have been developed.

Thus, a new trend appeared in chemometrics²²⁰ dealing with problems far from the problems of analytical chemistry. However, it was found that sensors and transducers used traditionally in various branches of industry do not provide information necessary for the control of complex (first of all, pharmaceutical) processes. There appeared urgent need for methods of real-time or even *in situ* monitoring of chemical reactions.²²¹ Traditional analytical methods, first of all, UV⁹⁴ and IR²²² spectrometry proved suitable for this purpose. The chemometric methods for the resolution of curves and estimation of kinetic constants from spectroscopic²²³ and chromatographic²²⁴ data were found to be useful for monitoring of chemical reactions and processes. A combination of MSPC with analytical monitoring and with process analytical chemistry²²⁵ gave an impetus to the development of a new line of research in analytical chemistry, process analytical technology (PAT).²²⁶ PAT is a system for designing, analysing and controlling the manufacture through timely measurements (*i.e.*, during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality.

The major problem faced by modern industry is to ensure high quality of the final product. In view of the increasing global competition and fluctuating market demands, the necessity of effective control of industrial processes in real-time becomes obvious, and chemometrics plays a crucial role in solving this problem. The USA Food and Drug Administration²²⁷ confirmed this role legislatively in September, 2004.

Within the framework of chemometrics, remarkable methods and algorithms have been created; however, they were approved very slowly and reluctantly by the regulating authorities of all developed countries. This is attributable to the fact that ideas of the multivariate approach are more difficult to perceive and visualise than the traditional univariate methods, which are not always able to reflect the full situation. For example, it is much easier to state that the product quality is described by the height of some peak at a particular wavelength than to explain that this quality is determined by whether or not the projection of the whole spectrum falls into a definite area in the PLS-score space found using the Mahalanobis distance, *etc.*

Throughout the whole history of the development of chemometrics, only one regulatory document has been adopted in this field.²²⁸ After the PAT document is approved, chemometrics will necessarily become a legitimate tool for any company willing to follow the FDA guideline principles. In our opinion, approval of this regulatory document would mark a crucial turn in technology and a new industry paradigm, the mission of which is to build quality into products. A fundamental distinction of this paradigm from the existing one is replacement of the standardisation and unification principles by flexible on-line control of the future product quality at every stage of the manufacture starting from raw material analysis. Consider a simple example: the products of catering facilities that work with the 'standardisation' paradigm have an obviously poorer quality than home-made food, which is produced with flexible on-line control. However, with the introduction of the PAT system, large-scale producers would be able to ensure the same high quality while maintaining large output.

2. Prospects of development

What is the role of analytical chemistry in the formation of this new technological paradigm? What can be chemists' answer to this question? In our opinion, the following trends would prevail in the development of analytics. First, the objects of analysis would become more complex and complicated. The industry requirements would not put peripheral questions such as how much of substance X is present in a sample but general questions of whether a product with the required quality will be obtained

from the given raw material or whether the chemical reaction in the given column develops in a right way. Second, methods of analysis will be changed to gain the required data directly in the plant in real-time (*in line*) rather than in the laboratory (*at line*). Third, the amount of multiway and multivariate data will sharply increase. The role of hyphenated and composite methods of analysis will grow. Fourth, the desired chemical information will be deeply hidden in these data; moreover, it will be less formalised, which will call for the use of fine methods for its retrieval. Fifth, the organisation of the analytical experiment will change: instead of analysis of a single sample in one experiment, it will be necessary to use a system approach according to which numerous samples are analysed simultaneously by different methods in an automated mode under different conditions. This large-scale computer-assisted experiment (which already exists, for example, in the microarray approach) will become a routine analytical practice. Sixth, the analytical investigation will be focused on biological objects and biochemical processes and on industrial processes as a whole.

All these trends are already visible in analytical chemistry. The role of analytical chemist will change: he will inevitably become more an analyst than a chemist. The problems tackled by the researcher will be reduced to two key problems. The first is to set up an experiment that could give data suitable for retrieving the required information. The desired information may be a prognosis for the final state of the system rather than a quantitative (concentration) or qualitative (yes/no) result. The second problem is how to retrieve the desired information from the data and interpret it from the utility and quality standpoints. To solve these problems, a researcher must use the experience and tooling of chemometrics. Thus, chemometrics as an inherent part of analytical chemistry will largely determine the trends of its development.[§]

It should be emphasised that the pronounced extension of the scope of analytical methods should be based on close cooperation of chemometric specialists not only with chemists but also with other scientists, first of all, mathematicians, physicians and biologists.

The authors are grateful to O N Karpukhin (Institute of Chemical Physics, Moscow) and A Yu Bogomolov (EMBL, Hamburg) for valuable advice during preparation of the review and to K Esbensen (Aalborg University Esbjerg, Denmark) for his effort aimed at popularisation of chemometrics in Russia.

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[§] When applying the foregoing to the practical training of specialists in chemometrics, note that it would be expedient to develop university classes in this discipline. Obviously, raising an issue of starting the corresponding specialties in the master specialisation and of the formation of Candidate and Doctor Councils is also justified.

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Prospects in analytical atomic spectrometry

A A Bol'shakov, A A Ganeev, V M Nemets

Contents

I. Introduction	289
II. Atomic absorption spectrometry	290
III. Atomic emission spectrometry	292
IV. Atomic mass spectrometry	293
V. Atomic fluorescence spectrometry	295
VI. Atomic ionisation spectrometry	296
VII. Sample preparation and introduction, atomisation and data processing	298
VIII. Conclusion	298

Abstract. The trends in the development of five main branches of atomic spectrometry, *viz.*, absorption, emission, mass, fluorescence and ionisation spectrometry, are analysed. The advantages and drawbacks of various techniques in atomic spectrometry are considered. Emphasised are the applications of analytical plasma- and laser-based methods. The problems and prospects in the development in respective fields of analytical instrumentation are discussed. The bibliography includes 279 references.

I. Introduction

Analytical atomic spectrometry embraces a multitude of techniques of elemental analysis that are based on the decomposition of samples into the state of free atoms followed by spectroscopic determination of their concentrations. One can distinguish five major branches of atomic spectrometry, *viz.*, absorption, emission, mass, fluorescence and ionisation spectrometry. The first three are most popular and versatile; atomic mass spectrometry is the most sensitive. Other methods used in elemental analysis (X-ray fluorescence, nuclear magnetic resonance, Auger electron spectrometry, neutron activation analysis, *etc.*), which are not based on the analyte atomisation and unrelated to the spectroscopy of atomic vapour, are not considered in this review.

The main goals of analytical atomic spectrometry are to attain the lowest limits of detection (down to single atoms) and the broadest dynamic range (ideally, from single atoms to 100% content), suppress the matrix effect, eliminate spectral interferences, minimise the time and cost required for sample preparation, and pass from multistage to direct methods. Fundamental studies on the development of methods for absolute and standardless analyses, aimed at avoiding calibration by standards, are in progress. Ever increasing is the role of the software development, which in certain cases facilitates substantially the deconvolution of complex background components, allows digital

processing (averaging) of noise and enhances the analysis accuracy due to the use of correlation models and neural network algorithms.

The development of analytical spectrometry and detection techniques is stimulated by the diverse and increasing demands in industry, medicine, science, environmental control, forensic analysis, *etc.* The development of portable analysers for the determination of elements in different media at the immediate point of sampling, which eliminates the stages of collecting, transportation and storage of samples, is one of the most important directions.

It should be noted that the development of atomic spectrometry slowed down in recent years; particularly, a trend towards a decreasing number of scientific publications occurred. Such a deceleration could be due to the fact that the overwhelming majority of issues in elemental analysis can successfully be solved using the available techniques and instrumentation.

The above statements may be supplemented by several general remarks.

1. According to the amount of scientific publications and conference presentations, the inductively coupled plasma emission and mass spectrometers (ICP-AES and ICP-MS) are the most popular. This is because of the fact that the inductively coupled plasma in argon heated to 6000–9000 K at the electron density of $\sim 10^{15} \text{ cm}^{-3}$ represents a virtually ideally linear atomiser and ioniser (*i.e.*, virtually independent of the sample matrix and providing the linear relationship between the analyte concentration and the analytical signal).

2. In practice, any sensitivity required for the majority of applications can be provided using commercial instruments, in particular, ICP-MS (high resolution double-focusing ICP-mass spectrometers are used in especially difficult cases).

3. Atomic absorption, arc and spark emission spectrometers remain a less expensive alternative to ICP-MS and ICP-AES instruments. Moreover, in practical applications, atomic absorption spectrometers have held the leading position for many decades. Current proliferation of ICP-AES spectrometers approaches that of the former.

4. The throughput of analysers has reached a sufficiently high level, which allows thousands of routine analyses to be performed daily. The main current tendency is to provide faster and more efficient performance using modern analytical instruments, thus spending less time and efforts.

5. Further development is aimed at improving sample introduction and simplifying the sample preparation, reducing the total

A A Bol'shakov, A A Ganeev, V M Nemets St Petersburg State University, ul. Ul'yanovskaya 1, 198504 St Petersburg, Russian Federation.
Fax (7-812) 428 72 00, tel. (7-812) 428 71 62, e-mail: alexandb@mail.ru (A A Bol'shakov), tel. (7-812) 466 41 29, e-mail: ganeev@lumex.ru (A A Ganeev), tel. (7-812) 428 44 53 (V M Nemets)

Received 4 April 2005

Uspekhi Khimii 75 (4) 322–338 (2006); translated by T Ya Safonova

Table 1. Main abbreviations used for particular techniques of analytical atomic spectrometry.

Atomic Absorption Spectrometry (AAS)	Atomic Emission Spectrometry (AES)	Atomic Mass Spectrometry (MS)	Atomic Fluorescence Spectrometry (AFS)	Atomic Ionisation Spectrometry (AIS)
Electrothermal Atomisation AAS (ETA-AAS)	Inductively Coupled Plasma AES (ICP-AES)	Inductively Coupled Plasma MS (ICP-MS)	Inductively Coupled Plasma AFS (ICP-AFS)	Laser-Enhanced Ionisation Spectrometry (LEIS)
Cavity Ring-Down Spectroscopy (CRDS)	Laser Ablation ICP-AES (LA-ICP-AES)	Laser Ablation ICP-MS (LA-ICP-MS)	Laser-Excited Atomic Fluorescence Spectrometry (LEAFS)	Laser Optogalvanic Spectrometry (LOGS)
Intracavity Laser Spectroscopy (ICLS)	Laser-Induced Breakdown Spectrometry (LIBS)	Laser Ablation Mass Spectrometry (LA-MS) Resonance Ionisation Mass Spectrometry (RIMS)		

cost, using new software for the automation of the analysis and data processing, making faster analysis and reducing the size of the instruments (while the earlier ICP-AES analysers could have the size of a wardrobe, the modern ICP-MS instruments measuring $110 \times 60 \times 58$ cm can be installed on a desk). An active progress is observed in the development of specialised equipment for the analysis of specific samples and determination of particular elements.

Annual reviews^{1–6} on the analytical atomic spectrometry published by the *Journal of Analytical Atomic Spectrometry* (London) represent the most convenient literature source to follow the trends in this field. They summarise new information on the progress along several directions, including optical and mass spectral methods, as well as use of spectrometric analysis in environmental monitoring, industry, biology and medicine. The total number of citations in these reviews and their distribution over different analytical methods reflect the trends of modern studies in atomic spectrometry. The publications cited in these reviews may be classified (on the average, over the last 5 years) as follows: modernisation of optical methods — 83%, improvement in ICP-MS — 17%, laser-based methods (including laser ablation in ICP-MS) — 16%. The latter figure illustrates an increased interest in the development of laser-based methods of analysis (publications on routine applications were not considered here).

The American journal *Analytical Chemistry* also publishes summarising overviews^{7,8} on the atomic spectrometry every two years. A particularly interesting comparison of different spectrometric methods was carried out on a five-grade scale.⁹ Several techniques at a glance were also compared.^{10,11} Moreover, several books were recently published and analytical series were supplemented with new volumes.^{12–21} The information contained in these sources allows us to consider the state-of-the-art in the field of analytical atomic spectrometry.

In this paper, we present the best detection limits achieved to date in the analytical techniques under discussion. However, these lowest detection limits can hardly be realised for each element; and thus, in many real analytical situations the detection limits may exceed those cited by several orders of magnitude. Most often we cite only the latest publications, in which the reader can find references to earlier articles. The list of references by no means reflects the chronological priorities. Table 1 lists the abbreviations used for individual spectrometric techniques; however, it does not exhaust all methods discussed in this review.

II. Atomic absorption spectrometry

While the pace of the development in modern atomic spectrometry continues to slow down (a reducing number of scientific publications, reports and presentations at exhibitions), the atomic absorption analysis continues to hold its position among the most dynamic themes, even though the history of commercial instrumentation in this field can be traced back to more than 40 years ago. Several new modifications of this method were discussed in reviews;^{22,23} first of all, it is atomic absorption spectrometry based on diode lasers (with the aim of size and cost reduction) and use of continuum spectrum sources that allow simultaneous multi-

element analysis. Studies on the improvement of graphite furnaces, automated introduction of powder and solid samples, flow-injection method and the use of echelle polychromators and charge-coupled detectors (CCD) for the rapid determination are in progress.

The advantages of continuum spectrum sources (e.g., a powerful xenon short-arc lamp), starting with the possibility of combining simultaneous multielement analysis with simultaneous background correction, were described.^{24–26} It was shown²⁷ that the use of the linear photodiode arrays or two-dimensional CCD arrays as detectors facilitated reduction of the inaccuracies caused by spatial absorption inhomogeneities in electrothermal atomisers (ETA). Some of the latest developments, in particular, use of continuum spectrum sources and cross-dispersed echelle spectrometers, as well as devices for automatic introduction of powder samples, have already found their application in commercial analysers.

Several summarising papers^{28,29} were devoted to the possibilities of the use of diode lasers in AAS. The advantages of broadly tuneable vertical-cavity surface-emitting laser diodes were illustrated in Ref. 30 that also cites the original publications on different experimental applications of diode lasers as the sources of tuneable radiation for determination of absorption by Al, Ba, Ca, Cr, Cs, Cu, Gd, Hg, I, In, K, La, Li, Mn, Pb, Rb, Sm, U, Y and Zr atoms. However, a much greater number of studies on the use of diode lasers were devoted to the determination of simple molecules such as H₂O, CO₂, CO, NH₃, HF, HCl and *etc.* (see reviews^{31–33}).[†] Simultaneous determination of several elements has been realised in multiplexing schemes with several diode lasers. It is also possible to use light emitting diodes in absorption spectroscopy.^{34,35}

The very narrow spectral width of the output emission of diode lasers (usually, $\sim 10^{-5}$ nm in a single-mode operation) is of primary importance for spectrometric purposes. The laser output radiation can be scanned over the wavelength throughout the absorption line from one wing to another. This allows one to assess the non-selective background absorption at both wings of the absorption line, thus eliminating the need for calibration with a reference beam. The signal can be detected by a photodiode without using dispersion optical devices (monochromators, spectrometers); in this case, high resolution achieved is due to the spectral narrowness of the laser output. Diode lasers can be modulated at frequencies up to 100 MHz; in combination with lock-in detection (on the fundamental or higher harmonics) of the absorption signal, this facilitates cutting off the low-frequency noise and drift effects. Moreover, the spectral resolution of diode lasers is sufficient for direct discrimination of isotopes of light (Li) and heavy (U) elements. The discrimination of intermediate isotopes is possible with the sub-Doppler saturation absorption spectroscopy.

Recently, an interest in cavity-based absorption techniques used for the many-fold increase in an effective optical path

[†] This subject was also thoroughly surveyed by T Imasaka *Talanta* **48** 305 (1999).

through the absorbing medium was renewed. It is known^{21, 36} that in the family of such techniques the method of intracavity laser spectroscopy (ICLS) in which the sample is placed inside an active laser cavity is characterised by the lowest detection limits. However, numerous non-linear effects that arise in an active cavity complicate severely the practical application of this method. Both a linear response and relative simplicity are achieved with laser-pumped passive cavities. Moreover, here the diode lasers can be used for pumping. These reasons along with the need for compactness and affordability of analytical instruments have defined the rapid development of the absorption methods based on passive optical cavities.

Here, in contrast to the ICLS technique, the sample is placed in an external (with respect to the laser) cavity with high-reflectivity mirrors. The higher the mirror quality the longer the photon lifetime in the cavity, *i.e.*, the longer is its path through the sample. Thus one can achieve pathlengths of several tens kilometres for a cavity 30–50 cm long, which makes it possible to obtain very low detection limits. One can use, as an analytical signal, either the intensity of the radiation leaking out of the cavity or the rate of signal decay upon the abrupt interruption of laser pumping, while a laser wavelength can be scanned through the absorption line. The first version corresponds to traditional extracavity absorption spectroscopy and is now often called the cavity-enhanced absorption spectroscopy (CEAS). In the second version called cavity ring-down spectroscopy (CRDS), the characteristic time of the energy loss in a passive cavity is measured.

In both versions utilising passive cavities, the analytical responses are directly related to the absolute concentration of absorbing impurities in the cavity. Both techniques exhibit approximately equal high sensitivities. The use of the CRDS method requires more complicated equipment, however it facilitates the absolute calibration. The output insusceptibility to fluctuations of the excitation laser radiation is one of the major merits of CRDS. Note that in both versions one has to match the cavity spectral modes to the pumping laser mode (or modes), the piezoelectric modulation of the cavity length being often used for this purpose. This technique, although being relatively new, has been the topic of a monograph²¹ and several reviews.^{37–40}

The use of cavities allows one to measure absorption signals that are several orders of magnitude weaker than those in conventional absorption spectroscopy. To date, only preliminary experiments have been carried out on the combination of the plasma atomisers with the CRDS detection.^{41–46} The optimum conditions for igniting the plasma used as the AAS atomiser substantially differ from those conventionally employed in the emission analysis (in the same way as the requirements imposed on plasma in ICP-AES and ICP-fluorescence spectrometry differ). At the same time, insofar as CRDS is a pulsed technique, it is reasonable to couple it with the synchronised pulsed plasma, which allows substantial reduction of the plasma background emission (this is implemented, for instance, in the plasma/laser-excited fluorescence spectrometry of gases⁴⁷).

So far, we are aware of only one paper devoted to the electrothermal atomisation combined with CRDS detection.⁴⁸ Despite experimental difficulties associated with thermal stabilisation of the cavity while an electrothermal furnace is placed inside, it was concluded that this method holds a great promise, especially related to the possibility of using diode lasers. Detection of trace amounts of mercury vapour was an example^{49, 50} showing that the sensitivity of the CRDS technique can far exceed that of the conventional atomic absorption.[‡] A relatively narrow spectral range in which the dielectric mirrors retain their high efficiency is a disadvantage of cavity-based methods. This limits the possibilities of these techniques regarding the number of elements that can be determined simultaneously.

‡ This is also evident from the results of determination of gallium in flame. See M Emig, R I Billmers, K G Owens, N P Cernansky, D L Miller, F A Narducci *Appl. Spectrosc.* **56** 863 (2002).

Diode laser-based atomic absorption spectrometry has not yet left the walls of research laboratories. However, progress in the development of absorption enhancement techniques in passive cavities and the gradual increase in the number of elements detectable with diode lasers give us the grounds to hope that such commercial analysers will be available in the future. In principle, diode lasers allow determination of up to 54 elements.²⁹ The scope of this method can be further extended to include the elements, resonance lines of which are beyond the wavelength range accessible with diode lasers, while their lower excited states may be highly populated in the high-temperature or plasma atomisers.

Studies on the use of the hollow-cathode glow discharge plasma as a 'cold' atomiser in absorption spectrometry are in progress.^{51, 52} Direct sputtering of the cathode material or the material of films coated on the cathode makes it possible in certain cases to simplify substantially the atomisation procedure and reduce the matrix effects on the results of determination of impurities owing to efficient dissociation of all sample components in the plasma. In principle, by using plasma atomisers, it is possible to simultaneously acquire the absorption and emission spectra. A miniature low-frequency (5–20 kHz) discharge in combination with a semiconductor laser source was proposed⁵³ as a prototype of absorption sensors.

Modernisation of conventional atomic absorption instrumentation leads to both the realisation of multielement analysis (by using continuum sources or sets of multielement lamps) and the increase in data acquisition rates, *i.e.*, rapid sequential determination of several elements in one sample. The latest improvements can boost the characteristics of the atomic absorption analysers with electrothermal atomisers (ETA-AAS) to approach those of the ICP-AES instruments, without compromising their simplicity and low cost. Although the dynamic range of AAS spectrometers usually does not exceed three orders of magnitude, their detection limits are low, *viz.*, down to $\sim 10^{-10}\%$ for electrothermal atomisation and $\sim 10^{-7}\%$ in flames. Using ETA-AAS, one can perform sequential determination of about 50 elements with high sensitivity.

Physico-chemical processes that occur in a graphite furnace with coatings and chemical modifiers used for the sample stabilisation, reduction of the graphite corrosion and decrease in the effect of thermochemical reactions on the graphite tube were considered.^{54–56} A kinetic model of the absorption signal was developed.⁵⁷ Studies on further corrections for the non-selective background absorption^{58, 59} and use of the principal component analysis⁶⁰ are in progress.

The application of AAS with gaseous sample introduction (in the case of volatile hydrides, halides, organometallic and other compounds) is being gradually expanded. The atomisation is provided by decomposition of the molecular vapours, *e.g.*, in a heated quartz tube. The merits of this method include nearly 100% efficiency of the gas-phase transport and low detection limits ($\sim 10^{-8}\%$). Determination of quite a number of elements (Ag, As, Au, Bi, Cd, Co, Cu, Ge, Ni, Pb, Sb, Se, Sn, Te, Zn, *etc.*) is possible by this method, however most often volatile hydrides are used for the determination of arsenic and selenium.^{61–64} Some of commercial instruments for atomic absorption are equipped with exchangeable atomiser modules, which include flame, ETA, and also a quartz tube for the introduction of volatile compounds and mercury vapour.

The concept of absolute absorption analysis is subject to continuous development. Thus, L'vov believes^{65, 66} that the possibility of the analysis without using standards for calibration might be realised in the future. For this purpose, one would need spectrally narrow and bright radiation sources, thermally stabilised atomisers that can provide complete atomisation in a defined volume, and matrix array detectors that would take into account all spatial inhomogeneities in the analysed vapour distribution. In our viewpoint, the former and latter conditions can be best met with diode lasers and two-dimensional CCD detectors.

III. Atomic emission spectrometry

In the field of atomic emission spectrometry, the leading role is played by ICP-AES. Such instruments have been commercially available for more than 30 years. Besides using conventional inductively coupled argon plasma in atmospheric-pressure torches, the emission spectra are also excited in other kinds of plasma, including direct-current plasma, glow discharge, radio-frequency discharge, microwave-induced plasma, as well as inductively coupled discharges at reduced pressure and other plasma sources. Several fresh reviews on this subject can be found in the literature^{67–71} (see also the monograph¹⁷). Such conventional sources as sparks and arcs are still used in practice.^{72,73} The plasma of laser-induced breakdown at the focus of the laser beam in the bulk of gas (air) or on the sample surface represents a special case.

Further progress is observed in advanced light-collection schemes in ICP-AES. An increase in the optical throughput of the instruments is achieved by using both aspherical optics and high-efficiency holographic gratings. Echelle gratings incorporated into the cross-dispersed schemes are utilised^{74–76} with the aim of collecting the whole spectrum on a single CCD array detector, thus providing virtually simultaneous recording of the whole data envelope, including information required for the automatic background correction. However, due to the high density of information per pixel, the spectral resolution is compromised in such schemes; hence, in the latest versions of ICP-AES instruments the plasma emission spectrum is dispersed along the Rowland sphere segment, with 10 to 20 CCD cameras installed along the spectrum span. This results in excellent resolution and very rapid recording. Most of the ICP-AES instruments allow simultaneous determination of 75 elements with a linear dynamic range of 5–6 orders of magnitude.

Simultaneous recording of a whole cluster of spectral lines opens up the possibility of more advanced processing of analytical information, particularly, when several lines for each element are considered.⁷⁷ Thus, one can reduce or correct the matrix effects on the results of analysis, avoid systematic errors due to self-absorption of strong lines, take into account the temporal instability of the electronic gain factor and the baseline drift, utilise multicomponent calibration and the regression relationships. Sometimes spectrometers filled or purged with inert gases are used, which enables recording of the vacuum UV spectrum where the most sensitive lines of many elements are located and fewer spectral interferences are found.

Microwave plasma with a relatively low gas temperature and high energy of free electrons is often used for the elemental analysis of compounds separated by chromatography or capillary electrophoresis. The advantages of this kind of plasma include the high excitation capability combined with the low power and compact equipment. However, due to the low temperature of plasma, its parameters strongly depend on the amount and composition of the introduced sample eluents. The analytical applications of the microwave plasma were surveyed.^{78,79}

Interesting publications^{80–82} were devoted to the combination of the graphite furnace atomisation with microwave plasma excitation of emission from the analysed vapour, which provided high atomisation temperature within a compact instrument and made it possible to determine all elements at once in micro-samples. Such plasma in a graphite furnace can also be used for the elemental analysis of compounds separated by gas chromatography.⁸¹ The dependence of the plasma parameters on the sample matrix composition (especially those rich in easily ionised elements) cannot be totally avoided; however, this dependence is weaker than that in conventional schemes where both atomisation and excitation take place in a microwave plasma.

Aimed at miniaturisation of spectrochemical analysers, keen attention is paid currently to the development of microplasma sources and analytical techniques based on their application. Echelle⁷⁵ and other microspectrometers (with a satisfactory

spectral resolution and the cigarette-pack dimensions) can be used to detect the emission. The evident advantages of such miniature analysers are the possibility of using them in field and constraint environments, the very small consumption of samples and reagents, the low cost and the possibility of forming wide sensor networks with a large number of remote detectors. Several reviews^{83–85} were devoted to the recent advances in the development and application of microplasma (sources of plasma volume ranging from 10^{-6} to 10^{-2} cm³ were discussed).

Rapid progress is observed in the development of methods and instrumentation in the field of laser-induced breakdown plasma (laser spark) used for the analysis of solids, liquids, gases, suspended dust and aerosols. The interest arises due to the possibility of developing universal emission analysers suitable for any kind of samples, including microscopic samples, for all elements simultaneously, with excellent spatial resolution along the surface and in depth, with no contact to the samples (remotely) and no sample preparation, that are designed for the real-time operation in a compact portable fashion. In practice, the greatest difficulties are associated with calibration ambiguities and modest detection limits ($\sim 10^{-3}\%$ with a relative error of 5%–10%). In many cases, only approximate calibration could be achieved. In the last 5 years, more than 1500 publications were devoted to the development of this method. The theory and diverse analytical applications of laser-induced breakdown spectrometry (LIBS), including laser-induced breakdown in gases and on ablated surfaces, were the subject of a book¹⁸ and several reviews.^{9,40,86–91}

To date, the major mechanisms of the formation and development of laser-induced plasma are well understood and can be predicted based on models. For the purposes of the analysis, it is desirable that the extracted mass is independent of possible heterogeneities in the sample; hence, very short pulses should be used (to eliminate the effect of thermalisation and heat transfer across the sample). For pulses of ~ 1 ps and shorter, the duration of the laser field is sufficient to heat up only the electrons in the vicinity of the laser-illuminated spot on the sample surface. An explosion-type ejection of these electrons causes simultaneous destruction and ejection of the 'cold' lattice material due to the Coulomb forces. Thus, in the femtosecond mode (≤ 1 ps), the process of instantaneous vaporisation and ionisation of the sample can be greatly simplified, without inducing any transfer of heat across the sample and any shielding of the laser irradiation by the plasma plume that forms only after the end of the laser pulse. These factors improve significantly the reproducibility of the analysis.

The use of short-wavelength (ultraviolet) lasers provides more efficient and reproducible ablation and hence higher accuracy of the analysis as compared to that attainable with less intricate infrared lasers. Advantages of the ultraviolet irradiation are associated with more efficient absorption in the sample bulk (*i.e.*, smaller losses due to reflection from the surface and less absorption in the plume above the sample surface), as well as due to the lower degree of the multiphoton ionisation as compared to the laser-induced breakdown in the infrared range. Because of the higher photon energy, the ultraviolet radiation can break lattice bonds even in a single-quantum absorption event.

Thus, the ablation by short-pulse UV lasers is a direct and the most efficient method of microextraction with the lowest probability of fractionation effects, which may cause the ratios of elements in a plume to differ from the stoichiometry of the sample. This occurs if the radiation power density is sufficient for a robust laser-induced breakdown; and this condition explicitly distinguishes the laser spark from the laser desorption mode. Although the fractionation cannot be entirely avoided in any case, it is the ablation with short-pulse UV lasers that allows one to reduce the difficulties associated with calibration, reproducibility and accuracy of the analysis.

The elimination of heat transfer and meltdown effects in the femtosecond mode becomes of particular significance for local

lateral and layer-by-layer analyses where one must avoid thermal 'mixing' of neighbouring areas in the sample. Moreover, the UV focus spot can be reduced to a smaller size compared to the infrared. At the same time, use of short-wavelength lasers results in deterioration of resolution in layer-by-layer analysis (due to deeper penetration of the UV laser field into the sample).

In a laser spark, very hot plasma is formed (up to 40 000 K at the electron density up to $\sim 10^{18} \text{ cm}^{-3}$). Moreover, plasma in plumes extracted from entirely different samples often exhibit similar characteristics. However, despite the efforts to minimise any differences, the amount of vaporised material and the plasma parameters depend on numerous factors. Therefore, laser-induced plasma as an atomiser is inferior to analytical ICP in linearity, completeness of atomisation and versatility (*i.e.*, the degree of insusceptibility to the matrix effects). As in a conventional ICP, argon is the ideal atmosphere for the formation of a plasma plume during laser spark. However, ambient air mixed with the vaporised sample material appears to be the most common medium.

The LIBS enables analysis of substances in any state, while recording the spectra on CCD arrays makes it possible to determine all emitting elements in each pulse. Numerous examples of using laser-induced plasma in emission spectrometers range from the detection of gases and aerosols in air^{92–94} to the analysis of melted minerals and steels in industry^{95,96} and even rocks on other planets.^{97,98} The recent development of miniature emitter modules of the laser-amplifier type⁹⁹ brings a hope that in future the LIBS analysers will fit into a flashlight-size module connected to the control-panel notebook by a fiberoptic cable. The examples of compact laser-induced plasma spectrometers are documented.^{88, 89, 95, 100–103}

Sometimes double-pulse lasers are used for reducing the detection limits in LIBS. Ideally, the first short-duration UV laser pulse induces extraction (generates a plume), while the second longer pulse in the infrared provides additional heating of the plasma in a plume, because the IR radiation is more efficiently absorbed by the plasma (*i.e.*, heats up the free electrons to a greater extent) as compared to the UV radiation. Due to this heating, more complete atomisation in a plume is achieved.^{92,96,104,105} In the other similar scheme, the second heating pulse uses the laser wavelength tuned in resonance with the absorption line of the main component of the sample.¹⁰⁶ Thus, one can reduce the detection limits by more than an order of magnitude.

The most direct way of achieving complete atomisation of the laser extraction products is their transport with a flow of argon into a conventional ICP torch. In this fashion, laser ablation is merely used for converting the sample into the aerosol state, *i.e.*, as a sampling method, followed by the analysis using ICP-AES or ICP-MS (see reviews^{40, 87, 90, 91}). This reduces the detection limits down to $\sim 10^{-7}\%$ at the expense of merits of compactness and viable remoteness of the analysis. The main application area of laser-ablation ICP-AES (LA-ICP-AES) is the analysis of heterogeneous samples with a micron resolution.¹⁰⁷

Note that the unique nature of laser ablation with direct recording of emission spectra, *i.e.*, LIBS, is fully revealed only if a remote or local microanalysis is required, since a classical electric spark (as opposite to a laser spark) can be easily made more powerful with a multi-fold superiority in the analytical volume and, correspondingly, in sensitivity. The cost of equipment for the electric spark is also much less than that for laser ablation. Moreover, the analysis of electrically non-conducting samples with no pretreatment, as well as the analysis of aerosols, dust and ash in gases can well be performed using compact electric spark sources.^{108,109} Nonetheless, the laser sparks provide more flexible control over the discharge parameters relative to the electric sparks. The laser-induced breakdown is free of a drawback typical for the electric sparks, *viz.*, the fast uncontrollable movement (twisting) of the contracted discharge body. The higher temperature in the laser-induced plasma determines both the higher

degree of atomisation and the linearity of calibration, and reduces spectral interferences.

Yet another relatively simple, rapid and inexpensive method for the analysis of surfaces and near-surface layers employs 'cool' glow discharges (usually at reduced pressure and room temperature) used for simultaneous atomisation, excitation and ionisation of samples. Both direct-current and capacitively coupled radiofrequency (RF) discharges using both hollow and planar cathodes are utilised (see reviews^{69,70}). The detection limits of hollow cathode-based analysers are usually somewhat better as compared to the planar-cathode instruments (order of $\sim 10^{-4}\%$). The advantage of radiofrequency discharges is the possibility of direct sputtering (*i.e.*, plasma-induced atomisation) of electrically non-conducting samples and coatings.

Gradual sputtering of the sample surface in a 'mild' discharge and the continuous recording of the emission spectra allow one to carry out the layer-by-layer analysis with unprecedented high resolution ($\sim 1 \text{ nm}$ of depth). A sputtering rate can be further decreased using a pulsed discharge. It is also advantageous to use pulsed discharges for the analysis of samples especially sensitive to high temperature (*e.g.*, films and polymers). Moreover, with the use of pulsed discharges, one can sometimes obtain two-dimensional spectral images of the surface, *i.e.*, perform an instantaneous analysis of heterogeneous surfaces. Using glow discharges, it is possible to analyse both very wide surface areas and very small samples. Application of different gas mixtures in glow discharges was reviewed;¹¹⁰ while analytical applications in the layer-by-layer analysis of thin films and for environmental purposes were also surveyed.^{111–113}

Standardless emission analysis is possible if one has an adequate theoretical model that relates the intensities of spectral lines to the concentrations of elements in a plasma.¹¹⁴ Dense plasmas such as an arc, ICP and a laser-induced breakdown can sometimes be considered within the framework of the local thermodynamic equilibrium (LTE). In the LTE model, the populations of all emitting states of atoms and ions are unambiguously related to the plasma temperature and the concentrations of elements, according to the Saha–Boltzmann law. By means of deriving the temperature from relative line intensities, one can then determine the concentrations of elements with normalisation at the sum of all concentrations set equal to unity. Such a procedure of the standardless analysis (including the effect of self-absorption of lines) was developed for the case of the laser-induced breakdown spectroscopy (see Ref. 115).[§] A similar idea was used for indirect calibration of ICP-AES in the analysis of gases.¹¹⁶ Generally, the models more complicated than LTE are often used for simulating plasmas (such as microwave, glow discharge, and *etc.*).

IV. Atomic mass spectrometry

In the mass spectrometric analysis, there is a number of different methods for ionisation of the analyte atoms. They include ionisation in plasma sources (electron impact, collisional charge exchange, plasma-chemical reactions or sputtering of secondary ions from the surface), electrothermal ionisation (heated filaments and graphite cups), ionisation of vapour in the resonance laser field, radioactive source ionisation, *etc.* The most comprehensive reviews on analytical atomic mass spectrometry can be found in books^{17,19,20} and papers.^{3,117–120} Each issue of the *Journal of Mass Spectrometry* (UK) contains a list of recent publications in the field of mass spectrometry.

Analytical mass spectrometry based on ionisation in plasma plays the leading role in the elemental analysis due to its capability of highly sensitive, multicomponent, versatile and rapid analysis.

[§] For recent publications on this topic, see I B Gornushkin, A I Kazakov, N Omenetto, B W Smith, J D Winefordner *Spectrochim. Acta, Part B* **60** 215 (2005).

To date, the potential of contemporary ICP-mass spectrometers (the first commercial instruments appeared more than 20 years ago) represents virtually the reference point for all other methods and instruments. Indeed, ICP-MS enables the simultaneous determination of several dozens of elements at trace concentrations down to $\sim 10^{-9}\%$ in solid samples and $\sim 10^{-13}\%$ in ideal aqueous solutions, within a dynamic range of up to 9 orders of magnitude.

This technique is applied most often to the analysis of environmental and geological samples, and high-purity substances. However, not only the ICP but also other kinds of plasma are widely used for ionising atoms, particularly, in glow and corona discharges, and also in laser-induced plasma (laser ablation and laser desorption from the surface). Inductively coupled and corona discharges are usually ignited at atmospheric pressure, whereas glow discharge is ignited at low and reduced pressures. Corona discharge is utilised in the mass-spectrometric analysis of gases.^{121, 122} Electric spark in vacuum is also successfully used as the atomiser/ioniser of conducting and non-conducting samples (the latter are pre-ground and pressed into graphite electrodes).¹²³

In the majority of cases, the IPC-MS instruments incorporate quadrupole mass spectrometers (they are usually more expensive than the AAS and ICP-AES analysers, but less expensive than other kinds of mass spectrometers). One of the main problems related to quadrupole-based ICP-mass spectrometers concerns the isobaric interferences, *i.e.*, overlaps of isotopes of different elements with equal charge-to-mass ratios. Moreover, in the argon plasma, in addition to the proper atomic ions, some parasitic molecular ions are also formed such as Ar_2^+ , ArO^+ , ArH^+ , ArOH^+ , ArN^+ and other, as well as multicharge ions, which introduce additional interferences. This can be alleviated if the high-resolution magnetic sector mass spectrometers in a double-focusing mode (with crossed electrostatic and magnetic fields) are used.^{124–127} High-resolution instruments are very expensive but highly sensitive and facilitate recording of extremely small differences in the isobaric masses of elements.

An attractive innovation for minimising the isobaric interferences is related to the development of the RF multipole reaction cells that can be installed in conventional quadrupole mass spectrometers.^{128–131} The cell is filled with a reactive gas (*e.g.*, ammonia, oxygen, or methane) under reduced pressure, and the field-driven analyte ions drift towards the main mass analyser (quadrupole) and the detector. In the simplest case, the buffer gas molecules collide with the parasitic molecular ions produced in an ICP and break them apart into the atomic form. However, transforming particular parasitic ions into the molecular ions with a different mass in ion–molecule charge exchange reactions is a much more efficient way of eliminating specific interferences. Quadrupole, hexapole and octopole systems are used as RF multipole cells.¹³¹ Sometimes RF ion traps are used for this purpose. The best performance was observed for quadrupole dynamic reaction cells, which can be tuned synchronously with the main mass analyser (*i.e.*, in resonance with the analyte mass), thus cutting off possible secondary interferences in the upper and lower mass ranges. As a result, the common quadrupole mass spectrometers equipped with RF multipole reaction cells are presently a sound alternative to the very expensive high-resolution magnetic sector mass spectrometers.

Since the quadrupole mass spectrometers are the scanning devices in their principle of operation, the speed (throughput) of detection is low in the multielement analysis, because the acquisition time required for determining each element in the vicinity of its detection limit is about ~ 10 s. As a result, further efforts take place in the development of magnetic sector mass spectrometers with multichannel/multicollector detectors for simultaneous detection of all ions arriving to the focal surface.^{125, 132–134} For the similar purposes, the time-of-flight mass spectrometers that can simultaneously record the whole spectrum of elements in each ion extraction pulse, are being used.^{135–138} There are commercial models of the ICP-time-of-flight mass spectrometers.

In contrast to magnetic sector multichannel (multicollector) mass spectrometers, the time-of-flight mass spectrometers have long been used in analytical studies and are available in various models. However, potential advantages of magnetic sector mass spectrometers are related to the fact that they are continuous, and consequently, superior in the integration time, accuracy, stability and noise averaging possibilities. Time-of-flight mass spectrometers can determine ions in a broad range of masses simultaneously; moreover, they are less bulky and less expensive. A certain method of simultaneous recording is specifically required in those cases where fast or transient processes are studied, *e.g.*, in chromatographic or electrophoretic separation, in flow-injection analysis, electrothermal vaporisation, laser ablation or laser desorption.

A combination of ICP-MS with the direct sampling based on laser ablation (LA-ICP-MS) facilitates circumventing the complex and lengthy sample preparation and atomisation procedures. The reviews on this subject have been mentioned above.^{87, 90, 91, 120} For the accurate trace determination by ICP-MS at very low detection limits, the sterile direct laser sampling plays an important role because omitting the sample preparation stage reduces sharply the probability of accidental contamination during sample preparation to the analysis. At the same time, undesirable fractionation of elements during the aerosol transport along the analyser ducts does sometimes occur in LA-ICP-MS.¹³⁹ The calibration reproducibility and accuracy may also become difficult to assure. In those cases where the acquisition of spectra from each laser pulse is essential, the ICP-sector mass spectrometers with detector arrays¹⁴⁰ or ICP-time-of-flight mass spectrometers¹⁴¹ are used.

The overall dimensions of the instrument can be substantially reduced by using the laser-induced plasma directly as an atomiser/ioniser in mass spectrometry.¹⁴² Usually, the time-of-flight mass spectrometers are employed in laser ablation mass spectrometry (LA-MS). In this case, the pulsed nature of the laser ablation almost perfectly matches the pulsed extraction of ions.^{143–146} Such instruments surpass the laser-induced breakdown emission analysers in sensitivity and could have been quite competitive in regard of compactness¹⁴⁷ if continuous evacuation was not necessary. Using ablation at the resonance wavelength, one can further reduce the detection limits.^{148, 149} Laser irradiation at lower power does not cause any crater-like destruction of the analysed surface, thus atomic and molecular ions can be detached from it in a desorption mode. Measurement of these ions with time-of-flight mass spectrometers enables very careful analysis of the art, jewelry and documents for forensic examination.¹⁵⁰

Thin films, coatings and other surfaces can be sputtered layer-by-layer in glow discharges with excellent depth-profiling resolution (but measurements are in emission most often). Using a mass spectrometer as the detector,^{69, 117} one can reduce the detection limits by several orders of magnitude (down to $\sim 10^{-7}\%$ for single element detection). The uncertainties of quantitative calibration are lower^{151, 152} in this case than in LA-ICP-MS. This method was successfully used for analysing the environmental samples and nuclear waste.¹¹³ In the ICP-MS spectrometers manufactured by Finnigan MAT, the ICP module was exchangeable with a direct-current glow discharge module. Recently, high-resolution mass spectrometers with ionisation in the direct-current glow discharge and the radiofrequency discharge have been introduced by VG Elemental. Despite their high cost, they have already found various applications ranging from analysis of high-purity metals to analysis of powders and dielectrics. The analysers that include both a pulsed glow discharge and a time-of-flight mass spectrometer have recently started to be produced in Russia.¹⁵³

Mass spectrometry can also be integrated with other plasma sources, such as microwave plasma^{154, 155} and capacitively coupled RF plasma in a graphite furnace.¹⁵⁶ However, these sources are used much more often in emission spectrometry. Their advantage is the possibility of small sample volume intro-

duction, including a continuous (flow-injection) mode. Microwave plasma enables the analysis at the temperature near ambient, whereas the discharge in a graphite furnace makes it possible to maintain high atomisation temperature with the independently regulated efficiency of ionisation in plasma. A mass-spectrometric detector facilitates the reduction of the detection limits relative to the corresponding emission detection; however, some setbacks in the design still remain unsolved. Application of such instruments is justified in those infrequent cases where the analytical problem cannot be solved using common ICP-MS analysers (*e.g.*, due to the specific spectral interferences).

The capability of determining different isotopes and their ratios is also among the advantages of mass spectrometry. To date, the thermal ionisation mass spectrometry continues to be the most precise technique for measuring isotope ratios (for a comparison with other techniques, see Refs 157 and 158). However, this technique requires complicated sample preparation and is almost inapplicable to both refractory substances and elements with high ionisation potentials. The precise data on the isotopic composition are necessary for studying the synthesis, evolution or the absolute age of samples (geological, organic, biological, *etc.*). Conventional methods of determination of stable isotopes in gaseous samples (and any other samples that can be converted into the gaseous phase) using magnetic sector mass spectrometers were surveyed¹⁵⁹ with a focus in climatology.

A unique possibility of minimising the isobaric interferences in mass spectrometry is offered by selective ionisation in the resonant laser radiation (resonance ionisation mass spectrometry, RIMS). A laser (or several lasers) is used for the optical excitation and selective stepwise transfer of the analyte atoms into the ionised or auto-ionised states. Sometimes the atomiser is placed in the electric field to reduce the effective ionisation potential of the atom. Examples of the atomisers include a graphite furnace,¹⁶⁰ or low-power laser ablation^{149, 161} or laser desorption¹⁶² at low power to minimise the non-selective ionisation. Use of tuneable solid-state lasers and particularly diode lasers holds a promise for this technique.¹⁶³ The main application field is the determination of stable and long-lived isotopes as well as radioactive contamination. The detection limits can be below a femtogram at a $\sim 10^{-11}\%$ relative content of the rare compared to the abundant isotopes. This method has already been used for determination of more than 40 elements; in some cases multielemental isotope analysis was performed.¹⁶⁴ Laser ionisation schemes for many elements were described.¹⁶⁵ Recent information on RIMS has been reported.^{166, 167}

High-energy accelerator mass spectrometry, which utilises tandem linear particle accelerators, is aimed at the determination of cosmogenic and other very rare isotopes (^3H , ^{10}Be , ^{14}C , ^{26}Al , ^{32}Si , ^{36}Cl , ^{39}Ar , ^{41}Ca , ^{55}Fe , ^{59}Ni , ^{81}Kr , ^{99}Tc , ^{129}I , ^{182}Hf , ^{244}Pu).^{168, 169} This method can be used for the determination of very low amounts of particular isotopes (at isotope ratios down to $\sim 10^{-14}\%$). Such a high sensitivity is determined by both several selection stages discriminating the ion mass and charge and selection in the kinetic energy loss per track unit in the gaseous or semiconductor detector. The specific energy loss depends on the nucleus charge (not the ion charge) that facilitates effective elimination of the isobaric interferences, however such detectors can determine only particles with high velocities. Sputtering of samples is usually performed using a beam of Cs^+ ions in vacuum. This method is applied in archaeology, dendro- and geochronology, climatology, medicine and forensic examination.^{168–172} The equipment usually occupies an area of several tens square metres; however new instruments with dimensions of only $2.25 \times 1.25 \text{ m}^2$ are already under development.

The theory, instrumentation, and applications of ion mobility spectrometry are being actively developed (see a review¹⁷³). This technique differs from the classical mass spectrometry in a way that the ions are separated by their charge-to-mass ratio while drifting in the gas medium driven by the electric field, rather than in vacuum. The main advantage is that there is no need for

evacuation and, correspondingly, the cost is lower and miniaturisation of such high-sensitivity instruments is possible. The ion mobility analysers have been applied so far only for the gas analysis (detection of contaminations and toxic compounds in air or trace impurities in technological gases).^{174–177} They will possibly find broader applications with the progress in this field because of the obvious advantages of combining such detectors with non-vacuum ionisation sources (*e.g.*, laser ablation and desorption, discharges at atmospheric and slightly reduced pressures, including microplasma discharges). An increasing body of information on applications of RF multipole reaction cells (based on drift and ion reactions in the gas medium) in mass spectrometry will also favour development in ion mobility spectrometry.

For quantitative calibration, especially in ultra-trace mass spectrometric analysis where the standards cannot be prepared, the method of isotope dilution is often used, *e.g.*, in ICP-MS.^{178, 179} An increase in accuracy of the semiquantitative analysis in ICP-MS can be achieved by simulation of the plasma-chemical processes.¹⁸⁰ Worth to note are the studies devoted to the calculation of the relative sensitivity¹⁸¹ and the standardless analysis¹⁸² in ICP-MS and LA-MS.¹⁸³ The possibility of simultaneous acquisition of spectra from atoms, molecules and fragments represents another advantage of mass-spectrometry. Moreover, this technique can be hyphenated to chromatography or other methods of preliminary separation of chemical compounds (see a review¹⁸⁴).

V. Atomic fluorescence spectrometry

At present, the atomic fluorescence spectrometry (AFS) plays a relatively minor role in elemental analysis. An attractive feature of the fluorescence techniques is the fundamental possibility of combining the advantages of absorption and emission spectrometry. Theoretically, the analytical signal is proportional to the concentration of atoms in the (most populated) ground state as in the case of absorption; but it is being measured on a 'zero' or weak background as in emission spectrometry. The selectivity of atomic fluorescence is very high because both mechanisms of absorbing and emitting of photons are discrete quantum processes. Excitation of the selected atoms only on their characteristic spectral lines and shielding the detector from direct rays of the light source enable measurement of fluorescence without recourse to any optical dispersion devices. Moreover, one can modulate the excitation source for better subtraction of the stray light background.

These advantages determine the application area of AFS. The development occurs in two major directions. Where high selectivity and high sensitivity are required that cannot be reached by other methods, one can use the laser-excited fluorescence (pulsed most often) with detection by means of optical and electronic schemes that are optimised for subtracting the non-selective background, reducing the spectral interferences and minimising the noises. In the other cases where moderate sensitivity is sufficient, while a simple and rapid analysis procedure and inexpensive equipment are desirable, then simple optical filters (in place of dispersion spectrometers) and traditional light sources, *e.g.*, hollow cathode lamps or RF electrodeless lamps, are used. Naturally, weak sources and thus unsaturated fluorescence bring about a number of drawbacks including the non-selective absorption of radiation in the atomiser.

In line with the development in chemistry of stable and unstable volatile compounds, there is an increasing interest in the simplest version of AFS that involves continuous sample introduction in the form of vapour (*e.g.*, mercury^{185–187}) or volatile hydrides^{188–193} with their low-temperature atomisation. High selectivity of this technique facilitates analysis of samples of a very complex chemical composition with high sensitivity. Modern commercial atomic fluorescence analysers¹⁹⁴ employ hollow-cathode lamps, graphite atomisers, and continuous flow-injection introduction of samples in the form of volatile hydride

compounds. The detection limits are often below $10^{-7}\%$. Note that it is the detection by fluorescence or absorption techniques rather than by emission that is more suitable for these compounds, because introduction of large amounts of volatile compounds into a plasma almost always causes instabilities in the discharge.

Commercial ICP-AFS instruments made earlier in USA were equipped with hollow cathode lamps and conventional nebulisers for sample introduction. These instruments were used for the determination of certain metals with weak emission spectra but easily excitable fluorescence spectra. The plasma was ignited in a relatively 'cool' regime in order to merely atomise the sample without generating too high emission background. Further development of this method is associated¹⁹⁵ with the use of new light sources of high spectral brightness, namely, diode lasers or narrow-band light-emitting diodes. These sources can also improve the characteristics of the simplest fluorescence analysers that involve introduction of samples in the form of vapour or volatile compounds.

One of the main advantages of the laser-excited fluorescence is that it makes possible the saturation (bleaching) of optical transitions. Thus, it is possible to obtain maximum analytical signals and simultaneously reduce both the effects of fluorescence quenching and its dependence on fluctuations of the excitation radiation. Unfortunately, during the past 25 years, laser-excited atomic fluorescence was developing very slowly (see a review¹⁹⁶) owing to the slow progress in the development of tuneable laser technologies. The real-time switching of dye lasers from one element to another is virtually impossible. It is the single-element nature of this technique that presents the main obstacle for its analytical application, although more than 40 elements were determined one by one using AFS with dye lasers.

The dynamic range of laser-excited atomic fluorescence spectrometry (LEAFS) can reach 7 orders of magnitude (much broader than in AAS). Moreover, LEAFS is characterised by better linearity compared to AAS. The lowest detection limits in LEAFS are of the order of $\sim 10^{-11}\%$ (~ 0.1 fg) in the analysis of ideal aqueous solutions using an electrothermal atomiser.¹⁹⁶ The best results for low-volatility elements (Eu, Y, Tl) were obtained using atomisation in a glow discharge. Use of flame, ICP, laser spark and other plasma atomisers has been studied. In the analysis of gases, the plasma was used for the pre-population of the metastable states, from which further excitation of laser-induced fluorescence was performed.⁴⁷

About ten years ago, new solid-state laser sources appeared;^{197–200} they are the optical parametric oscillators (OPO) with tuneable output radiation, which can be scanned over the whole spectrum from 220 to 2000 nm in ~ 20 min (previously, such sources were called parametric light generators). Using the modern software, it is possible to scan discretely the OPO output radiation, *viz.*, by jumping from one characteristic line to another, thus facilitating reduction in the scanning time (similarly to the newest analytical mass spectrometers). Obviously, OPO open up the prospects for the development of multi-element LEAFS. However, so far only few studies devoted to simultaneous detection of several elements using the OPO-excited fluorescence technique have been accomplished.^{201, 202}

In our viewpoint, the commercial LEAFS instruments based on OPO can be developed in the future, despite their high cost at present. An ICP-AFS spectrometer based on OPO would be comparable in cost with a high-resolution ICP-mass spectrometer. However, despite the virtually equally high sensitivity of mass spectrometry and laser-excited AFS, the selectivity of the latter technique is higher relative to high-resolution mass spectrometry and much higher relative to either quadrupole or time-of-flight mass spectrometry. Furthermore, theoretically, the sensitivity of AFS should be higher than that of mass spectrometry, because each atom can produce only one ion but can emit up to $\sim 10^8$ photons per second. The throughput of mass spectrometers is usually $\sim 10^{-6}$ of the ion flux, whereas the typical efficiency of collection and registration of photons is of the order of $\sim 10^{-4}$.

Perhaps, the commercialisation of LEAFS analysers will be aided by the development of multifunctional laser spectrometers with modular architecture aimed at enabling application of several analytical techniques within a single instrument.

New potentials in LEAFS are opening up with the development of magneto-optical traps (laser traps) for neutral atoms.²⁰³ Single atoms including their particular isotopes can be captured in a laser trap, and the resonance fluorescence of each individual atom can be reliably detected. Using this method, rare isotopes ^{81}Kr and ^{85}Kr with the natural abundance of the order of $10^{-11}\%$ and $10^{-9}\%$, respectively, were determined.²⁰⁴ The detection limit of the ^{41}Ca isotope in biological samples atomised in a furnace was below $10^{-7}\%$ with respect to the abundant ^{40}Ca isotope.²⁰⁵ So far, such low amounts of rare isotopes could only be detected using high-energy accelerator mass spectrometry. Certainly, the LEAFS instrumentation based on magneto-optical traps is less expensive and less massive. Laser traps have already been successfully used for confinement of alkali and alkali-earth atoms, as well as noble gas atoms (pre-excited in plasma into the metastable states for laser manipulation).

It is hoped that further development of atomic absorption techniques based on diode lasers will also be beneficial for their application in AFS. The high spectral brightness of the diode lasers (due to the very spectrally narrow output emission) at their typical optical power of ~ 1 mW with a beam focused into a zone of a diameter of ~ 1 mm allows one to achieve complete saturation of fluorescence on strong transitions, if the quenching is not considerable. Multielement analysis can be achieved (as in AAS) by using diode laser arrays incorporated into multiplexing schemes. However, so far AFS with excitation by diode lasers has been used only in a single-element fashion.^{206–212}

Similar to the absorption spectrometry, the saturated (laser-excited) AFS provides a theoretical possibility of the absolute analysis. This possibility arises from both the simple theoretical dependence of the saturated fluorescence intensity on the analyte atom concentration and the reliable knowledge of the photon detection efficiency achievable in practice. In the case of AFS, the conditions originally formulated by L'vov^{65, 66} as necessary for the absolute absorption analysis, are supplemented here by an additional requirement for the sufficient power of the output radiation of the excitation laser. The measurement of the non-selective background is made by detuning the laser from the absorption line. If the power of the excitation source is far from saturating, the fluorescence intensity usually depends on many unaccountable factors, which necessitates the use of standards to implement the calibration for the quantitative analysis.

Note that at this stage the practical applications of LEAFS are largely limited by the tasks that require the highly sensitive and selective analysis. The preparation, storage and use of standard solutions for calibrating the instruments in the range of extremely low concentrations of elements pose serious problems and require certain measures to be undertaken due to the high probability of accidental contamination at any step of calibration. Hence, the development of methods for the absolute (even if semi-quantitative) analysis has gained crucial importance. The idea of the absolute AFS analysis appears even more attractive, since this method usually demonstrates a precisely linear dependence of the analytical signal on the analyte concentration.

VI. Atomic ionisation spectrometry

The atomic ionisation analysis is based on selective stepwise ionisation (laser-induced in most cases) of atoms. It resembles in essence the RIMS technique. However, the intensity of the current formed by the electron–ion pairs upon ionisation is measured in this method rather than the ion masses. One such technique called resonance ionisation spectrometry implies usually two- or three-step laser-induced photoionisation of atoms, most often in vacuum as in RIMS. The other more popular version of the method is the laser-enhanced ionisation (LEI) spectrometry in flames at

atmospheric pressure, where the analyte atoms are selectively excited by the laser irradiation into the highly excited states, thus enhancing (by up to 8 orders of magnitude) the collisional thermal ionisation. Optogalvanic spectrometry is also based on a similar scheme, which employs the plasma discharge at reduced pressures for cathodic sputtering of the samples followed by laser-induced excitation of atoms and registration of the change in the current owing to the change in the ionisation rate, that is largely of the non-thermal origin in this case.

The main advantage of all forms of the atomic ionisation spectrometry is the high sensitivity achievable with relatively simple instrumentation, especially if the diode lasers are used. The efficiency of collection and registration of single electrons in both vacuum and weakly ionised flames (the electron density in flames is usually $< 10^9 \text{ cm}^{-3}$) can, in principle, be brought close to 100%. High-stability hollow-cathode lamps characterised by fluctuations of plasma current only at the shot-noise level, facilitate reliable measurements of the very weak optogalvanic signals ($\sim 1 \text{ nA}$). The selectivity in this method with simple recording of current is lower than in more sophisticated mass spectrometric or laser-excited fluorescence detection. The main disadvantage of the method is a strong matrix dependence (especially in the presence of easily ionised elements that not only increase the background noise but can also change the electric field between the electrodes owing to the space charge formation). The interferences due to the parasitic multiphoton ionisation of the flame-generated molecules and radicals such as NO , CO , O_2 , *etc.* are also encountered in laser-enhanced ionisation in flames.

Laser-enhanced ionisation spectrometry (LEIS) is the leading technique among other techniques of the atomic ionisation analysis, although its development is also impeded because the suitable tuneable lasers are still unavailable. LEIS provides low detection limits of $\sim 10^{-10}\%$ ($\sim 1 \text{ fg}$) at very small sample amounts (less than 1 pg) and with a fairly simple design. Further increase in sensitivity can be achieved with avalanche ionisation, *i.e.*, with the 10^3 – 10^5 -fold multiplied current of the primary electron–ion pairs.^{213, 214} Application of nanosecond lasers and nanosecond-resolution registration electronics in some cases enables separating the fast response due to the parasitic molecular ionisation from the slower collisional ionisation response in LEIS at reduced pressures.²¹⁵ The parasitic ionisation can also be minimised by shielding the flame from air with an outer concentric argon flow.^{216, 217}

For the purpose of sample introduction into the flame and more complete atomisation in LEIS, one can use either electrothermal vapourisation²¹⁸ or transformation of samples into volatile compounds,²¹⁷ or flow-injection introduction with a possibility of sorption pre-concentration.²¹⁹ The advantage of the microsample analysis in LEIS is most evident when it follows either chromatographic separation²²⁰ or laser ablation sampling into the flame.^{216, 221–223} As the laser-induced plasma creates high temperature and high densities of charged particles, one may opt to separate the sampling from the signal registration either temporally^{221, 222} or spatially.^{216, 223} In the latter case, the product of laser ablation (aerosol) is carried by the argon flow into the miniature flame where the LEIS signal is generated. This concept is similar to LA-ICP-MS and LA-ICP-AES. Use of a miniburner reduces the effect of aerosol dilution during the analysis. Such schemes open up the possibilities of detecting trace impurities in each laser ablation pulse (15 atoms per pulse²¹⁴). Moreover, it is possible to simultaneously determine several elements (Pb, In) in samples.²²³

Electrothermal atomisation in an inert atmosphere of a graphite furnace can become an alternative to the use of flames in LEIS. This method provides very low detection limits for noble metals.²²⁴ A direct comparison of the detection limits in LEIS and LEAFS under the same conditions indicates the latter to be more sensitive,^{217, 225} if the optical pumping power of the laser is sufficient for the fluorescence saturation. However, under the

conditions most favourable for LEIS (collision frequency $> 10^9 \text{ s}^{-1}$), the fluorescence quantum yield is small due to the quenching processes. In the case of unsaturated transitions, LEAFS is inferior to LEIS.²²⁰ It is fundamentally difficult to achieve complete saturation of all optical steps in LEIS, because transition probabilities to reach highly excited states are usually low.

It is interesting to compare the detection limits of LEIS and purely optical laser-induced resonance photoionisation in metal vapour at atmospheric pressure.²²⁴ Thus for silver atoms, the two-step resonance photoionisation through the auto-ionising state provides a better detection limit ($2 \times 10^{-11}\%$) compared to the two-laser LEIS ($2 \times 10^{-10}\%$). Generally, a success of any of these schemes depends on the relationship between the efficiency of collisional ionisation and the rate of optical pumping into auto-ionising states. However, an increase in the ionisation rate provided by two- and three-step schemes, is usually several orders of magnitude greater than in a single laser excitation step. A complex laser spectrometer for the laser-enhanced ionisation in both vacuum and flame was developed for the analytical research purposes.^{226, 227} Recent developments associated with the LEIS technique were discussed in a review;²²⁸ the earlier records were systematised in monographs^{36, 229} and a review.⁴⁰

Laser optogalvanic spectrometry (LOGS) may be appealing due to its simple electric gas-discharge assembly used simultaneously for both sample atomisation and photoelectron detection. The literature records on optogalvanic detection of overall 40 elements were summarised^{230, 231} (data on indium are also documented²³²). Uncomplicated design can apparently be achieved only with diode lasers,^{233–235} the advantage of which is not only their miniature size but also their capability to resolve the isotopic spectra. A narrow single-mode spectrum generated by a diode laser enhances the selectivity of analysis. To our knowledge, the methods for determination of mercury²³⁶ and uranium isotopes^{233, 234} are the only real analytical applications that have been developed so far.

A prototype of the portable analyser for uranium isotopes (most important element in the nuclear power industry) based on LOGS with a modulated diode laser and lock-in detection was described.²³³ This device enabled determination of isotopes ^{235}U , ^{236}U and ^{238}U in the enriched and depleted samples of uranium oxides and fluorides. Such a method under laboratory conditions²³⁴ enables measurements of the isotope ratio $^{235}\text{U}/^{238}\text{U}$ down to 0.02% with the detection limit in atomic number density $\sim 10^7 \text{ cm}^{-3}$ in the analytical zone. This sensitivity is comparable to that provided by AAS with the same modulation of the diode laser wavelength.²³⁴ A similar technique may be used for the determination of many other isotopes of actinides and lanthanides.

The LOGS technique propped with the RF electrodeless discharges²³¹ may eliminate introduction of the impurities by electrodes and, in principle, makes it possible to analyse non-conducting samples directly. In this case, the laser-induced changes in the plasma impedance are measured using a separate resonant induction coil. The optogalvanic spectrometry usually utilises ‘cold’ plasmas with the temperature of about 300 K. This is convenient, *e.g.*, for the analysis of gases,^{231, 235} but problematic for atomising aerosols. A comparison of the analytical merits of LOGS and LEIS for the detection of metals in smoke particles²³⁷ revealed the undeniable advantages of LEIS regarding the completeness of atomisation at the flame temperature of $\sim 2500 \text{ K}$.

At the same time, the characteristic noise in LEIS is determined by fluctuations of thermal (and turbulent) velocities of charged particles in flame. Thus, in principle, the noise can be reduced by decreasing the temperature. On the contrary, in LOGS, a number of atoms in the analytical zone can be increased by increasing the pressure. For this purpose, it was proposed²³⁵ to use a non-sustained discharge at atmospheric pressure and room temperature with the electron density $\sim 10^{12} \text{ cm}^{-3}$ below a threshold of the self-sustained gas discharge. The electric current

noise in this arrangement is reduced to ~ 0.1 pA ($\Delta I/I \approx 10^{-8}$). The detection limit for the excited hydrogen atoms H^* in neon was estimated from an optogalvanic response to the modulated irradiation by a diode laser to be $\sim 10^{-12}$ g (at the 656-nm line). For other elements, the sensitivity may be even higher if the laser excitation scheme provides a chance to climb closer to the ionisation potential.

A problem of the space charge formation is also largely curbed, because only a weak electric field (~ 100 V cm $^{-1}$) preserving the plasma parameters unperturbed, is used for the proper electron collection, whereas in LEIS the fields of ~ 1000 V cm $^{-1}$ are commonly used. Note that the conditions necessary for this concept may be realised in a late afterglow of the laser-induced plasma.

Generally, the atomic ionisation spectrometry is yet of little use in practice but continues to be developed and has its potentials. As with other laser-based techniques, a hindering factor relates to a slow progress in the development of tuneable lasers that cannot yet support in practice the multielement analysis. High susceptibility of the ionisation degree to the matrix composition presents another serious drawback of this technique. A fundamental possibility of the absolute analysis is one of the potentially important merits of the atomic ionisation technique. An absolute number of the collected electrons (charge) is equal to the absolute number of the analyte atoms, the 100% ionisation of which can be easily achieved in the analytical volume limited by the intersection area of the laser beams, while a correction for the non-selective background is obtained by tuning the laser over the full profile of the analytical absorption line. It is necessary to know either the atomised mass or the degree of sample vaporisation, as well as the dynamics of vapour transport. These parameters can be estimated using mathematical models.

VII. Sample preparation and introduction, atomisation and data processing

Here we cite only a small part of the latest reviews among the vast number of publications on the modernisation, automation and miniaturisation of the instrumentation for sample preparation,^{238–241} including those dealing with the programmed microwave reaction systems,^{240, 241} as well as with further integration of the sample preparation and introduction stages. In particular, there are many different methods of the physicochemical separation, pre-concentration and extraction (e.g., see a review²⁴² on the pre-concentration of microcomponents). Many studies were devoted to coupling of the chromatographic separation with continuous atomic spectrometric analysis of the eluates.^{184, 243–247} Recently, the method of continuous flow-injection sample introduction became very popular.^{248–251} The methods of sample introduction in the form of vapour of volatile compounds find an increasing number of application.^{252–256}

The methods of electrothermal vaporisation^{257–259} and their combinations with chemical transformations of the samples into volatile compounds for flow-injection introduction^{260, 261} are also subject to further development. The possibilities²⁶¹ of complete automation of the whole process of pre-concentration, separation, vaporisation, introduction and atomisation of samples including microwave-assisted decomposition of samples, and a possibility of the direct introduction of large amounts of undiluted organic solvents, viscous liquids as emulsions and solid insoluble samples as slurries are considered. The reviews^{262, 263} devoted to the simple tungsten and molybdenum electrothermal atomisers were also published. Great attention is being paid to further research on improvement of nebulisers for introduction of the analysed solutions into inductively coupled and microwave-induced plasmas.^{264, 265} Many studies in elemental analysis were devoted to introduction and vaporisation of the dissolved samples using high-voltage electrohydrodynamic micronebulisers^{266–269} (originally this method was named the 'Extraction of Dissolved Ions at

Atmospheric Pressure' but now it is most often called electro-spray).

Many studies ponder about the software issues on automation of analytical instrumentation and about new mathematical methods for data processing. The journal *Analytical Chemistry* publishes detailed reviews on this subject every two years (for the latest review, see Ref. 270). Most popular approaches used in the modern spectroscopy were systematised.^{271, 272} A substantial improvement in both reproducibility and correctness of the analytical results could be achieved using the multidimensional matrix and cluster methods of statistical data treatment. Such methods allow one to recognise and take into account unknown active factors (e.g., the presence of hidden impurities, drift, etc.) without carrying out frequent calibrations of the equipment or to restrict oneself to only one 'permanent' calibration. In some cases, it is possible to transfer the calibration from one spectrometer to the whole family of this kind of spectrometers.²⁷³ As mentioned above, the mathematical simulation also opens up possibilities for the absolute (standardless) analysis.

A progress in the computer-assisted methods of operation, self-diagnosis and self-control in analytical instrumentation, as well as the comprehensive processing of analytical data, is largely due to the impressive development in the neighbouring fields. In future, one can expect application of the methods of digital image recognition, machine self-learning, digital filtration of noises and processing of the hyperspectral spatial images. The computational methods using genetic algorithms and artificial neural networks will certainly find their application for spectrometric purposes.²⁷⁴ There is a wealth of prospects for further development in these directions but even today the software and continuous automatic self-diagnosis enable the analytical instruments to 'advise' the operator the ways for resolving problems or identifying the possible errors.

VIII. Conclusion

At present, AAS, ICP-AES and ICP-MS are the undeniable leaders among a multitude of the techniques in the analytical atomic spectrometry. During several past decades, the inductively coupled plasma displaced other sources of excitation and ionisation of atoms in the emission analysis and mass-spectrometry. Among these universal multielement techniques, the ICP-MS exhibits the best overall sensitivity. Electrothermal atomisers continue to play the key role in the absorption analysis. Currently, the laser-induced plasma is becoming the leading technique for the direct analysis of solids, while the further development evolves in the three main directions: direct laser-induced breakdown emission spectrometry, direct laser ablation mass spectrometry, and laser ablation with aerosol transport into ICP-MS.

In the atomic absorption spectrometry, one should expect the increasing use of both diode lasers and light-emitting diodes as the sources of radiation, as well as the use of optical cavities to expand the effective path of absorption. Application of the atomic fluorescence and ionisation will still be limited to unique special tasks, while further progress will depend primarily on the development of the tuneable solid-state lasers. Nonetheless, in those cases where the extreme sensitivity is required for detecting single atoms and their individual isotopes, the laser-excited fluorescence and resonance ionisation techniques have already begun to compete with the accelerator mass spectrometry.

In the development of analytical instrumentation, the following most general trends may be outlined:

- combine all stages of the analysis in a single device including sample preparation (the latter remains being intricate and the least reproducible procedure);
- provide high sensitivity and low detection limits, while decreasing the sample amount and increasing the throughput of the analysis;
- develop more advanced software, maximum degree of automation, on-line capabilities of the instrument diagnostics,

switching on and off, and remote acquisition of the results through the Internet;

– design miniature (using diode lasers, microplasma, *etc.*), compact or portable analysers;

– make steps towards a modular architecture of the multi-functional spectrometers combining the capabilities of several analytical techniques in a single instrument.

The importance of the issues discussed in this paper is further supported in the most recent reviews on the subject.^{275–279} There is no doubt that the analytical atomic spectrometry will continue to play an indispensable role in science, research, laboratory practice, industry and other diverse fields of human activity.

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Spatially resolved atomic absorption spectrometry

A Kh Gilmutdinov, A V Voloshin, K Yu Nagulin

Contents

I. Introduction	303
II. Spatial distribution of transmitted radiation intensity	304
III. Dynamics of spatial temperature distributions in atomisers	306
IV. Three-dimensional structures of absorbing layers	306
V. Influence of spatial inhomogeneities of absorbing layers on absorption	310
VI. Spatially resolved atomic absorption analysis	311
VII. Conclusion	314

Abstract. The review provides an overview of the main steps of development of spatially resolved atomic absorption spectrometry. The results of research on the dynamics of spatial distributions of atoms, molecules, condensed nanoparticles, temperature fields in atomisers and the transmitted radiation intensity are generalised. The influence of spatial inhomogeneities on the formation of absorption signals is considered. The advantages of spatially resolved atomic absorption spectrometry are illustrated with examples. The bibliography includes 82 references.

I. Introduction

Due to high sensitivity and selectivity, atomic absorption spectrometry (AAS) has found wide application in physics (in measurements of oscillator strengths, diffusion coefficients, gas temperatures, *etc.*), astrophysics (in studies of the chemical composition of stars) and physical chemistry (for the determination of the saturated vapour pressure, heats of vaporisation, rate constants, *etc.*). However, this method is most widely used in analytical chemistry. This technique provides the basis of atomic absorption analysis as a method of quantitative chemical analysis based on atomic absorption spectra. Nowadays, analytical atomic absorption spectrometry is one of the most commonly used methods for elemental analysis.¹ Initially, flame atomic absorption spectrometry has been developed.² However, AAS with electrothermal atomisation has received most attention in more recent years.³ The use of semiclosed graphite tube atomisers made it possible to reduce the method detection limit by a factor of $\sim 10^3$. As a result, it becomes possible to perform microanalysis and direct analysis of solid substances and suspensions. Presently, more than 60 chemical elements can be determined by AAS at ppb (or lower) levels in virtually all substances and materials.⁴

Atomic absorption spectrometry is based on interaction of transmitted radiation (generally, at the resonance wavelength λ) with a cloud of free analyte atoms produced in an atomiser. The larger the amount of absorbing atoms in the gas phase in an atomiser, the stronger the absorption of transmitted radiation. Two aspects of this interaction can be distinguished. First, the absorption depends on the overlap of the spectral profile of the analytical line of the radiation source $J(\lambda)$ with the absorption line profile of the analyte atoms $k(\lambda, T)$ (Fig. 1 *a*). The mechanism of this interaction, which can be referred to as the spectral interaction, has been studied and described in detail.^{5, 6}

The absorbance (A), which is determined as the logarithm of the ratio of the luminous flux (Φ_0) incident on the absorbing layer to the flux passed through the atomiser (Φ_t), serves as the quantitative measure of absorption. The absorbance in AAS plays the same role as the analytical line intensity in atomic emission spectrometry. If the spectral linewidth of transmitted radiation is substantially smaller than the absorption linewidth, the absorbance of a spatially homogeneous absorbing layer is directly proportional to the number of absorbing atoms (N) as follows from the Bouguer–Lambert–Beer law

$$A = \log \frac{\Phi_0}{\Phi_t} = C(\lambda, T) N, \quad (1)$$

where the coefficient $C(\lambda, T)$ depends on the atomiser temperature and accounts for the spectral features of the analytical line. Taking

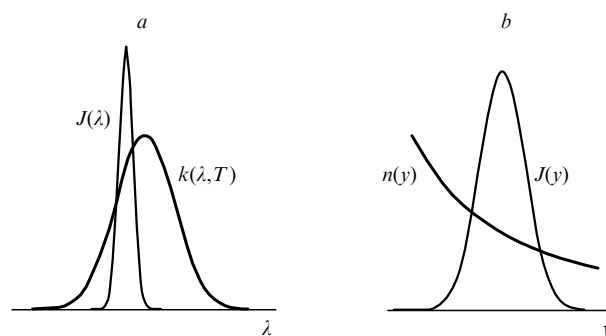


Figure 1. Scheme illustrating spectral (*a*) and spatial (*b*) interactions of the transmitted radiation beam with an absorbing layer. T is the atomiser temperature.

A Kh Gilmutdinov, A V Voloshin, K Yu Nagulin Department of Physics, Kazan State University, ul. Kremlevskaya 18, 420008 Kazan, Russian Federation. Fax (7-843) 231 52 20, tel. (7-843) 231 53 64, e-mail: Albert.Gilmutdinov@ksu.ru (A Kh Gilmutdinov), Alexandr.Voloshin@ksu.ru (A V Voloshin), Konstantin.Nagulin@ksu.ru (K Yu Nagulin)

Received 3 October 2005

Uspekhi Khimii 75 (4) 339–353 (2006); translated by T N Safonova

into account broadening and shifts of the spectral lines and the hyperfine structure of the spectral transition, linear dependence (1) is violated: each factor leads to a decrease in the slope of the plot and its curving in the high-absorption region.⁴

Another aspect of interaction is associated with spatial inhomogeneity of the absorbing layer and the transmitted radiation intensity. The transmitted beam characterised by the intensity distribution $J(x, y, z)$ is absorbed by atoms and molecules non-uniformly distributed in an atomiser $n(x, y, z)$. This aspect can be referred to as the spatial interaction (Fig. 1 *b*).

Evidently, the atomic absorption depends not only on the spectral characteristics of the analytical line but also on the characteristic features of the spatial distribution of the analyte atoms and the probe beam. In addition, it should be taken into account that absorption of transmitted radiation occurs in the volume of an atomiser characterised by spatially inhomogeneous temperature fields. However, in spite of this fact, AAS has been developed over many years with consideration only for spectral interaction,[†] because it has been implicitly assumed that the absorbing layer in the cross-section of an atomiser is spatially homogeneous. In this case, $n(y) = \text{const}$ (see Fig. 1 *b*), and the detected absorption is independent of the transmitted radiation intensity distribution. This assumption was not in doubt because atomisation temperatures are thousands of degrees centigrade and it seemed reasonable that all spatial inhomogeneities would be smoothed in the transmitted beam with a height of only 2–5 mm due to fast gas-phase diffusion. However, more recently it has been demonstrated that all key parameters of AAS, *viz.*, the temperature of the absorption zone and the distributions of atoms, molecules and condensed species, are characterised by substantial non-uniformity. In this connection, the need arose to take into account the spatial factor.

The present review briefly summarises the results and the state of the art in the field of spatially resolved AAS, which equally takes into account both the spectral and spatial aspects of interactions between the resonance radiation and absorbing atoms. Initially, the spatial distributions of the transmitted radiation intensity, absorbing atoms, molecules and condensed species and the temperature fields in the volume of an atomiser are considered. Then analysis of the influence of the non-uniformity of the distributions of these parameters on the atomic absorption is presented and the ways of eliminating this influence are described. Finally, examples of the analytical use of spatially resolved AAS are given and this method is compared with conventional AAS (where spatial inhomogeneities are ignored).

II. Spatial distribution of transmitted radiation intensity

1. Hollow cathode lamps

Hollow cathode lamps are the most common transmitted radiation source for AAS. Narrow (with a width of about 1 pm) spectral lines $J(\lambda)$ of analyte atoms are generated in the glow discharge plasma in a hollow cylindrical cathode. The cathode material includes the analyte element, the line spectrum of which is necessary to record. This chemical element is introduced into the plasma by vaporisation of the cathode by fill gas ions (generally, neon or argon) at a pressure of a few Torr. Results of studies of physical processes occurring in the glow discharge plasma and the spectral characteristics of the generated radiation are summarised in reviews.^{5–9} The spatial characteristics of the radiation beam from hollow cathode lamps at resonance and non-resonance lines of different elements and the atomic and ionic lines of a fill gas were studied in-depth.^{10–12} The character of the spatial distribution of the spectral intensity in hollow cathode lamps was demonstrated to depend primarily on the cathode radius. A typical distribution of the spectral intensity in the cross-section

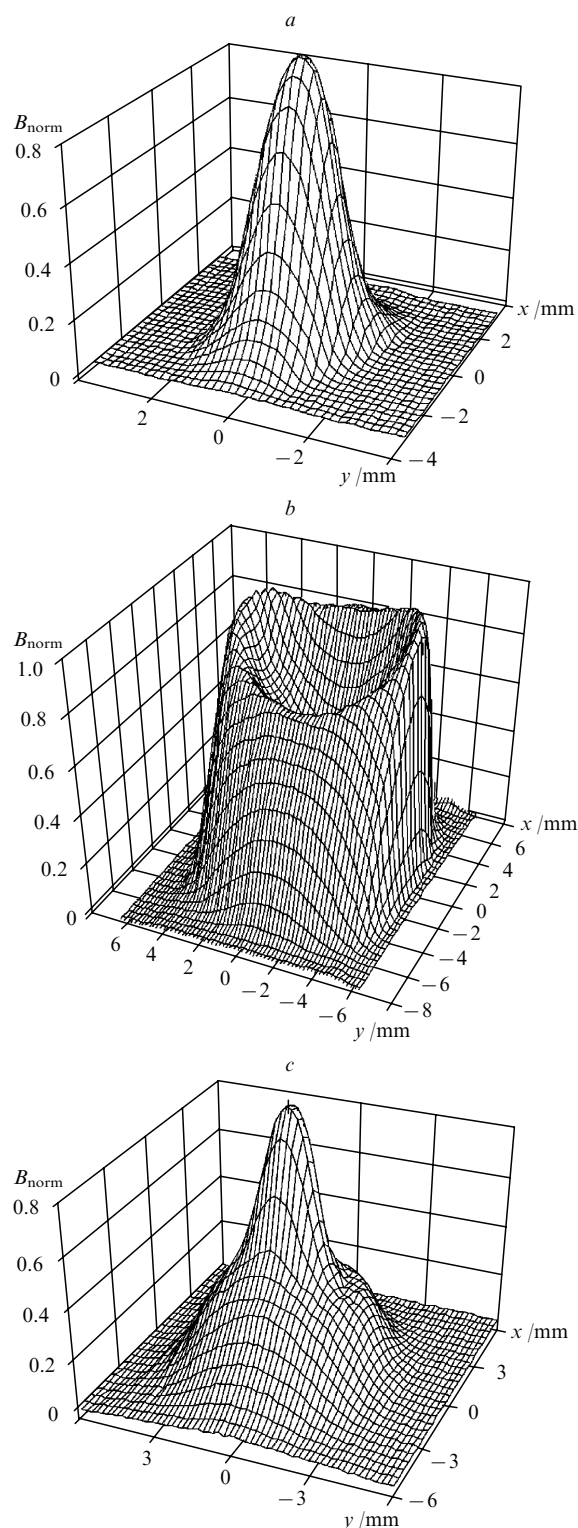


Figure 2. Spatial distributions of the normalised radiation intensity of a hollow cathode lamp (*a*), an electrodeless lamp (*b*) and a deuterium lamp (*c*) measured at the resonance wavelength of lead (283.3 nm).

of a hollow cathode lamp is illustrated in Fig. 2 *a*. The radiation was detected at the resonance wavelength of lead (283.3 nm). The distribution is dome-shaped, has an intensity maximum at the cathode axis and decreases monotonically to zero at the ends of the cathode. These distributions are characteristic of not only the metal lines but also the fill gas lines and are well described by parabolic functions. This is indicative of charge localisation in the cathode hollow and direct electron impact excitation of metal and

[†] This technique is called classical or conventional AAS.

fill-gas atoms. The distribution presented in Fig. 2a is typical of most hollow cathode lamps. However, lamps designed for analysis of non-volatile elements include hollow cathodes with larger radii. In such hollow cathode lamps, electron impact excitation/ionisation can be accompanied by other processes. In particular, this is evidenced by the fact that the spatial intensity distribution for barium ion has a dip in the near-axis region due to Penning ionisation.¹⁰

2. Electrodeless discharge lamps

Hollow cathode lamps used in AAS for most analyte elements give rather intense and narrow spectral lines. However, electrodeless discharge lamps (EDL) offer better metrological characteristics for some volatile elements, such as As, Hg, Se, Cd, Pb, *etc.* The service time of these lamps is much longer and they give more intense (5–100-fold more intense) radiation at the resonance wavelengths than the corresponding hollow cathode lamps. Line spectra in EDL are excited by inductively coupled plasma generated in a sealed valve at a frequency of tens of megahertz (and higher). Argon or krypton is used as a fill gas at a pressure of ~ 1 mm Hg. Analyte atoms are introduced into the high-frequency plasma by thermal vaporisation from the base of the valve as the latter is heated. Therefore, the valve must be preheated for 30–40 min to provide a steady-state mode.

The results of investigations of the spectral characteristics of EDL were summarised in a review.¹³ The intensity distributions of electromagnetic fields were reported.^{14–16} As in hollow cathode lamps, the widths of the spectral profiles are about 1 pm and are determined primarily by the hyperfine splitting and Doppler broadening. Spatial distributions of the radiation intensity in EDL for different elements with the use of different fill gases were examined.^{17,18} It was found that the excited argon atoms and ions are characterised by a dome-shaped distribution with the maximum radiation intensity in the near-axis region of plasma.¹⁷ This distribution is due to direct (or stepwise) electron impact excitation.

The introduction of metal atoms substantially complicates the situation. In this case, the plasma in EDL becomes strongly structured. Clouds of metal and argon atoms are spatially separated. A typical radiation intensity distribution for metal atoms in the cross-section of EDL is exemplified by the radiation intensity distribution for lead at the resonance wavelength of 283.3 nm¹⁷ presented in Fig. 2b. It can be seen that this distribution is strongly non-uniform. A pronounced minimum is observed on the axis of the plasma and the radiation beam is located primarily in the narrow region along the walls of the valve (optical skin effect). Detailed studies demonstrated¹⁷ that neither the electromagnetic skin effect nor self-absorption can account for such anomalous distributions. It was found¹⁷ that the observed distributions are determined by the radial cataphoresis effect resulting in a strongly non-uniform distribution of neutral metal atoms with a maximum near the walls of the valve. Together with the dome-shaped distribution of the electron concentration, this leads to the spatial distribution of the excited atoms presented in Fig. 2b.

3. Continuous spectrum radiation sources

In addition to line radiation sources, continuous spectrum radiation sources are also widely used in AAS. These are deuterium, hydrogen, xenon, tungsten and halogen lamps. Generally, xenon arc lamps are used as transmitted radiation sources for the detection of selective absorption,¹⁹ whereas deuterium lamps are widely used for non-selective absorption correction.

In deuterium lamps, radiation is generated in a low-pressure non-self-sustained arc discharge. This discharge provides a high-intensity continuous spectrum in the 190–360 nm spectral range, which contains the majority of analytical lines used in AAS. Since electron impact is the main excitation channel in these sources,²⁰ the radiation intensity distribution is evidently determined by the electron concentration distribution in the positive column of an

arc discharge. It was shown²⁰ that the maximum electron density occurs on the discharge axis and monotonically decreases toward its ends. Measurements of the spectral intensity distribution in the cross-section of a deuterium lamp confirmed the above suggestion. The spatial distribution of the spectral intensity of a deuterium lamp is presented in Fig. 2c.¹² The distribution is dome-shaped with a maximum on the axis of the cathode hollow and minima at the cathode ends. A plateau present at the base of the distribution is associated with the presence of a circular screen near the arc cathode.

Analysis of the data presented in Fig. 2 showed that spatial distributions of radiation generated by sources used in AAS are strongly non-uniform (in the case of EDL, they are additionally non-monotonic), and the character of non-uniformity strongly depends on the type of the source.

4. Spatial structure of transmitted radiation in an atomiser

Special optics is used to convert the radiation from the source into a transmitted beam, which is directed to an atomiser. An optical system of an atomic absorption spectrometer focuses a source image onto the centre of the atomiser and then it is directed to the entrance slit of the monochromator with the use of another optical system. Then a probe beam, which is passed through an absorbing layer in the atomiser and through a narrow vertical slit of the monochromator is recorded by a detector at the outlet of the spectrometer. The spatial structure of the transmitted beam in an atomiser was examined.²¹ A typical radiation intensity distribution in the transmitted beam produced by a lead hollow cathode lamp is shown in Fig. 3. Since a source image is formed in the

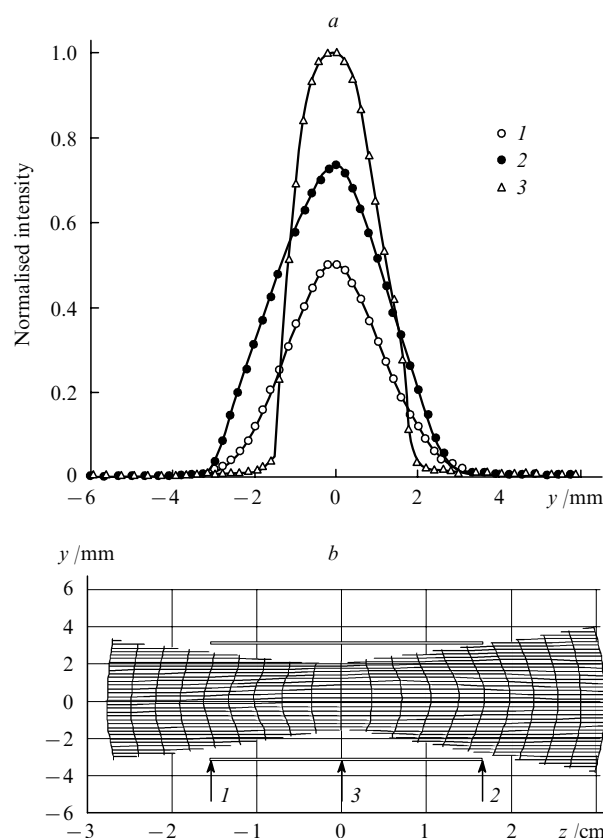


Figure 3. Radiation intensity distribution in the vertical cross-section of the transmitted beam at the inlet (1), at the output (2) and in the centre (3) of an atomiser (a) and the shape of the transmitted beam inside the atomiser (b);²¹ (b): horizontal lines indicate the walls of the tube atomiser and arrows show the cross-sections of the beam, in which curves 1–3 presented in (a) were measured.

centre of an atomiser, curve 3 coincides with the central cross-section of the distribution presented in Fig. 2*a*. These results reveal an interesting fact. As can be seen from Fig. 3*a*, the areas under the distribution curves differ from each other. The radiation intensity in the vertical cross-section at the inlet of the atomiser is much lower than that at the output. This accounts for the change in the shape of the cross-section of the beam as it passes through the atomiser. At the inlet and outlet of the atomiser, the beam is elongated in the horizontal and vertical directions, respectively.²¹ Radial radiation intensity distributions analogous to those presented in Fig. 3*a* were constructed with a step of 1 mm along the axis of beam propagation. As a result, the structure of the beam in the atomiser was quantitatively characterised. The beam thus constructed is shown in Fig. 3*b*. It can be seen that the beam becomes narrower in the centre of the atomiser and again becomes broader at the outlet.

The spatial structure of the transmitted beam produced by electrodeless lamps is different in principle.²¹ It should be noted that this beam is also characterised by a strongly non-uniform radiation intensity distribution.

III. Dynamics of spatial temperature distributions in atomisers

The overwhelming majority of substances analysed by atomic absorption methods exist in the condensed state. However, only free atoms in the gas phase can be detected by AAS. Consequently, it is necessary to convert the analyte into the gas phase before atomic absorption analysis. Atomisation is performed in atomisers with the use of different flames, plasma, laser radiation and electrothermal vaporisation (graphite atomisers). The main parameters governing the kinetics of vaporisation and atomisation, diffusion, absorption coefficients and distribution coefficients of atoms and molecules in an atomiser depend on the temperature.^{22–24} Therefore, it is necessary to know the temperature field dynamics for the interpretation of all effects in AAS. Nowadays, only plasma and electrothermal atomisers are commercially produced, the latter being characterised by substantially more complicated temperature distributions and gradients. Below, we focus on the temperature fields in graphite electrothermal atomisers. The temperature fields in spectroscopic flames used for atomisation were examined.^{25–28}

Graphite tube atomisers are used for converting an analyte from the condensed state into an atomic vapour by thermal vaporisation using fast ($> 2000 \text{ K s}^{-1}$) heating to ~ 2000 – 3000 K . Presently, two types of electrothermal atomisers (with longitudinal and transverse heating) are commercially produced. In the former type of atomisers, a graphite tube is heated by passing the electric current along the tube [Heated Graphite Atomiser (HGA)]. In another type of atomisers, the electric current is passed transversely [Transversely Heated Graphite Atomiser (THGA)].

The temperature of the walls of tube atomisers is measured by optical pyrometry.^{29–31} The temperature distributions on the surface of end-heated HGA-type atomisers are strongly non-uniform both in the longitudinal and radial directions. The dynamics of the longitudinal temperature distribution in a graphite tube during its heating to 2273 K is characterised by the plots presented in Fig. 4*a*.³⁰ It can be seen that at the initial instant of time (within the first second), the temperature distribution along the atomiser is virtually uniform because thermal exchange is a sluggish process. Then the longitudinal temperature drops progressively increase as a result of heat transfer to cold contacts and, in a steady-state mode, the temperature drops are larger than 900 K .

The changes in the gas-phase temperature in electrothermal atomisers were studied by different methods.^{31–33} Coherent anti-Stokes Raman scattering (CASR)^{32,34} proved to be the most informative for this purpose. This method allows one to record the gas temperature with a high space-time resolution. The gas-phase

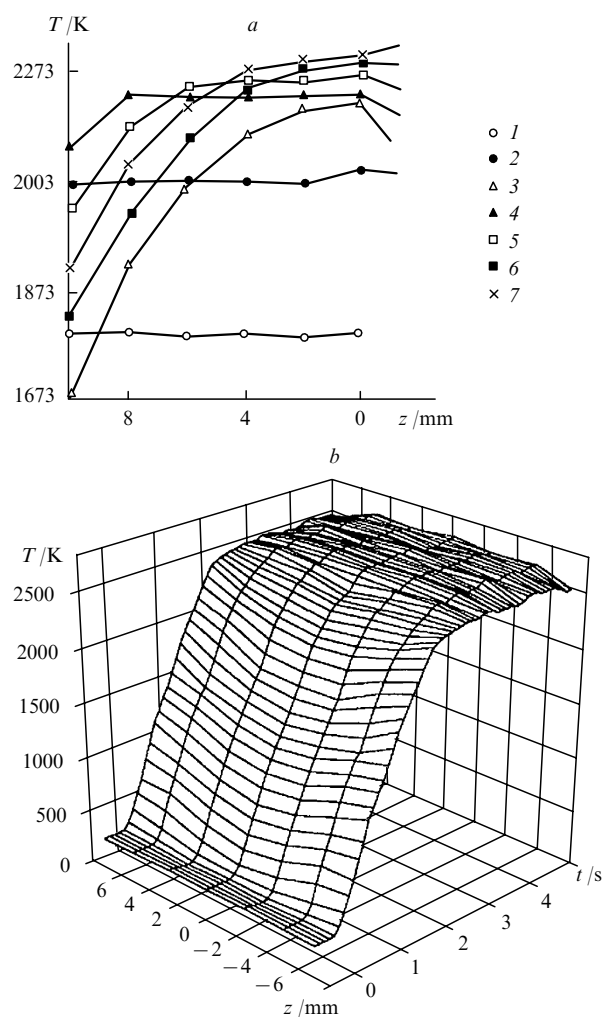


Figure 4. Plots characterising the space-time dynamics of the longitudinal temperature distributions in HGA- (*a*) and THGA-type (*b*) atomisers.

Time /s: (1) 0.8, (2) 1.0, (3) 10, (4) 1.2, (5) 1.5, (6) 3.0, (7) 2.0.

temperature depends substantially on protecting gas flows. In HGA-type atomisers, the gas-phase temperature drops in the longitudinal direction can be as large as 1500 K , and the drops in the radial direction can reach 800 K (with the use of a platform).^{32,35}

The temperature distributions in THGA-type atomisers were also studied by CASR. The changes in the gas-phase temperature along the axis of such atomisers are evident from the plots presented in Fig. 4*b*.³⁴ It can be seen that THGA-type atomisers (unlike HGA-type atomisers) are virtually isothermal throughout the tube length. As a result, the memory effects in measurements are reduced and the determination of non-volatile elements becomes much easier. However, the available THGA-type atomisers are not completely isothermal because substantial temperature gradients occur in the radial section, which is associated with the design parameters of these atomisers (see below).

IV. Three-dimensional structures of absorbing layers

1. Structure of absorbing layers in longitudinally heated atomisers

The dynamics of the formation and dissipation of absorbing layers in electrothermal atomisers was examined in numerous studies. The results of these investigations were summarised in monographs.^{4,31} However, only a few methods provide both the

time resolution and the spatial resolution in measurements. The spatial structures of absorbing layers are studied by Schlieren spectroscopy,³⁶ spatial separation³⁷ and different laser imaging techniques.^{38–43} These methods were used in a series of studies aimed at atomising various elements. Shadow spectral filming⁴⁴ has gained wide acceptance. According to this method, monochromatic radiation at the wavelength of analyte atoms or molecules is passed through an atomiser. When this radiation is transmitted through the absorbing layer, a shadow image of a cloud of atoms (molecules or condensed nanoparticles) that absorb light at this wavelength appears on the detector surface. The higher the concentration of absorbing particles, the larger the absorbance of the shadow. The advantage of shadow spectral filming is that it allows one to visualise the structures of layers consisting of different atoms (molecules or particles) that absorb in the 190–900 nm range with a space-time resolution in the cross-section of an atomiser.

a. Spatial distributions of free atoms

The dynamics of the formation and dissipation of absorbing layers of atoms of elements, which differ substantially in the physicochemical properties under different experimental conditions (atomisation from the walls and the platform in the gas-stop mode or purging with an inert gas), were studied by shadow spectral filming.^{44–62} It was demonstrated that the structure of the absorbing layer is determined by physical (vaporisation, diffusion and convection mass transfer, condensation and reevaporation) and chemical (chemisorption, gas-phase and heterogeneous reactions) processes. The distributions of noble metal atoms in the cross-section of an atomiser appeared to be virtually uniform upon atomisation from both the platform and the walls of an atomiser.^{40–42, 44–46, 63–65} A typical pattern giving an insight into the dynamics of the formation and dissipation of the absorbing layer of silver atoms is shown in Fig. 5*a*. Each photograph in the figure is a monochromatic image of the inner surface of an atomiser with a platform. The measurements were carried out at the resonance wavelength of silver (328.1 nm). Silver atoms are vaporised from the platform, absorb light and are observed as a shadow image. The virtually uniform atom distribution in the cross-section of the atomiser is indicative of high efficiency of diffusion mass transfer (due to which the spatial non-uniformity of the distribution is smoothed) and the absence of chemical reactions involving silver atoms.

A completely different atomic distribution is observed in atomisers with internal inert gas purging. The absorbing layer

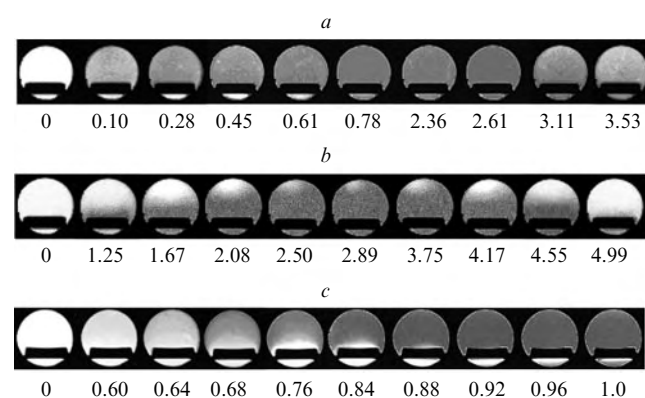


Figure 5. Images of the inner cavity of an HGA-type atomiser equipped with a platform, which were obtained by shadow spectral filming at the resonance wavelengths of silver (*a*, *b*) and gallium (*c*);^{44, 47} (*a*) 50 ng Ag, the gas stop mode; (*b*) 50 ng Ag, internal purging at a rate of 300 ml min^{−1}; (*c*) 50 ng Ga in the gas stop mode. Hereinafter, the time intervals from the onset of the atomisation cycle are given in seconds below the shots.

becomes strongly inhomogeneous with a sharp decrease in the atomic concentration from the bottom to the top of the atomiser (Fig. 5*b*). This distribution is associated with the character of the inert gas flow. The gas enters from the ends of the atomiser and leaves the latter through a small dosing hole in the centre, which results in a substantial acceleration of the gas flow.

Anomalous effects were observed when performing atomisation of Group III elements (Al, In, Ga and Tl).^{47–51} The dynamics of formation of an absorbing layer of gallium atoms is illustrated in Fig. 5*c*. These results are indicative of a pronounced anomaly; that is, the atoms are introduced into the gas phase from the upper part of the atomiser rather than from the platform onto which a sample was dosed, *i.e.*, inverse atomisation occurs. This effect is attributed to initial vaporisation of a substance in the form of gallium suboxide molecules, which do not absorb at the atomic wavelength, and their reduction on the walls of the graphite atomiser followed by introduction of gallium into the gas phase, now, as free atoms.^{44, 48}

The anisotropy of the propagation velocity of metal vapour in the longitudinal and cross-sections of the atomiser was revealed. Vapour diffusion along the atomiser tube occurs in a medium, in which the temperature sharply decreases (see Fig. 4*a*), and the diffusion rate is limited by the velocity of thermal front propagation in this direction. In addition, some shots in Fig. 5*c* show a sharp decrease in the concentration of atoms near the platform due to their condensation on the substantially colder platform. Then the condensed atoms again pass to the gas phase as the platform is heated. Therefore, the dynamics of formation and dissipation of an absorbing layer consisting of gallium atoms is complicated by the simultaneous occurrence of numerous physicochemical processes. Analogous features of the dynamics of formation of absorbing layers were revealed in studies of Tl, In, Ge and Bi atomisation.

An even more complicated dynamics was observed in studies of aluminium atomisation.^{48, 52–54} The analytical signal recorded on a conventional Perkin-Elmer Zeeman 5000 atomic absorption spectrometer (Fig. 6*a*) appears as a regular peak without anomalies. However, investigation of this process by shadow spectral filming revealed a series of effects, which were not manifested in the conventional absorption signal. Images obtained by digital shadow spectral filming (Fig. 6*b*) show that the atomic distribution in the cross-section of the atomiser is strongly non-uniform. The maximum concentration is observed near the graphite walls, and the minimum is observed near the dosing hole. This is indicative of oxygen diffusion into the atomiser through the dosing hole and a high rate of gas-phase oxidation of aluminium. The near-axis region of the atomiser also contains a large amount of aluminium, but it is involved in oxides, which do not absorb at the atomic wavelength. A region selected by the entrance slit of the monochromator is indicated by a rectangle in shot 1 (see Fig. 6*b*). The radiation from only this region is focused onto the detector and is recorded by a conventional atomic absorption spectrometer. In the plot $A(t)$ (see Fig. 6*a*), the instant of time corresponding to this shot is indicated by point 1. The absorbance detected by a spectrometer at this instant of time is virtually equal to zero. However, the atomiser contains a substantial amount of aluminium atoms, which are located along the walls (see Fig. 6*b*, shot 2) and are beyond the detection limit of conventional spectrometers.

The above results also suggest that free atoms are redistributed inside the atomiser. In the early steps of atomisation, the concentration of aluminium atoms is higher above the platform. In the final step, the concentration maximum is shifted to the region under the platform (see Fig. 6*b*, shots 3 and 4). This additionally confirms a substantial role of oxygen in the distribution of aluminium. Evidently, the conditions under the platform are more reductive than those in the upper part of the atomiser. In addition to the above-mentioned anomalies of the atomic spatial distribution, atomisation of aluminium (as well as of ytterbium

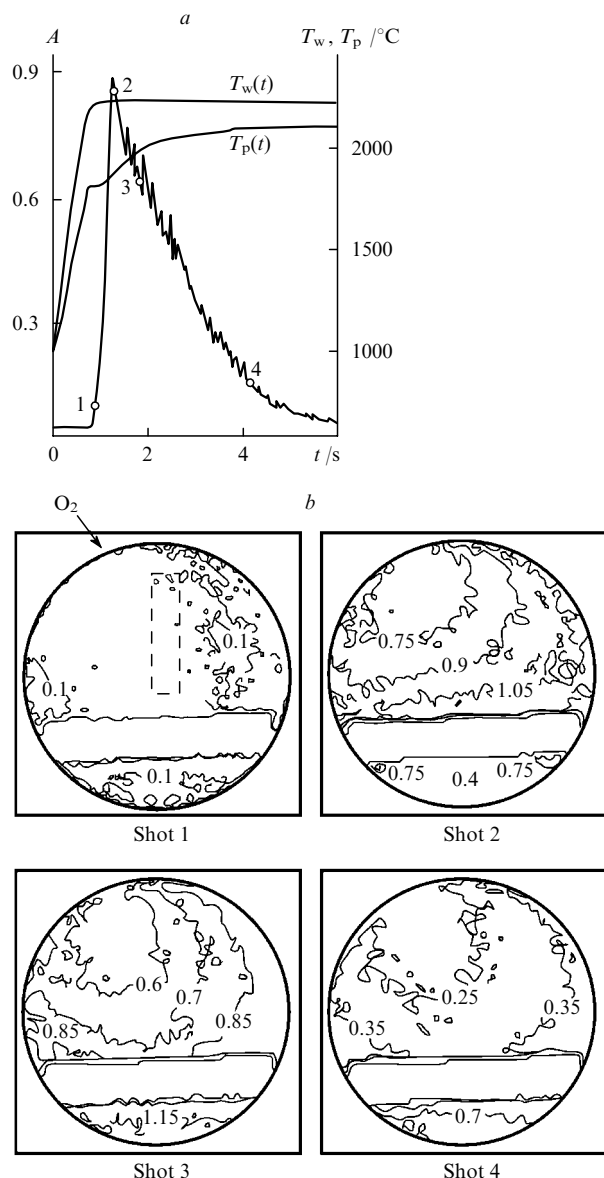


Figure 6. Results of the detection of platform atomisation of 15 ng of aluminium by atomic absorption (a) and spatially resolved digital shadow spectral filming (b);⁵³

(a): points 1–4 in the plot $A(t)$ correspond to shots 1–4 in (b); $T_w(t)$ and $T_p(t)$ are the changes in the temperature of the walls and platform of the atomiser, respectively;

(b): contours of the absorbance are given, the arrow in shot 1 indicates the position of the dosing hole.

and some other elements) is accompanied by explosive atomisation.^{53, 54, 66, 67}

The results obtained in the study⁵⁵ of boron atomisation also provide evidence that oxygen diffusion through the dosing hole has a strong effect on the atomic distribution of this element.

b. Spatial distributions of non-selectively absorbing particles

In electrothermal AAS, molecules play a very important role in the formation of free atoms.^{68, 69} In addition, molecules are responsible for non-selective absorption.^{70, 71} Studies of the dynamics of formation of molecular layers by shadow spectral filming also revealed a number of anomalies.^{46, 48–51, 54, 56, 57} The structure evolution of an absorbing layer composed of gallium molecules in graphite tube atomisers is illustrated in Fig. 7a. The images were obtained at the wavelength of 254 nm, where one of the molecular absorption maxima of gallium is located.

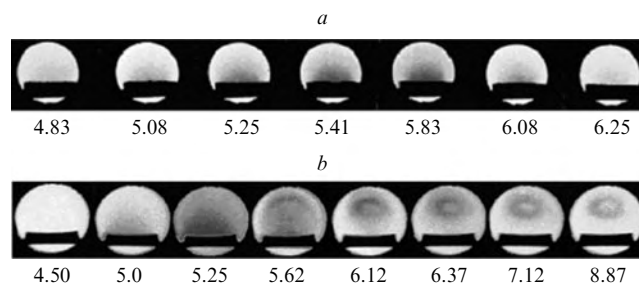
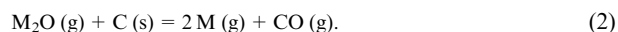


Figure 7. Images of the inner cavity of a graphite tube atomiser obtained by shadow spectral filming at a wavelength of 254 nm for vaporisation of 1 µg of Ga (a) and Al (b) salts.⁴⁸

Contrary to the commonly accepted opinion that molecules are located at the colder ends of atomisers, their true distribution is quite opposite. Vaporisation leads to a strongly non-uniform distribution of molecules inside an atomiser. The concentration maximum is located near the platform, and the concentration minimum is near the graphite walls. No molecules are observed under the platform, whereas molecules are observable in the central regions of the atomiser. Taking into account this distribution, it was concluded that these are metal suboxide molecules. A comparison of the atomic (see Fig. 5c) and molecular (see Fig. 7a) distributions of gallium revealed the following fact. Molecules disappear in the regions where atoms appear. The same situation was observed in studies of the structures of absorbing layers composed of indium- and aluminium-containing molecules. This led to the conclusion that reduction of gaseous metal oxide on the graphite surface is a heterogeneous process, which can be described in the general form by the equation



This is one of the most important processes in electrothermal AAS.

Studies of absorbing layers of aluminium suboxide molecules showed yet another anomaly.^{48, 54, 56} The dynamics of formation of such layers is typical of two-step processes. Initial vaporisation of molecules from the platform (the characteristic features of this process are virtually identical to those described above for gallium vaporisation) is followed by the formation of an absorbing cloud having a complicated toroidal structure inside the atomiser (Fig. 7b). A detailed analysis demonstrated that the cloud consists of aluminium oxide nanoparticles condensed in the gas phase. Vaporisation of microgram amounts of various elements affords analogous structures consisting of nanoparticles. Therefore, not only atoms and molecules but also nanoparticles are present inside electrothermal atomisers at extremely high temperatures, and all these species are characterised by a strongly non-uniform spatial distribution.

2. Structures of absorbing layers in transversely heated atomisers

In the previous section, we noted that temperature fields in transversely heated atomisers differ radically from those in longitudinally heated atomisers.⁵⁸ Transversely heated graphite atomisers are almost longitudinally isothermal but are characterised by considerable temperature inhomogeneities in the cross-section.⁵⁹ This is responsible for the formation of new three-dimensional atomic, molecular and nanoparticulate structures in THGA.

a. Atomic distribution

The dynamics of formation and dissipation of an adsorbing layer of silver atoms in THGA⁵⁹ is evident from an analysis of the results of shadow spectral filming presented in Fig. 8a. It can be seen that atoms appear directly above the bottom of the atomiser

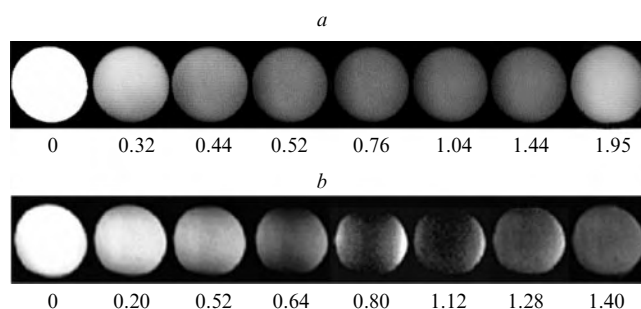


Figure 8. Images of the inner cavity of THGA obtained by shadow spectral filming for atomisation from the walls of 25 ng of Ag (a) and 200 ng of In (b).⁵⁹

onto which a sample was dosed, and their spatial distribution in the initial step of atomisation is normal, *i.e.*, the atom concentration monotonically decreases from the bottom to the top. However, the absorbance maximum is gradually shifted to the side walls of the atomiser. This redistribution can be accounted for only by vapour adsorption (condensation) on colder regions followed by revaporisation during further heating of the atomiser. In the study,⁴⁷ a cascade mechanism of the substance transfer in the longitudinal direction of HGA-type atomisers was proposed. The same mechanism (but in the radial section) is observed in THGA-type atomiser. An analogous substance transfer in transversely heated atomisers was documented.^{41, 42} Interestingly, the vapour concentration is somewhat higher near the left side surface. This is due to the fact that the temperature in the left part of the tube in the atomiser used in experiments was somewhat lower than that in the right part because the cooling liquid is introduced from the left to the right contact.

The dynamics of formation and dissipation of an indium absorbing layer is presented in Fig. 8 b. A sample was dosed from the bottom of the tube.⁵⁹ It can be seen that the spatial atomic distribution is opposite to that observed in the case of silver atomisation. Indium atoms appear simultaneously in the upper and lower parts of the atomiser (shots obtained within 0.20 and 0.52 s after the onset of atomisation), and a pronounced absorbance minimum is observed on the side surfaces during the whole cycle. Analogous distributions are also typical of Ga, Tl and Bi atoms. It is known that, when vaporisation of aqueous samples of In, Tl, Bi and Ga is performed in graphite furnaces, oxides of these elements are the first to go into the vapour phase, and these oxides do not absorb at the resonance wavelengths of the corresponding atoms.⁴⁸ The effect presented in Fig. 8 b is indicative of decomposition of indium suboxide molecules. Evidently, the gas-phase temperature along the vertical diameter is higher than the decomposition temperature of oxides. This accounts for the minimum concentration of atoms near the side walls of the tube characterised by the lowest atomiser temperature.

Small inhomogeneities of the absorbing layer are observed during silver atomisation in THGA-type atomisers (Fig. 9 a). The atoms appear directly above the platform onto which a sample was dosed and gradually fill the whole volume of the atomiser (shots obtained within 1.32 and 1.40 s after the onset of the atomisation cycle). In this case, as in above-considered experiments (see Fig. 8 a), the vapour redistribution to the left side of the atomiser is observed (shots obtained within 2.32 and 2.84 s after the onset of the atomisation cycle). In the presence of a platform, this effect is less pronounced because atoms appear in the gas phase at a higher atomiser temperature. Analogous spatial structures of absorbing layers were observed also in manganese and copper atomisation. The observed atomic redistributions in the cross-section of atomisers also substantially influence the temperature gradients in atomisers.

The effect of inverse atomisation, which has been observed for the first time in HGA-type atomisers,^{44, 48} is clearly pronounced in

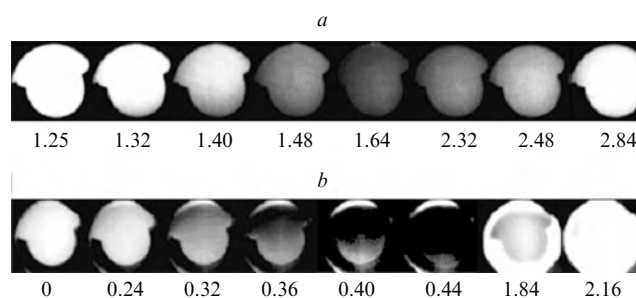


Figure 9. Images of the inner cavity of THGA with a platform obtained by shadow spectral filming for atomisation of 5 ng of Ag (a) and 675 ng of Ga (b).⁵⁹

the case of gallium atomisation in THGA-type atomisers equipped with a platform. The dynamics of the formation and dissipation of absorbing layers of gallium atoms is presented in Fig. 9 b.⁶⁰ An excess of gallium was used to improve visualisation of the process. As in the earlier study,⁴⁴ the characteristic features of the atomic distribution are attributed to the fact that gallium is initially vaporised as suboxides, which do not absorb at the atomic wavelength of 417.2 nm and, consequently, remain invisible in these measurements. Then suboxide molecules are reduced on the opposite surface of the atomiser (shots obtained within 0.24–0.40 s after the onset of the atomisation cycle) according to reaction (2).

An analogous dynamics of atomic spatial distributions was observed also for In, Tl and Bi atomisation. Therefore, inverse atomisation of Group III elements occurs also in THGA-types atomisers.

b. Molecules and condensed particles

The above-considered structures of absorbing layers were determined at wavelengths that did not overlap with the wavelengths of molecular absorption bands. Vaporisation of a salt containing 10 µg of indium was studied by shadow spectral filming and the results of this study are presented in Fig. 10 a. Shadow shots were measured at a wavelength of 294.4 nm⁶⁰ corresponding to the absorption maximum of indium suboxide.⁴⁸ It can be seen that a vapour cloud was initially formed at the bottom of the atomiser directly above the sample and had a normal three-dimensional structure (the vapour density monotonically decreases from the bottom to the top of the atomiser; see the shots obtained within 0.46 and 0.50 s after the onset of the atomisation cycle). However, the cloud is then transformed into a diffuse horizontal band between the side walls of the atomiser (shots obtained within 0.54–0.70 s after the onset of the atomisation cycle). In the final step of vaporisation, the band is broken and the vapour is accumulated near the side surfaces of the tube. The distributions

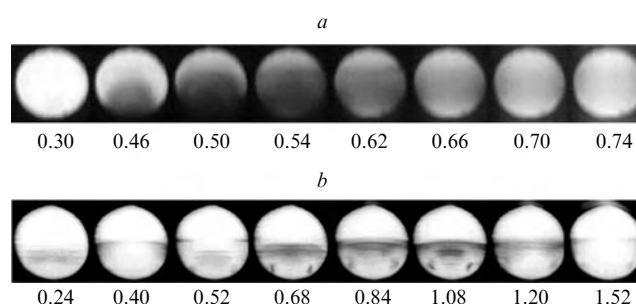


Figure 10. Images of the inner cavity of THGA obtained by shadow spectral filming for vaporisation from the wall of salts containing 10 µg of In (a) and 50 µg of CaCl_2 (b).^{60, 61}

of indium-containing molecules differ from those of indium atoms (see Fig. 8 *b*; the atoms were distributed along the vertical diameter of the atomiser, the density being higher at the ends). The observed three-dimensional structures of the absorbing layers are due to the characteristic features of the temperature gradients in the radial section of the atomiser.^{59, 60} The lower-temperature region inside THGA-type atomisers is located along their horizontal diameter. Evidently, the lowest degree of dissociation of molecules occurs in this region. A higher-temperature region of the gas phase inside atomisers is located along the vertical diameter far from the cooled side contacts. It is this region where indium atoms are predominantly located.

Vaporisation of an excess of a substance in an atomiser gives rise to a cloud of condensed nanoparticles. Their distribution in the cloud is strongly non-uniform and complicated. The results of study of vaporisation of CaCl_2 (50 μg) in a THGA-type atomiser by shadow spectral filming are given as an example in Fig. 10 *b*. Visualisation was performed at a wavelength of 352 nm, which differs from the wavelengths of both molecular and atomic absorption bands. Therefore, it is evident that the above-considered structures of the absorbing layers are formed by particles condensed in the gas phase. Further studies demonstrated⁶⁰ that the absorbing cloud consists of nanoparticles the sizes of which are smaller than the wavelength of the light beam used. Interestingly, the absorbing cloud has a well-defined shape and is located along the horizontal diameter of the atomiser. This is consistent with the character of the temperature field distribution inside the atomiser. Evidently, vapour condensation should occur in lowest-temperature regions. However, shots obtained within 0.52–1.08 s after the onset of the atomisation cycle show an anomaly, *e.g.*, two small symmetrically arranged absorption regions appear in the lower part of the atomiser. This anomaly was reproduced in all experiments and its nature remains unclear. These regions can be due to the complex gas dynamics in atomisers as a result of the simultaneous occurrence of convective heat transfer from the ends of the tube and gas expansion caused by fast heating. The internal gas flow is also complicated by fast vaporisation of a considerable amount of the substance, which can cause a substantial change in the pressure distribution inside the atomiser. Under these conditions, the appearance of local vortex flows is probable, and the vapour can be partially trapped (and retained) by these flows. It should be noted that the cloud of condensed particles oscillates about the horizontal diameter of the atomiser (see Fig. 10 *b*), which is manifested as insignificant oscillations of absorption signals as the pulse is gradually changed.⁶²

V. Influence of spatial inhomogeneities of absorbing layers on absorption

The above-considered data show that the distributions of all key parameters in AAS are characterised by spatial non-uniformity. This brings up the question of how these parameters influence the atomic absorption.

The spectrophotometric absorbance A serves as the analytical signal in AAS. In the ideal case of an infinitesimally narrow spectral line of the source and on the assumption that the absorbing layer is spatially homogeneous, the absorbance is proportional to the number of absorbing atoms [see Eqn (1)]. However, real measurements are performed with the use of sources the spectral lines of which are of finite width, for inhomogeneous absorbing layers. This substantially complicates the basic dependence of AAS, which has the following general form⁷²

$$A = \log \left\{ \left[\int_0^H \int_{-b/2}^{b/2} \int_{-\lambda^*}^{\lambda^*} J(x, y, -L/2) J(\lambda) dx dy d\lambda \right] \times \right. \quad (3)$$

$$\times \left[\int_0^H \int_{-b/2}^{b/2} \int_{-\lambda^*}^{\lambda^*} J(x, y, -L/2) J(\lambda) \times \right.$$

$$\left. \times \exp \left(- \int_{-L/2}^{L/2} K(x, y, z; \lambda) dz \right) dx dy d\lambda \right]^{-1} \left. \right\}.$$

In this equation, H and b are respectively the height and width of the transmitted radiation beam selected by the entrance slit of the monochromator, $\{-\lambda^*, \lambda^*\}$ is the spectral region selected by the monochromator (Fig. 11), $J(x, y, -L/2)$ is the intensity distribution of the transmitted beam at the entrance of the atomiser, L is the atomiser length, $J(\lambda)$ is a function describing the spectral profile of the incident beam, and $K(x, y, z, \lambda)$ is the absorption coefficient

$$K(x, y, z, \lambda) = C(\lambda, T) n(x, y, z),$$

where $C(\lambda, T)$ is the coefficient dependent on the temperature and spectral characteristics of the analytical line (the direct expression for this coefficient was reported in the study²⁴) and $n(x, y, z)$ is the local concentration of absorbing particles.

From Eqn (3) it follows that the absorbance in conventional AAS depends on three factors: (1) spectral characteristics of the analytical line (the dependence of J , T and K on λ); (2) spatial distributions of absorbing particles and the atomiser temperature (the dependence of K on x , y and z); (3) spatial intensity distribution of the transmitted radiation beam. In the limiting case of the uniform distributions of absorbing particles, temperature and transmitted radiation intensity and on the assumption that the analytical line is single and infinitesimally narrow, the absorbance is directly proportional to the number of absorbing particles inside the atomiser at each instant of time. Equation (3) is substantially simplified and reduces to Eqn (1). The most comprehensive analysis of the influence of the spectral factors on the atomic absorption was performed in the study.²⁴ In the general case, the spectral profiles of emission lines $J(\lambda)$ and absorption lines $K(\lambda)$ are determined by Doppler and impact broadening, the absorp-

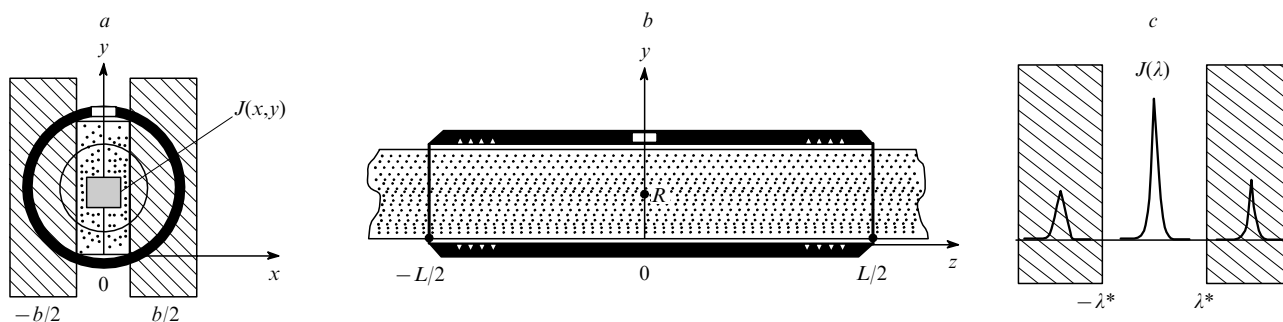


Figure 11. Cross- (*a*) and longitudinal sections (*b*) of a tube electrothermal atomiser and the transmitted beam as well as the spectral line $J(\lambda)$ selected within the transmitted band $\{-\lambda^*, \lambda^*\}$ of the monochromator (*c*).²⁴

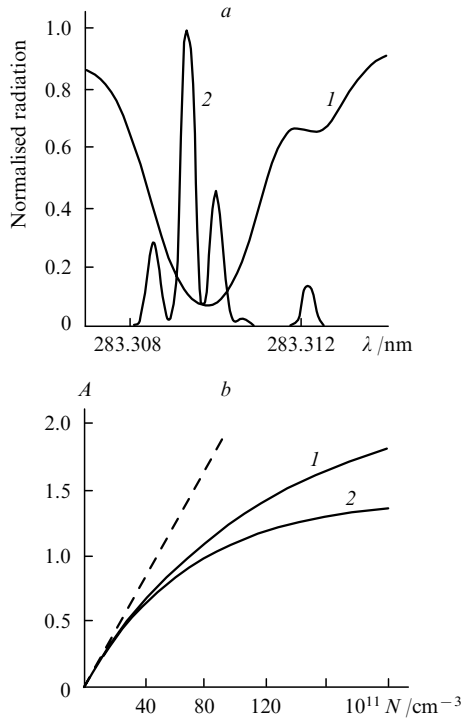


Figure 12. Spectral profiles of absorption (1) and emission (2) for the resonance line of Pb at 283.3 nm (a) and the dependence of the absorbance on the number of absorbing atoms for this line, which takes into account all spectral characteristics of the line (1) and inhomogeneity of the absorbing layer (2) (b).²⁴

tion line shift and the hyperfine structure of the spectral transition. Figure 12 a gives the emission and absorption line contours for the resonance line of lead at 283.3 nm, which were calculated for the typical conditions of AAS taking into account the above-mentioned mechanisms of broadening.²⁴ The plot of the absorbance vs. the number of absorbing atoms corresponding to this spectral transition is shown in Fig. 12 b (curve 1). In calculations of this dependence, the spatial distribution of absorbing atoms was assumed to be uniform. It can be seen that broadening of the spectral line leads to curving and a decrease in the slope of the plot $A = f(N)$, which are particularly substantial for the spectral lines consisting of far-separated hyperfine components.

In addition to the above-described spectral factors, the shapes of the concentration curves strongly depend on the spatial distributions of the temperature gradients in the atomiser and the concentration of absorbing atoms. This influence is manifested in two directions. The longitudinal temperature and concentration gradients lead to a decrease in the slope of the plot given by Eqn (3), whereas the transverse gradients lead to further curving (see Fig. 12 b, curve 2).

The spectral transitions for some other elements were studied analogously. It was demonstrated²⁴ that the inhomogeneity of absorbing layers in the cross-section is one of the major factors responsible for curving of the calibration plots in AAS.

Therefore, the absorbance in conventional AAS depends not only on the number of absorbing atoms but also on their distribution inside the atomiser, as well as on the spatial structure of the probing beam, and is described by the following equation⁷²

$$A = A_t(N) - \Delta A(N', J'),$$

in which the first term can be referred to as the true absorbance (which depends only on the number of absorbing atoms N) and the second term depends on the gradients of spatial distribution of atoms (N') and the transmitted radiation intensity (J') and is

essentially the photometric error of the atomic absorption detection associated with inhomogeneity of the absorbing layer.

This error in conventional atomic absorption spectrometry is explained as follows. The luminous flux Φ_0 incident on the atomiser can be represented as consisting of n beams with intensity J_{i0} each. Then

$$\Phi_0 \sim \sum_{i=1}^n J_{i0}.$$

Analogously, the luminous flux Φ_t passed through the absorbing layer can be represented as

$$\Phi_t \sim \sum_{i=1}^n J_i,$$

where J_i is the local intensity of the probing beam passed through the corresponding region of the atomiser.

Therefore, the absorbance measured by conventional spatially integrated detection (SID) systems is described by the following equation:

$$A_{\text{SID}} = \log \frac{\Phi_0}{\Phi_t} = \log \frac{\sum J_{i0}}{\sum J_i}. \quad (4)$$

As demonstrated above, the absorbance depends on all types of inhomogeneities and is not proportional to the number of absorbing atoms N . At the same time, the number of these atoms can be represented by the sum

$$N = \sum_{i=1}^n N_i \Delta S_i,$$

where N_i (in cm^{-2}) is the atom density in the i th beam and ΔS_i is the cross-section area of the i th beam. If the elemental beams have equal cross-sections,

$$\Delta S_i = \frac{S}{n},$$

where S is the cross-section area of the total beam. Evidently, the local absorbance A_i becomes proportional to N_i as the transverse size of the beam decreases

$$A_i = \log \frac{J_{i0}}{J_i} \sim N_i.$$

Therefore, if the absorbance is represented as

$$A = \frac{1}{n} \sum_{i=1}^n A_i = \frac{1}{n} \sum_{i=1}^n \log \frac{J_{i0}}{J_i},$$

this parameter is proportional to the number of absorbing atoms regardless of their spatial distribution and the distribution of transmitted radiation intensity. Consequently, the spatially resolved detection (SRD) is required for correct photometric measurements of the absorbance of spatially inhomogeneous layers. The analytical signal A_{SRD} determined by the sum

$$A_{\text{SRD}} = \frac{1}{n} \sum_{i=1}^n \log \frac{J_{i0}}{J_i}, \quad (5)$$

is the true absorbance, which depends on spatial inhomogeneities, i.e.,

$$A_{\text{SRD}} = A_t(N).$$

VI. Spatially resolved atomic absorption analysis

The above-formulated idea of the spatially resolved detection was realised in practice in the studies.^{73,74} Below we describe an original experimental apparatus for the space-time resolved light absorption detection. The new detection system includes a linear position-sensitive detector (a photodiode bar or a charge-

coupled device) vertically located along the exit slit of the monochromator in the plane optically coupled with the centre of the atomiser. In this method, in contrast to conventional AAS, the distribution of transmitted radiation intensity along the vertical diameter of the atomiser, rather than the spatially integrated luminous flux passed through the absorbing layer, is measured at each instant of time.

Let us consider an example of the detection for atomisation of 0.1 ng of cadmium from a platform. The spatial intensity distributions of the radiation beam from cadmium EDL passed through the atomiser under different conditions are shown in Fig. 13. The spectral intensity distribution at the resonance wavelength of 228.8 nm is qualitatively analogous to that presented in Fig. 2*b*. The maximum is located at the periphery of the source. Since the diameter of EDL is approximately twice as large as the inner diameter of the atomiser (6 mm), the radiation beam from only one-half of the distribution shown in Fig. 2*b* enters the system. The tube of the atomiser substantially shields the incident beam. Curve 1 in Fig. 13 shows the intensity distribution of the radiation beam, which is passed through the cylindrical tube of the atomiser, along the exit slit of the spectrometer.

In atomisers equipped with a platform, the lower part of this distribution is substantially transformed (curve 2). The intensity near the platform ($y = 1$ mm) is equal to zero and has a small peak of the radiation beam passed under the platform ($y = 0.5$ mm). In conventional electrothermal AAS, a short slit (with a height of 2 mm) of the monochromator of the spectrometer is used to shield intrinsic emission of the atomiser. This slit selects a small region above the platform along the vertical diameter of the atomiser. This region is dashed in the inset to Fig. 13 and the spatial profile of EDL radiation passed through this short slit is shown by curve 3. In conventional AAS, the total luminous flux passed through the short slit, *i.e.*, the surface area under curve 3, rather than the intensity distribution is measured. In spatially resolved AAS, the profile of the radiation beam passed through the total cross-section of the tube, $J(y)$, (curve 2) is measured at each instant of time. This is the main difference between the methods under consideration. Spatially resolved AAS is substantially more informative than conventional AAS.

The evolution of the distribution of transmitted radiation intensity $J(y, t)$ in the course of platform atomisation of 0.1 ng of cadmium is shown in Fig. 14. The intensity dip starting from 0.25 s is determined by resonance radiation absorption at a wavelength of 228.8 nm by cadmium atoms vapourised from the platform. After completion of the atomisation cycle ($t > 1.5$ s), the spatial profile of the incident beam is completely restored.

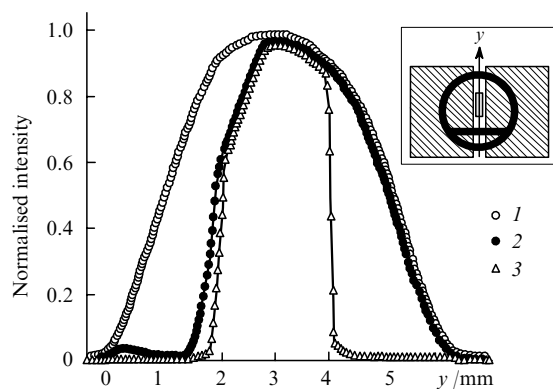


Figure 13. Intensity distribution of radiation from cadmium EDL passed through an atomiser without a platform (1), with a platform (2) and through a short monochromator slit (3).⁷⁹

The cross-section of a tube atomiser equipped with a platform and regions inside the atomiser selected by tall and short slits is shown in the inset.

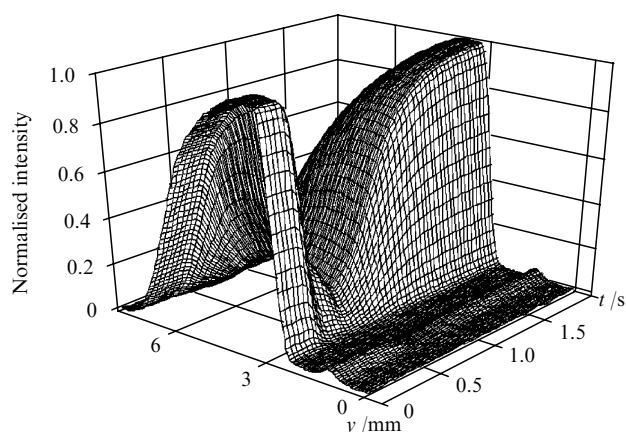


Figure 14. Changes with time in the spatial profile of the transmitted radiation intensity in the case of platform atomisation of 0.1 ng of Cd.⁷⁹ The detection was carried out at the resonance wavelength of cadmium (228.8 nm).

With a knowledge of the changes with time in local intensities, it is easy to obtain spatially resolved absorbances $A_i(t)$ corresponding to the absorption in different regions of the atomiser along its vertical diameter. Therefore, the spatially resolved detection gives a family of pulses recorded in different regions of the absorbing layer (Fig. 15*b*) instead of one atomic absorption

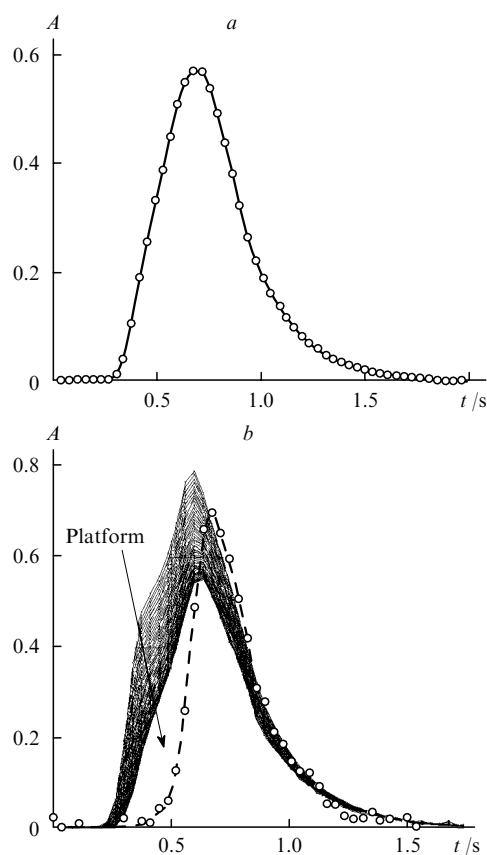


Figure 15. Absorption pulse obtained with the use of a conventional detection technique (a) and a family of 149 pulses obtained with the use of the spatially resolved detection (b) of atomisation in an HGA-type atomiser.⁷³

The absorption pulse detected for a region under the platform is indicated by a dashed curve. The absorption pulses obtained when moving from the platform to the upper part of the atomiser are indicated by an arrow.

pulse integrated over the cross-section of the atomiser, which is obtained in conventional AAS (Fig. 15a). Evidently, such a high spatial resolution is excessive. Consequently, the signals from the adjacent pixels of the detector can be combined to obtain the desired degree of spatial resolution. For HGA-type atomisers, depending on the degree of spatial inhomogeneity of particular distributions, 10–20 pulses along the diameter (6 mm) of an atomiser are sufficient.

The atomic absorption peaks monotonically decrease from the platform to the upper region of the atomiser (an arrow in Fig. 15b). The integrated absorption

$$\int_0^{\infty} A_i(t) dt,$$

which was measured directly above the platform onto which a sample was placed, is almost twice as large as the integrated absorption in the upper region of the atomiser. Interestingly, the radiation beam passes under the platform (see the small peak at $y = 0.5$ mm in Fig. 13), which makes it possible to obtain an atomic absorption pulse even from this region (the latter is indicated by a dashed curve in Fig. 15b). It can be seen that cadmium atoms appear in the region under the platform with a substantial delay.

Atomic absorption spectrometry is widely used in fundamental physicochemical studies,³¹ in particular, for the determination of the activation energies of vaporisation or atomisation. Evidently, the signal detected directly above the vaporisation source (the upmost curve in Fig. 15b) most adequately describes the kinetics of sample vaporisation in the above-considered example. It can be seen that this signal is not an absorption monopulse, which is evidence that cadmium vaporisation occurs by a complex mechanism. In measurements with the use of conventional spatially integrated detection systems, these features become less pronounced (see Fig. 15a), with the result that the activation energies of vaporisation are incorrect. In measurements with the use of spatially resolved detection systems, each measurement becomes much more informative due to which the conditions of atomisation and the formation of an absorbing layer of atoms can be better controlled.

A photometric error in the detection of atomic absorption of spatially inhomogeneous layers does not necessarily lead to an error in the determination of the number of absorbing atoms. If the character of spatial distribution of atoms in the analyte is identical to that in a reference sample, conventional atomic absorption analysis provides correct results. However, the spatial distribution of an analyte often depends substantially on the influence of the matrix of the analyte. In this case, the photometric error necessarily leads to an analytical error. This is clearly demonstrated by the following example.⁷⁴ Figure 16a shows the dynamics of changes in non-selective absorption detected at the resonance wavelength of cadmium (228.8 nm) for atomisation of the certified reference sample SRM 1572 (Citrus Leaves). The distributions are clearly non-uniform, the absorbance being changed by a factor of 10–20 from the platform ($y = 0$) to the upper wall of the atomiser ($y = 3$ mm). The pulses of space-time resolved selective absorption of cadmium atoms shown in Fig. 16b are characterised by substantially larger spatial gradients than those observed for atomisation from aqueous solutions (see Fig. 15b). In this case, the difference (relative change) between the analytical signals

$$\int_0^{\infty} A_{\text{SID}}(t) dt \text{ and } \int_0^{\infty} A_{\text{SRD}}(t) dt$$

is 86%. In atomic absorption spectrometry with the use of the conventional (spatially integrated) detection, this leads to an analytical error of 67%. The possibility of appearing a considerable analytical error associated with the photometric error

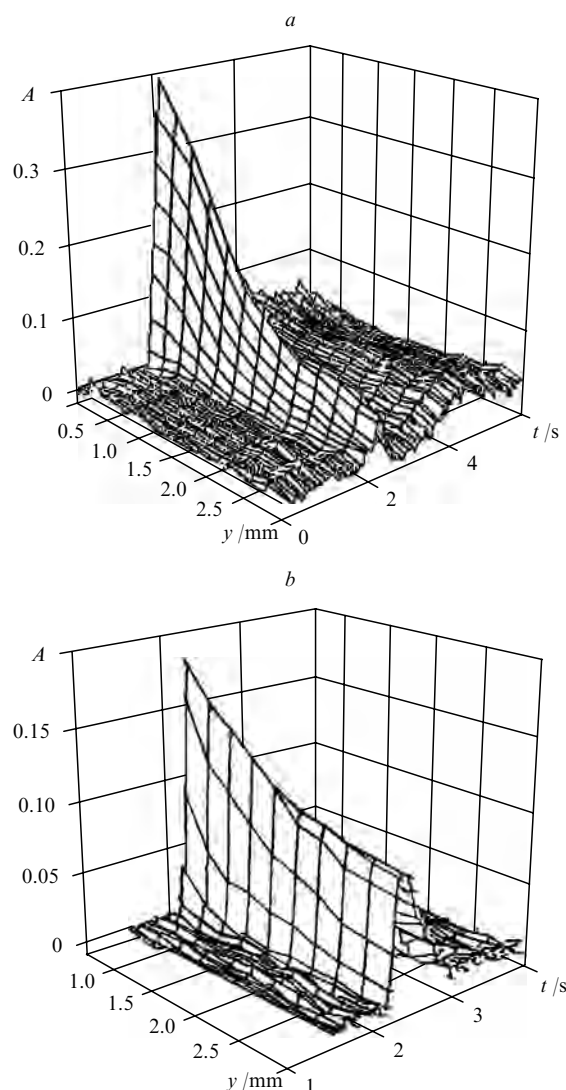


Figure 16. Space–time distribution of non-selective (a) and selective (b) absorption measured at the resonance wavelength of cadmium (228.8 nm) in the detection of cadmium in a certified sample SRM 1572 (Citrus Leaves).⁷⁴

in measurements with the use of the conventional detection of inhomogeneous layers was also demonstrated.⁷⁵

It is necessary to use matrix modifiers in electrothermal atomic absorption analysis of most substances. Taking into account the above-considered data, it is evident that the matrix modification of a sample leads not only to the known effect of separation of vaporisation of the analyte and the matrix but also to a unified spatial distribution of the analyte when it is atomised from an aqueous reference sample and from a real sample.

In conventional atomic absorption spectrometers, short monochromator slits are used with the aim of shielding intrinsic emission of the atomiser (see the rectangular region in the first shot in Fig. 6b and the inset to Fig. 13). Tall slits used in spatially resolved spectrometers provide the space-time resolved detection of radiation beams from both a source and the walls and platform of the atomiser. The results of these studies can be used for the on-line monitoring of temperature changes. An example is illustrated in Fig. 17. Thermal emission from the platform and walls sharply increases as their temperature raises and the detection wavelength increases. In this example, the measurements were performed at the resonance wavelength of calcium (422.7 nm) in the visible spectral region. The peaks corresponding to glow of the

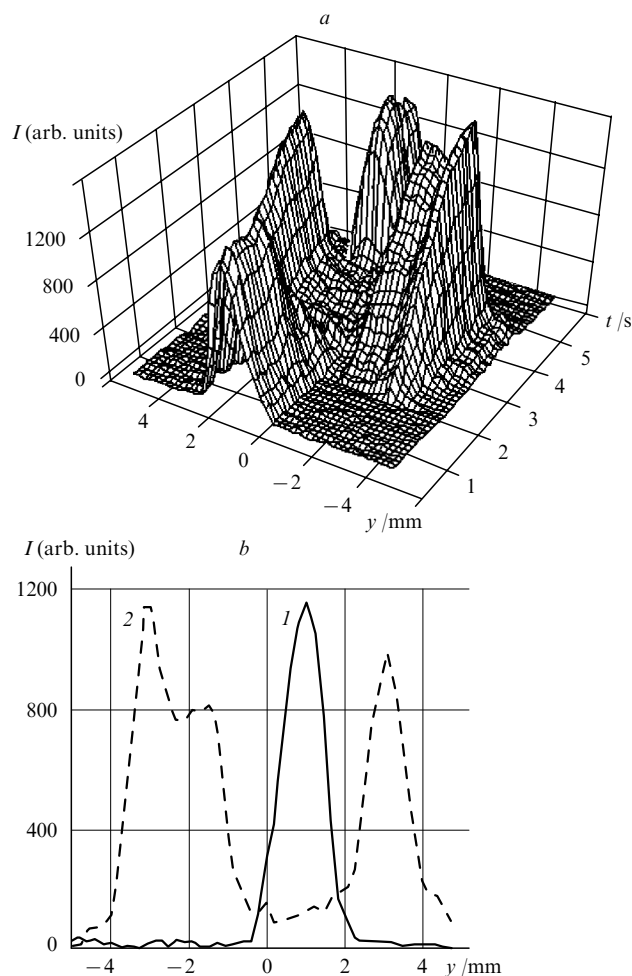


Figure 17. Changes in the intensity (I) of the radiation from the source, the walls and the platform of a tube atomiser measured with the use of the space-time resolved detection for calcium atomisation (a) and the radiation intensity distribution along the vertical diameter of the atomiser before atomisation (1) and at the instant when the maximum absorption was achieved (2) (b).⁷³

Calcium atomisation from the platform, $\lambda = 422.7$ nm, $T = 2500$ °C.

walls of the atomiser and the platform are seen in Fig. 17 *a*. Before heating of the atomiser, when its walls are cold, only the intensity profile of the source is detected (curve 1, Fig. 17 *b*). At the instant the atomisation temperature is achieved, the intensity profile of the transmitting source virtually disappears (vaporisation of a large amount of absorbing calcium atoms occurs), but three other peaks corresponding to emission from the upper and lower walls and the platform of the atomiser appear (curve 2, Fig. 17 *b*). Changes with time in emission from the walls of the atomiser and the platform follow directly after a rise of the atomiser temperature (see Fig. 17 *a*). This fact can be used to estimate quantitatively the degree of heating of the system. The relative peak intensities of emission from the upper and lower walls strongly depend on the alignment of the atomiser.⁷⁶ The difference in the peaks of emission from the walls (see curve 2, Fig. 17 *b*) indicates that the measurements were performed so that the atomiser tube was inclined to the optical axis of the spectrometer. This information can be used for the quantitative control of the alignment of the atomiser. The spatially resolved detection provides the possibility of seeing the exact position of the transmitted beam relative to the axis of the atomiser (see curve 1 in Fig. 17 *b*), which also substantially simplifies the alignment of the radiation source.

With a knowledge of the transmitted radiation intensities measured with the use of space-time resolved detection systems (see Fig. 14), it is always possible to obtain the absorption signal, which can be detected by a conventional spectrometer. For this purpose, it is sufficient to process the measured data according to Eqn (4). Therefore, AAS with the spatially resolved detection has all advantages of conventional AAS and includes them as a special case.

An idea of absolute atomic absorption analysis has been proposed back in 1955,² which marked the beginning of the development of analytical AAS. Over the history of AAS, this idea was extensively developed.^{77–79} Taking into account the above-considered results of investigation of spatial distributions and their influence on the formation of analytical signals, it is evident that reference-free atomic absorption analysis cannot be performed without the space–time resolved detection.^{80, 81}

Consequently, AAS with the spatially resolved detection appeared as the development of conventional AAS. The inclusion of additional measurements, *i.e.*, the measurements of the dependence of the key parameters on the spatial coordinate, provides substantially more informative data and higher accuracy of atomic absorption analysis.

VII. Conclusion

The development of methods and apparatuses, which could give higher-quality analytical signals, is one of the main fields of instrumental analytical chemistry. Atomic absorption signals detected in conventional AAS depend not only on the atomic concentration of the analyte element (the informative component of the signal), but also on their spatial distribution and the distribution of transmitted radiation intensity (the interference component of the signal). In AAS with the use of the spatially resolved detection, atomic absorption signals are independent of the spatial effects, due to which the resulting analytical signals are of higher quality. The present review shows that the key parameters of AAS (the atomiser temperature, distributions of atoms, molecules and condensed particles and transmitted radiation intensities) are characterised by a high degree of spatial inhomogeneities. The atomic absorption signal depends on these inhomogeneities, which are responsible for the photometric error in measurements with the use of conventional AAS. The absorption in spatially inhomogeneous media can be correctly measured only with the use of the spatially resolved detection. The above-considered examples of atomic absorption analysis of real substances confirm the practical importance of spatially resolved AAS.

According to the general classification of analytical chemistry methods,⁸² AAS with the spatially resolved detection is a second-order method, because it provides two-dimensional data sets, *viz.*, the absorbance as a function of the time and the spatial coordinate. Conventional AAS belongs to first-order methods. A higher order of a method always provides higher-quality analytical signals.⁸²

This review has been written with the financial support of the Russian Foundation for Basic Research (Project No. 05-03-04001NNIO_a).

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^a — *J. Anal. Chem. (Engl. Transl.)*^b — *J. Appl. Spectrosc. (Engl. Transl.)*

Analytical potential of Mössbauer spectroscopy

V G Semenov, L N Moskvina, A A Efimov

Contents

I. Introduction	317
II. Physical principles of Mössbauer spectroscopy and its modifications	317
III. Mössbauer spectra as a source of analytical information	319
IV. Methods of processing of Mössbauer spectra and databases	321
V. Geochemical and cosmochemical analyses	321
VI. Mössbauer spectroscopy in the analysis and investigations of biological objects	322
VII. Mössbauer spectroscopy in structural studies	323
VIII. Mössbauer spectroscopy and the studies and monitoring of corrosion and catalytic processes	324
IX. Conclusion	325

Abstract. Basic knowledge about Mössbauer spectroscopy, necessary for gaining qualitative and quantitative information on the substance composition from Mössbauer spectra, is considered. Methods of Mössbauer spectra processing are discussed and databases ensuring the search for information on objects under study are described. Applications of Mössbauer spectroscopy in various fields of chemistry, mineralogy, biology and materials science are considered. The bibliography includes 135 references.

I. Introduction

More than 45 years ago Rudolf Mössbauer discovered the phenomenon of resonant nuclear fluorescence of γ -radiation in ^{191}Ir .¹ A spectral method based on the phenomenon was named Mössbauer spectroscopy (more rarely, it is also called nuclear gamma-resonance spectroscopy). The technique immediately became a powerful tool for studying the structural and chemical state of solids and found wide application in various areas of science and technology,² such as materials science, chemistry, biology, geology, mineralogy, etc. At present, a number of monographs devoted to Mössbauer spectroscopy are available (see, e.g., monographs^{3–9}). In these books, the emphasis is placed on consideration of the physical principles and theoretical aspects of the method and on the most interesting objects of investigation. The number of such objects continuously increases, especially in connection with increasing interest in the materials science. Now we can say with certainty that Mössbauer spectroscopy is no longer an exotic physical method of investigation. At present, this is a routine analytical method with its specific methodology and objects of analysis.

Comprehensive information on Mössbauer spectroscopy studies and their results can be found on the Website of the Mössbauer Effect Data Centre (MEDC) at the University of North Carolina (USA) at URL <http://www.unca.edu/medc>. The MEDC database includes about 40 000 records, including a reference to the discovery of the Mössbauer effect. New references are published on a regular basis in *Mössbauer Effect Reference and Data Journal* (MERDJ, ten issues per year).¹⁰ MEDC publications also include collections of works aimed at summarising information concerning various avenues and objects of Mössbauer spectroscopy studies (mineralogy, materials science, analytical chemistry, catalysis, etc.).¹¹

Until recently, Mössbauer spectroscopy took a back seat among other analytical chemistry methods. Often, analyst chemists simply had no information on the analytical potential of Mössbauer spectroscopy. Recently, the situation has become better. In particular, two Mars exploration rovers, 'Spirit' and 'Opportunity', were equipped with Mössbauer spectrometers, which is evidence of increasing interest in the analytical potential of Mössbauer spectroscopy. This made it possible to obtain reliable information on water-driven chemical processes on Mars. The aim of this review is to attract the attention of analytical chemists to the title method. We will consider the key methodological issues of Mössbauer spectroscopy, methods of processing of Mössbauer spectra in order to obtain qualitative and quantitative information and the most typical objects of analysis in chemistry, geology, mineralogy, biology and materials science. In considering the results of analysis of particular objects, the emphasis will be placed on the experimental design depending on the nature of the object under study.

II. Physical principles of Mössbauer spectroscopy and its modifications

Mössbauer spectroscopy is based on recoilless resonant absorption of γ -quanta with energy E_0 , emitted by nuclei of Mössbauer isotopes in an excited state (source of radiation), by corresponding nuclei in an object under study (absorber) that are in the ground state. After absorption of γ -quanta, the latter nuclei undergo transition to the excited state of energy E'_0 . Resonant absorption is only possible at $E_0 = E'_0$. Mössbauer's merit consisted in that he found the conditions suitable for observation of resonant absorption of γ -quanta by atomic nuclei. He found that if the

V G Semenov, L N Moskvina, A A Efimov Department of Chemistry, St Petersburg State University, Universitetskii pr. 26, Petrodvorets, 198504 St Petersburg, Russian Federation. Fax (7-812) 428 69 39, tel. (7-812) 428 40 39, e-mail: semenov@moss.spb.ru (V G Semenov), tel. (7-812) 428 68 33, e-mail: leonid.moskvina@pobox.spb.ru (L N Moskvina), tel. (7-812) 428 67 77, e-mail: efimov@mail.ru (A A Efimov)

Received 3 October 2005

Uspekhi Khimii 75 (4) 354–365 (2006); translated by A M Raevskiy

emitting nuclei are incorporated into a solid,[†] it becomes highly probable that emission will occur in a recoilless fashion (without energy loss), because energy is transferred to the entire crystal rather than a particular atom, thus converting into energy of crystal lattice vibrations. In this case the emission and absorption lines have the same natural width (Γ) that is determined by the quantum-mechanical Heisenberg uncertainty relation:

$$\Gamma = \frac{\hbar}{\tau},$$

where $\hbar = h/2\pi$ and τ is the excited-state lifetime of the Mössbauer nucleus. Typical lifetimes of excited nuclear states lie between 10^{-10} and 10^{-6} s, which corresponds to linewidths $\Gamma = 10^{-5}$ – 10^{-9} eV. The relative linewidths of nuclear transitions with energies in the range 10^4 – 10^5 eV are 10^{-10} to 10^{-15} eV, being responsible for extremely high resolution of Mössbauer spectroscopy with respect to energy, which much exceeds the resolution of all other physical methods.

In real situations one should allow for a change in the γ -quantum energy due to thermal motion of atoms. Therefore, measurements of Mössbauer absorption (scattering) spectra require a controllable variation of the γ -quanta energy of the source of radiation in the range from a few neV to tens of neV. Most often, this is achieved by mounting the source of radiation on a Doppler modulator that provides continuous motion of the source relative to absorber (sample under study). The Doppler energy change, ΔE_D , due to the motion of the source of radiation with controllable speed v , is calculated as follows:

$$\Delta E_D = \frac{E_0 v}{c},$$

where c is the speed of light. In this case the energy of γ -quanta emitted towards the absorber is given by

$$E(v) = E_0 \left(1 + \frac{v}{c} \right) = E_0 + \Delta E_D, \quad (1)$$

where $E(v)$ is the energy of the γ -quantum emitted by the source moving at velocity v and E_0 is the energy of the γ -quantum emitted by the immobile source.

The Mössbauer absorption spectrum is usually represented as the dependence of the relative intensity of radiation passed through or scattered by the sample on the velocity of the source of radiation relative to the sample (Fig. 1). In fact this means that the Mössbauer spectrum represents the dependence of the γ -quanta absorption section on the Doppler energy (ΔE_D) added to the energy E_0 of these quanta. In order to obtain a convenient quantitative estimate of the signal, the effect (relative difference between the signal and background) is used instead of the relative

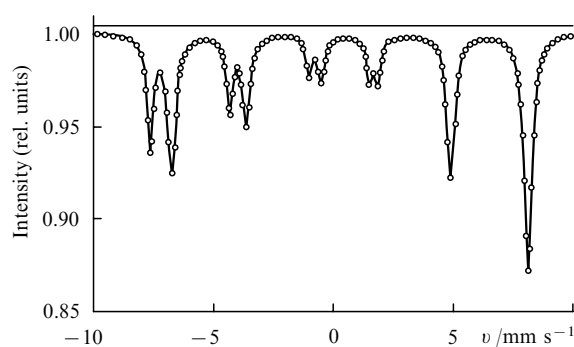


Figure 1. Mössbauer spectrum of Fe_3O_4 .

intensity. Additional information on the object under study can usually be obtained by varying external parameters that affect the resonant absorption effect (e.g., temperature, pressure and external magnetic field and electric field).

Measuring Mössbauer spectra includes registration of either γ -radiation that has passed through the absorber (absorption geometry) or radiation associated with resonance processes and scattered by the absorber (scattering geometry). Since the Mössbauer transitions are to some extent converted, experiments with the scattering geometry allow not only the resonance γ -radiation but also X-ray radiation or conversion electrons accompanying resonant scattering of γ -rays to be detected. X-Ray radiation contains information on the state of a thin (several tens of micrometres) surface layer of the sample and conversion electrons contain information only on the state of the surface layer 200–300 nm thick, which is determined by the short distance they travel within the sample material. The corresponding modification of Mössbauer spectroscopy is called conversion electron Mössbauer spectroscopy.⁷ Since recently, ultrathin surface layers (2–200 nm thick) have been studied using a new modification of conversion electron Mössbauer spectroscopy, namely, small-angle conversion electron Mössbauer spectroscopy.^{14–16} By varying the angle of incidence of γ -quanta it is possible to vary the depth to which γ -rays penetrate the surface layers of the sample under study.

Conventional sources of radiation represent long-lived parent radionuclides that are necessary for creating an intense flux of monochromatic resonant γ -radiation, which is then used for studying the state of corresponding Mössbauer nuclei in the absorber or in the scatterer. However, yet another experimental geometry is possible. Here, the sample to be analysed contains an incorporated Mössbauer isotope and acts as the source of γ -quanta and a known compound containing the same isotope characterised by a single monochromatic line for corresponding Mössbauer radiation acts as absorber or scatterer. This modification is called emission Mössbauer spectroscopy.¹⁷ This type of Mössbauer spectra is sensitive to specific features of the chemical environment of the resonance atom and of the structure that contains the resonance atom. The sensitivity of emission Mössbauer spectroscopy is as high as 10^{12} atoms per cm^2 of the surface area of the sample, which is much higher than the sensitivity of the scattering and absorption Mössbauer spectroscopies. An important feature and limitation of emission Mössbauer spectroscopy is the need of non-protected manipulation of radioactive substances. Therefore, this modification of Mössbauer spectroscopy is of limited practical use.

The possibility of studying certain objects by Mössbauer spectroscopy is determined by their elemental composition. At present, the Mössbauer effect is documented for more than 40 elements whose isotopes can be used in Mössbauer spectroscopy studies. However, physical and technological limitations reduce the number of isotopes suitable for being used for analytical purposes to at most seven (^{57}Fe , ^{119}Sn , ^{121}Sb , ^{125}Te , ^{129}I , ^{151}Eu and ^{197}Au). The ^{57}Fe and ^{119}Sn isotopes are of the greatest practical value. In spite of a relatively small number of 'Mössbauer' isotopes, numerous objects can be studied by Mössbauer spectroscopy, because the 'Mössbauer' elements are constituents of many objects to be analysed. For instance, iron belongs to the most abundant elements on Earth; therefore, ^{57}Fe Mössbauer spectroscopy has been intensively employed in geochemical and materials science studies of iron-containing solid samples.

^{119}Sn Mössbauer spectroscopy is of lesser use, because tin is 1000 times less abundant than iron. Nevertheless, numerous studies of tin-containing materials and minerals were carried out and tailor-made instruments for geological exploration for tin were designed in the early stage of development of Mössbauer spectroscopy.

[†] More recently, it was shown that Mössbauer effect can be observed not only in solids (regular crystals), but also in amorphous solids or solutions.^{12, 13}

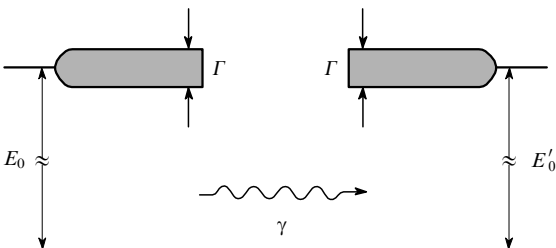
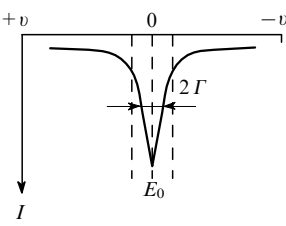
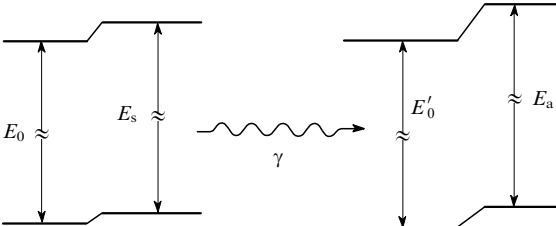
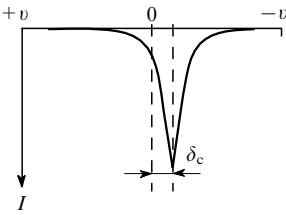
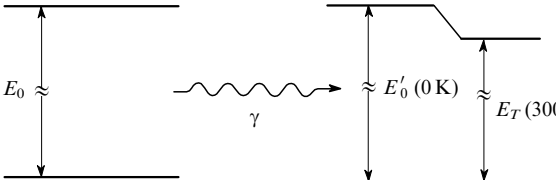
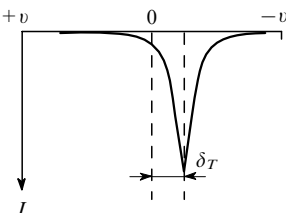
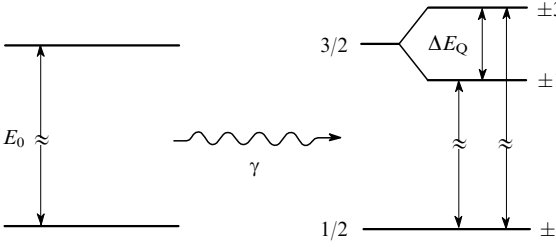
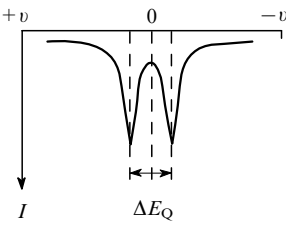
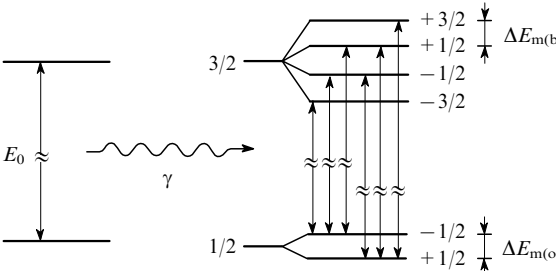
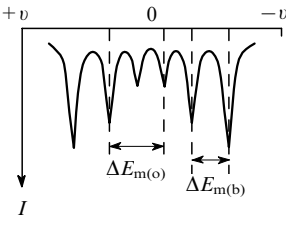
III. Mössbauer spectra as a source of analytical information

The nucleus of a Mössbauer atom is a highly sensitive probe, namely, the energies of nuclear sublevels vary depending on the electronic environment of the nucleus and on the internal and external electric and magnetic fields.

The Mössbauer spectra bear information on various interactions, many of which are indirectly related to the chemical nature

of the Mössbauer atom and its nearest environment. The relation is indirect because the chemical properties of an atom are determined by its outer electrons, which are shielded from the Mössbauer nucleus by inner electrons. Table 1 lists the most important parameters that can be extracted from Mössbauer spectra and used for qualitative analysis. We also present here the energy diagrams that demonstrate the influence of the parameters in question and the corresponding patterns of Mössbauer spectra. As resonance nuclei we consider those of the most widely

Table 1. Most important parameters of ^{57}Fe and ^{119}Sn Mössbauer spectra.

Characteristics of Mössbauer spectra	Schemes of energy levels and transitions for ^{57}Fe (or ^{119}Sn) isotopes in		Mössbauer spectral pattern
	source of radiation (s)	absorber (a)	
Resonance linewidth (Γ)			
Isomer (chemical) shift (δ_c)			
Second-order temperature (Doppler) shift (δ_T)			
Quadrupole energy splitting (ΔE_Q)			
Magnetic splitting			

used Mössbauer isotopes, ^{57}Fe and ^{119}Sn , having the ground- and excited-state nuclear spins of $I_g = 1/2$ and $I_e = 3/2$, respectively.

Each parameter of the Mössbauer spectra listed in Table 1 has its own physical nature and bears analytical information. Detailed consideration of these parameters is available in the literature.^{4–9} The set of parameters listed in Table 1 should be augmented with the probability of Mössbauer effect (f_M), which plays an important role in quantitative analysis using Mössbauer spectroscopy.

Quantitative analysis is based on the assumption that the area, S , under a line in the spectrum of a thin absorber is proportional to the number, n , of the atoms containing Mössbauer nuclei:

$$S = kf_M n,$$

where k is the factor including the resonant absorption cross section, emission intensity, time taken to collect the spectral data, energies of γ -quanta, effect of background emission and the angle between the direction of the γ -quanta flux and the normal to the absorber surface; and f_M is the Mössbauer effect probability (*i.e.*, probability of recoilless elastic processes). The f_M value depends on the root-mean-square displacement of the absorber nuclei from their equilibrium positions ($\langle x^2 \rangle$) at temperature T

$$f_M = \exp\left(\frac{-p^2 \langle x^2 \rangle}{\hbar}\right),$$

where $p = E_\gamma/c$ is the momentum of the γ -quantum ($E_\gamma = \hbar\nu$ is the photon energy).

The stronger the coupling between atoms in the crystal lattice, the higher the characteristic (Debye) temperature of the substance Θ_D and the smaller the root-mean-square nuclear displacement at a given temperature and, hence, the higher the probability of the Mössbauer effect. This dependence of the area under the spectral curve on the number of resonance nuclei is valid in the thin absorber approximation where $n\sigma \ll 1$ (σ is the resonant absorption cross section), *i.e.*, when the shape of the resonance line is undistorted by saturation effect.

Resonance linewidth. In the thin absorber approximation an experimental Mössbauer spectral line has a Lorentzian shape¹ (see Table 1) and the minimum linewidth is given by the doubled natural width of the absorption line, Γ . It was theoretically shown and experimentally proved that there exists line broadening due to diffusion of atoms. The linewidth is influenced by crystal lattice defects that cause changes in the local environment of resonance atoms. Line broadening is most pronounced in the spectra of amorphous and glassy materials.

Isomer (chemical) shift (δ_c) arises in the case where Mössbauer nuclei in the source and in the absorber are in different chemical environments. The isomer shift manifests itself as a shift of the resonant absorption line relative to the absorption line at $\nu = 0$. The δ_c value is given by:

$$\delta_c = \frac{4\pi}{5} e^2 Z R^2 \frac{\Delta R}{R} \{ |\Psi(0)|_a^2 - |\Psi(0)|_s^2 \}, \quad (2)$$

where e is the charge of electron, Z is the charge of the nucleus, R is the average radius of the nucleus, ΔR is the change in the nuclear radius on going from excited state to the ground state and $|\Psi(0)|_a^2$ and $|\Psi(0)|_s^2$ are the electron densities at the nuclei of the resonance atoms in the absorber (a) and source (s), respectively. For a particular nucleus, the $\Delta R/R$ ratio is a constant and the chemical shift is determined only by the difference between the electron densities at the resonance nuclei in the source and in the absorber, which in turn mainly depends on the s-state populations. Electrons from other shells (p, d, f) can indirectly affect the δ_c value through partial shielding of s-electrons or formation of hybrid states with the s-orbitals (generally, this should be allowed for when interpreting the chemical shift values). The δ_c values obtained by Mössbauer spectroscopy make it possible to draw conclusions about the character of a chemical bond, its degree of covalence, coordination, degree of electron delocalisation, *etc.*

Second-order temperature (Doppler) shift (δ_T) is due to the energy difference between emitted and absorbed γ -quanta (owing to temperature difference between the source and absorber) and manifests itself as a shift of the resonant absorption line. The shift value is calculated as follows

$$\delta_T = -\frac{\langle v^2 \rangle}{2c^2} E_0, \quad (3)$$

where $\langle v^2 \rangle$ is the temperature-dependent root-mean-square velocity that characterises atomic motions in solids.

Thus, the energy shift δ observed in Mössbauer spectra is the sum of two contributions

$$\delta = \delta_c + \delta_T.$$

Quadrupole splitting (ΔE_Q) is a result of the interaction between the quadrupole moment of non-spherical resonance nucleus with the gradient of the electric field created at the nucleus by the electron shell and ligands. This interaction leads to splitting of a nuclear energy level into sublevels. For ^{57}Fe nuclei the separation, ΔE_Q , is calculated as follows:

$$\Delta E_Q = \frac{eQ}{2} V_{zz} \sqrt{1 + \frac{\eta^2}{3}}, \quad (4)$$

where eQ is the quadrupole moment of the nucleus, V_{zz} is the principal component of the electric field gradient at the nucleus along the z axis and $\eta = (V_{zz} - V_{yy})/V_{xx}$ is the asymmetry parameter (V_{xx} and V_{yy} are the electric field gradients along the x and y axes). The coordinate axes are chosen in such a way that $0 \leq \eta \leq 1$. The electric field gradient at the nucleus is determined by the environment geometry, by the effective charges of ions surrounding the resonance nucleus in the object under study and by the presence of partially filled non-spherical electron shells (p, d, f) in the resonance atom. Thus, in the general case the quadrupole interaction of a Mössbauer nucleus bears information on the structure of the atomic environment of the nucleus in the crystal lattice and on the state of its valence shells.

If the Mössbauer spectrum simultaneously exhibits the chemical shift and quadrupole splitting (these parameters are affected by s- and p-electrons in different fashion), it is possible to obtain more diverse information on the state of the electron shell of the resonance atom and on the local structure of the crystal lattice.

Magnetic (Zeeman) splitting (ΔE_m) arises due to the interaction between the magnetic moment of the nucleus (in both ground and excited states) with the effective magnetic field (B) created by the electron shell at the nucleus. The Zeeman splitting is given by

$$E_m = -g_I \mu_N B \Delta m_I, \quad (5)$$

where g_I is the nuclear gyromagnetic ratio for a given nuclear level (I is the nuclear spin), μ_N is the nuclear magneton, m_I is the magnetic quantum number and Δm_I is the change in the magnetic quantum number corresponding to transition of a ^{57}Fe , ^{119}Sn or ^{125}Te nucleus from excited state (spin $I_e = 3/2$) to the ground state ($I_g = 1/2$). Emission of a γ -quantum from each of the four excited-state sublevels ($+3/2$, $+1/2$, $-1/2$, $-3/2$) causes a transition of the nucleus to one out of two ground-state sublevels ($+1/2$, $-1/2$). The transition occurs in accordance with the selection rule for dipole transitions ($\Delta m = 0, \pm 1$) and results in the appearance of magnetic hyperfine structure (magnetic sextet) in the Mössbauer spectrum (see Table 1). If the nucleus in question is simultaneously involved in the magnetic and quadrupole interactions, energy level calculations are complicated. The magnetic field strength B is a function of structural and electronic parameters, namely, the number of unpaired d-electrons, the type of the chemical bond formed by the resonance atom, the environment geometry, *etc.* Therefore, the appearance of hyperfine magnetic splitting makes the Mössbauer spectra much more informative and allows one to reveal peculiar features of the electronic, crystal and magnetic structures of compounds analysed.

The informativity of the key parameters of Mössbauer spectra (see above) shows that this relatively simple (from experimental standpoint) method not only has a great potential for studies of the structure and electronic properties of solids but is also an efficient method of analysis of solid samples in spite of a limited number of Mössbauer isotopes. A proof of this statement is provided by numerous examples of solution of complex analytical problems using Mössbauer spectroscopy.

The possibility of obtaining unique information on the local chemical state of a resonance atom and on the electric and magnetic fields at the atomic nucleus led to setting up emission Mössbauer spectroscopy experiments in which the resonance atoms were introduced into the sample as specific probes (see, e.g., Ref. 18). This approach was employed, in particular, in a study of high-temperature superconductors. For instance, the copper atoms in the crystal lattices of $\text{Ti}_2\text{Ba}_2\text{CuO}_6$ and $\text{Ti}_2\text{Ba}_2\text{CaCu}_2\text{O}_8$ superconductors were replaced by ^{67}Cu isotopes by diffusion doping and then the ^{67}Cu (^{67}Zn) Mössbauer spectra were measured at 4.2 K with ^{67}ZnS as absorber.¹⁸ In this case the main problem is to confirm the fact that the resonance (dopant) atoms occupy the substitution sites in the crystal lattice.

IV. Methods of processing of Mössbauer spectra and databases

An important moment in Mössbauer spectroscopy is processing of experimental spectra using special programs that permit theoretical description of an experimental spectrum using a set of resonance lines. The aim of the spectral data processing is to determine the physical parameters considered in the previous Section.

The Mössbauer spectra are usually processed by the least squares method.^{19–21} The functional to be minimised has the form

$$\chi^2 = \sum_{i=1}^n \frac{1}{N_i} [N_i - S_i(p_0, p_1, \dots, p_k)]^2 \quad (6)$$

where $p_0, p_1, \dots, p_k$ are parameters, N_i is the number of counts in the i th channel[‡] of the experimental spectrum, $S_i(p_0, p_1, \dots, p_k)$ is the model spectral amplitude for the i th channel and n is the total number of channels. Processing of an experimental spectrum is preceded by the choice of the model spectral shape. The choice is based on *a priori* information on the object analysed. A model spectrum is assumed to be a spectrum comprising a set of resonance lines corresponding to a particular type of the hyperfine structure of resonance nuclei.[§] The model spectrum of a thin absorber can be represented by superposition of Lorentzian lines with negative (absorption spectra) or positive (scattering spectra) amplitudes with respect to the baseline.

The model spectrum of a thick absorber is represented by either convolution of a Lorentzian and a Gaussian function²² or the transmission integral,²³ which describes the motion of the resonance γ -quantum through an absorber containing resonance nuclei. This approach is best for quantitative analysis.

In a large class of substances, such as amorphous solids, alloys, ultradisperse media, *etc.* the nearest spatial and elemental environment of the atoms containing resonance nuclei continuously changes. The spectra of such substances represent superpositions of continuous series of subspectra and cannot be processed using the algorithms considered above, because the problem becomes ill-posed (no unique solution exists). The approach employed in this case is based on representation of the model spectrum by convolution of k elementary subspectra $L_i^k(p_0, p_1, \dots, p_k)$ with one or two continuously varying hyperfine

interaction parameters and the weight function $P^k(p_0, p_1, \dots, p_k)$ of these subspectra, which is often called the hyperfine field distribution function.^{24,25} This function provides information on the distribution of chemical bonds and electric or magnetic fields at nuclei of the resonance atoms in the substance under study.

An alternative approach to solution of ill-posed problems is based on the principle of limited density of spectral lines depending on the statistical significance of the spectrum.²⁶ The efficiency of this approach was demonstrated taking analysis of complicated Mössbauer spectra of high-temperature superconductors as examples.

Informativity of Mössbauer spectra for qualitative and quantitative analysis can be exemplified by the processing of a γ -ray scattering spectrum of oxidised surface of metallic iron (conversion electrons were detected). Figure 2 presents the experimental Mössbauer spectrum (points) and its decomposition into subspectra corresponding to iron atoms in different phases. Using the Mössbauer parameters of the subspectra, it is possible to identify iron-containing phases (qualitative analysis), while measuring the areas under individual lines provides a quantitative estimate of the relative content of these phases. To obtain a more correct estimate, the surface areas should be corrected for the f_M factor (probability of resonant absorption in each phase). However, determination of the f_M factor faces practical and theoretical difficulties and therefore the relative content of phases is estimated to an accuracy of the f_M factor.

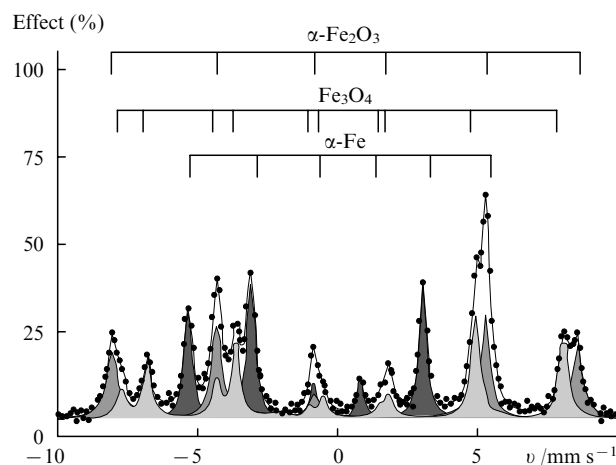


Figure 2. Decomposition of experimental Mössbauer spectrum into subspectra corresponding to iron atoms belonging to a particular phase.

V. Geochemical and cosmochemical analyses

Applications of Mössbauer spectroscopy in chemical analysis mainly concern solution of topical problems of geochemistry and cosmochemistry. They include determination of the oxidation states and coordination numbers of iron and tin atoms in minerals,^{27–35} phase analysis of rocks,^{36–39} meteorites^{40–42} and lunar soil⁴³ and determination of the age and genesis of minerals.^{44,45}

Among the last-named group of research avenues, of special interest are the Mars surface studies,^{46–48} in particular, investigations of the mineralogical composition of Martian soil using tailor-made Mössbauer spectrometers MIMDS II. These studies are aimed at understanding the evolution of the planet and answering the question on the existence of water on Mars. Iron-based minerals were studied. Analysis was carried out using the conversion resonant radiation backscatter geometry. The results of analysis of Martian soil near the Gusev crater and on the plain were different. The detection of olivine and pyroxene (silicate

‡ The intensity of γ -quanta flux is fixed using a multichannel analyser. The channel number is proportional to the velocity of the source of radiation.

§ If resonance nuclei are in inequivalent positions, the shape of the model spectrum corresponds to superposition of hyperfine structures.

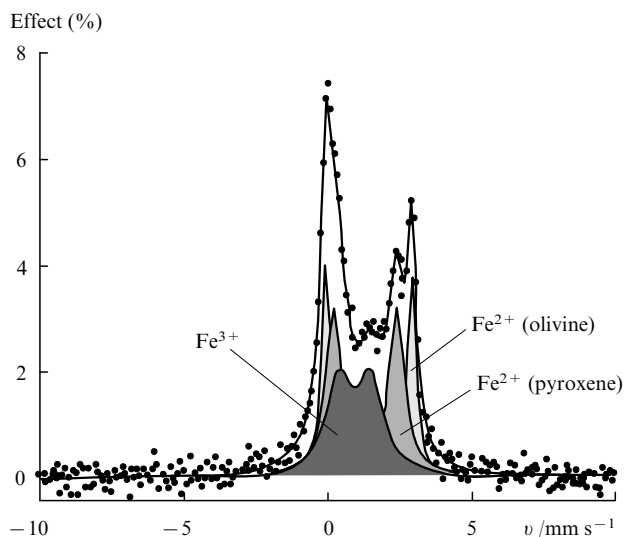


Figure 3. First Mössbauer spectrum taken on the Mars surface near the Gusev crater (points) and its decomposition into subspectra corresponding to iron atoms in different environments.

minerals that are usually contained in volcanic rocks, Fig. 3) near the Gusev crater appeared to be unexpected. The greatest portion (~95%) of the Mössbauer spectra of Martian soil taken on the plain falls on the component corresponding to such a highly abundant Earth mineral as hematite, Fe_2O_3 (Fig. 4). The formation of hematite is usually preceded by hydrolytic transformations of water-soluble forms of Fe(III) , which provides indirect evidence for the existence of water on Mars. Confirmation of conclusions about the genesis of Martian minerals requires continuous research involving drilling in order to obtain soil from greater depth.

Mössbauer spectroscopy belongs to the main methods of investigation of the genesis of minerals in the Earth crust. In the last decade there has been a rapidly increasing interest in studies of microbiological pathways of formation of iron-containing minerals *via* anaerobic dissimilatory iron-reducing bacteria involved in reduction of iron oxides. It was assumed that these bacteria could participate in formation of pre-Cambrian iron–silicon formations. Being a highly sensitive method of analysis of

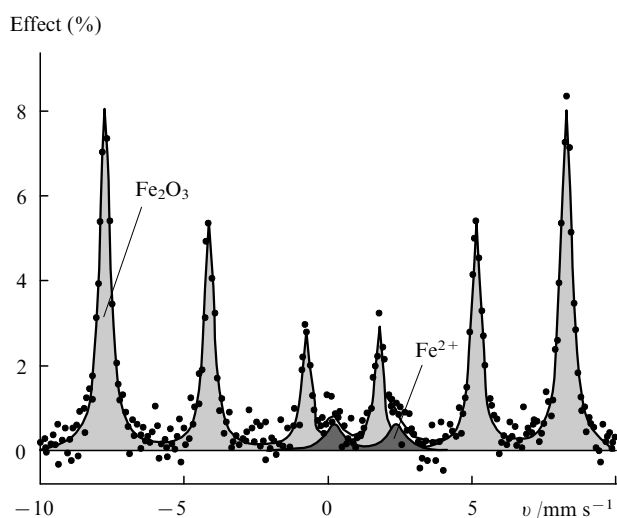


Figure 4. Mössbauer spectrum of Martian soil taken on the plain and its decomposition into subspectra corresponding to iron atoms of hematite Fe_2O_3 (sextet) and olivine Fe^{2+} (doublet).

iron-containing objects, Mössbauer spectroscopy allowed not only the kinetics of the phase transformations induced by iron-reducing bacteria to be studied but also factors affecting this process to be determined.^{49–54} The results obtained suggested the existence of various pathways of biosynthesis of iron-containing minerals by micro-organisms that favour the reduction of Fe(III) to Fe(II) . At present, the biosynthesis mechanisms are still to be clarified and there has been intensive accumulation of experimental information.

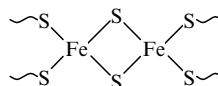
VI. Mössbauer spectroscopy in the analysis and investigations of biological objects

Iron atoms play an important role of active centres in such vitally important proteins as hemoglobin, myoglobin, cytochromes, *etc.* These proteins are responsible for reversible binding and transfer of oxygen and participate in photosynthetic redox chains owing to electron transport. The possibility of application of Mössbauer spectroscopy in studies of biomolecules (mainly proteins) has been best considered in Refs 55–57. An important avenue of biological research is comparison of the Mössbauer parameters obtained in studies of healthy (normal) organisms and the organisms with various diseases or affected by external factors.^{58–61}

Methods of measuring the Mössbauer spectra of biological objects are generally identical to those employed in the studies of inorganic objects. However, the concentration of iron in the samples under study (except for ferredoxin) is so low that obtaining statistically significant results requires enrichment with ^{57}Fe isotope. Therefore, an important aspect of the studies and analysis of biological objects is establishing sample preparation conditions suitable for directed exchange of iron atoms in the sample by the ^{57}Fe isotope without destruction of the initial protein structure. This can be attained using incubation of microorganisms in ^{57}Fe -containing media or by injecting a ^{57}Fe salt solution into living organisms.

Using Mössbauer spectroscopy, heme and non-heme proteins (*e.g.*, constituents of photosynthetic centres), iron–sulfur, iron-transport and iron-accumulating proteins were studied. Fine details of the electronic and spin transformations of iron in heme and in sulfur-containing proteins were investigated. In particular, the Fe(II) atom in heme is responsible for reversible binding of oxygen in hemoglobin (Hb) and the operation of hemoglobin. Mössbauer spectroscopy studies showed that violation of normal heme functions is accompanied by oxidation of Fe(II) to Fe(III) . Iron(II) in heme is in two spin states, a high-spin ($I = 2$) and a low-spin state ($I = 0$). The high-spin state is observed only for the Fe(II) atom of the deoxy form of Hb in a pentaligand environment. The low-spin state is characteristic of the Fe(II) compound with six ligands, with an O_2 or CO molecule as the sixth ligand. The spectra of Hb, HbO_2 and HbCO are significantly different. The addition of O_2 to Hb is accompanied by dramatic change in the chemical shift value, which is due to transition of Fe^{2+} from the high-spin state in Hb to the low-spin state in HbO_2 . The addition of CO to hemoglobin causes the formation of a symmetrical structure HbCO (as indicated by a decrease in the quadrupole splitting) with the $\text{Fe(II)}-\text{CO}$ bond being stronger than the $\text{Fe(II)}-\text{O}_2$ bond. Since CO adds to Hb irreversibly and thus prevents Hb from doing oxygen exchange, poisoning with carbon monoxide leads to fatal case.⁵⁵

Iron-sulfur proteins were among the first biological objects studied by Mössbauer spectroscopy, because they contain a relatively large number of iron atoms in the molecule. The active centre of sulfur-containing proteins comprises the iron and sulfur atoms.^{62–66}



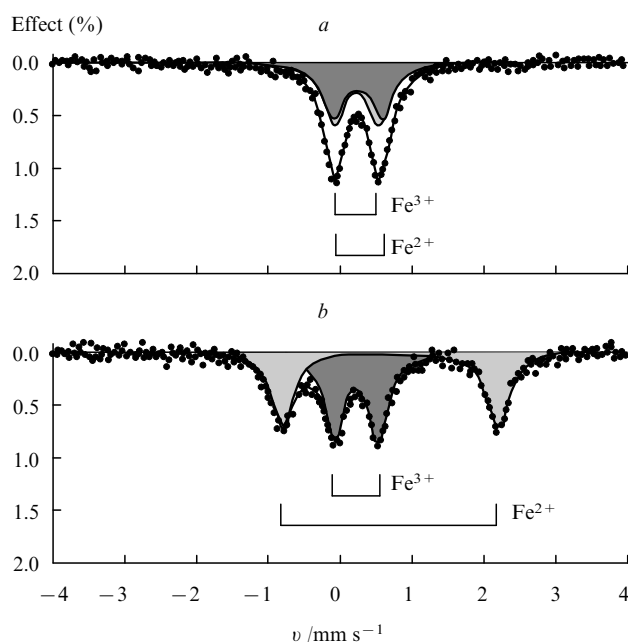


Figure 5. Mössbauer spectra of plant ferredoxin measured at 195 K. Oxidised Fd (a) and reduced Fd (b). Vertical lines denote positions of the doublet lines.

Usually, the Fe(II) and Fe(III) atoms in sulfur-containing proteins are in the high-spin state. Figure 5 presents the classical Mössbauer spectra of plant ferredoxin (Fd)[¶] in the oxidised [Fe(III)] and reduced [Fe(II)] states.

The Mössbauer spectrum of oxidised Fd containing two tetrahedrally coordinated Fe(III) atoms exhibits two doublets with nearly identical parameters ($\delta = 0.22\text{--}0.25\text{ mm s}^{-1}$ and $E_Q = 0.6\text{--}0.7\text{ mm s}^{-1}$) at a measurement temperature of 195 K. The low δ value indicates a high degree of covalence of Fe–S bonds. In spite of the same ligand composition, it is clear that positions of the iron(III) atoms in the active centre of Fd are inequivalent. This is probably due to the effect of polypeptide chains, resulting in changes in the bond lengths and bond angles in the active centre. This inequivalence is well pronounced in the reduction of Fd. Transfer of an electron to Fd leads to its localisation on a Fe(III) ion and to reduction of this ion to Fe(II) ($\delta \approx 0.7\text{ mm s}^{-1}$ and $E_Q = 3.0\text{ mm s}^{-1}$), the electronic state of the other Fe(III) ion being changed insignificantly.

In pharmacology, Mössbauer spectroscopy is used in studies of the state of iron atoms in iron-containing pharmaceuticals used in medical practice. Most of the preparations contain divalent iron, because in this case [in contrast to Fe(III)] the side effects characteristic of iron compounds are less pronounced. Besides, specific biological activity of the Fe(II)-containing preparations is higher than that of the preparations containing Fe(III) ions. Therefore, for pharmaceutical analysis it is important to determine the oxidation state of iron in iron-containing drugs. Mössbauer spectroscopy is also used for the determination of the oxidation state of iron on storage of drugs. The results of Mössbauer spectroscopy tests of iron-containing vitamins produced by the leading pharmaceutical companies were reported.^{67,68} It was shown that all vitamins contain small amounts of trivalent iron; however, in some samples the content of Fe(III) exceeded the permissible rates. This suggests that Mössbauer spectroscopy should be included in the group of methods for control of iron-containing pharmaceuticals.⁶⁸

[¶] Ferredoxin is an iron-containing protein acting as electron carrier in many biological redox processes.

In addition to conventional absorption Mössbauer spectroscopy, biological objects are also analysed by emission Mössbauer spectroscopy^{12,69–72} (here, a radioactive isotope ⁵⁷Co is introduced into the object to be analysed). Despite the fact that this technique allows the sensitivity of Mössbauer spectroscopy to be improved by several orders of magnitude, it is rarely used due to the need of unprotected operation with radioactive preparations (see above).

Mössbauer spectroscopy studies of the molecular mobility of proteins, biopolymers and their fragments occupy a special position. These experiments are carried out using the Rayleigh scattering of Mössbauer radiation. The technique made it possible to reveal various groups of motions and to determine corresponding frequency ranges and vibrational amplitudes.^{55,73–77}

VII. Mössbauer spectroscopy in structural studies

Mössbauer spectroscopy has been an efficient tool for structural analysis in studies of structural and magnetic phase transitions in organic and inorganic compounds^{78–87} containing such Mössbauer isotopes as ⁵⁷Fe, ¹¹⁹Sn, ¹²¹Sb, ¹⁵¹Eu, ¹⁵⁵Gd or ¹⁹⁷Au. In this case Mössbauer spectroscopy makes it possible to significantly complement the results obtained from IR and NMR spectroscopies. High structural sensitivity of Mössbauer spectroscopy is due to the fact that parameters of the hyperfine structure of the Mössbauer spectrum (chemical shift, quadrupole splitting and magnetic hyperfine splitting) depend on the population of the valence states of the Mössbauer atom in the compound under study and on the spatial structure of this compound. Changes in the parameters of Mössbauer spectra depending on the external factors, affecting the samples under study (temperature, pressure, magnetic fields, *etc.*), provide additional information on the structural and phase transitions in such compounds. The application of Mössbauer spectroscopy to structural studies of Fe(II) complexes can be exemplified by the investigation of the spin-transition state (so-called spin-crossover^{88–90}), *i.e.*, an equilibrium state between the high-spin (HS) and low-spin (LS) states. Spin-crossover can occur in d⁴-, d⁵-, d⁶-, d⁷- and d⁸-transition metal complexes. Depending on the ratio of the splitting energy of the transition metal atom in the ligand field (Δ) to the spin pairing energy (P) the ground state of the transition metal complex can be high-spin (for weak ligand field $\Delta < P$) or low-spin (for strong ligand field $\Delta > P$). If the difference $|\Delta - P|$ becomes comparable in magnitude with the thermal energy $k_B T$, the equilibrium coexistence of the high-spin and low-spin states becomes possible. Figure 6 presents the energy diagram of Fe(II) 3d-AO energy levels (3d⁶-electron configuration) in octahedral complex for the high- and low-spin states and for the spin equilibrium state.

The Mössbauer spectra of [Fe(phen)₂(NCS)₂] measured at different temperatures are shown in Fig. 7. The spectrum obtained at 300 K (see Fig. 7f) exhibits a single doublet with

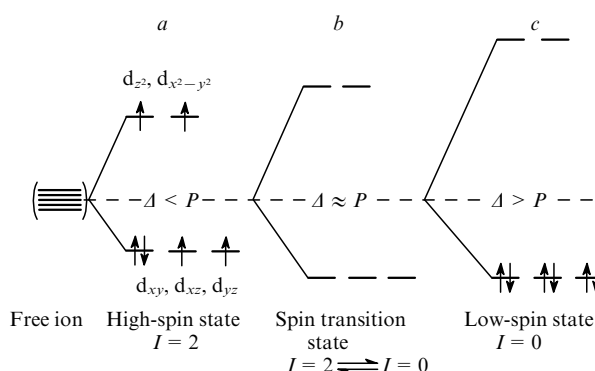


Figure 6. Fe(II) 3d-orbital levels in octahedral complex at weak (a), intermediate (b) and strong (c) ligand field. $\text{Fe}^{2+} : \text{Fe}_{\text{tot}} \approx 0.6$.

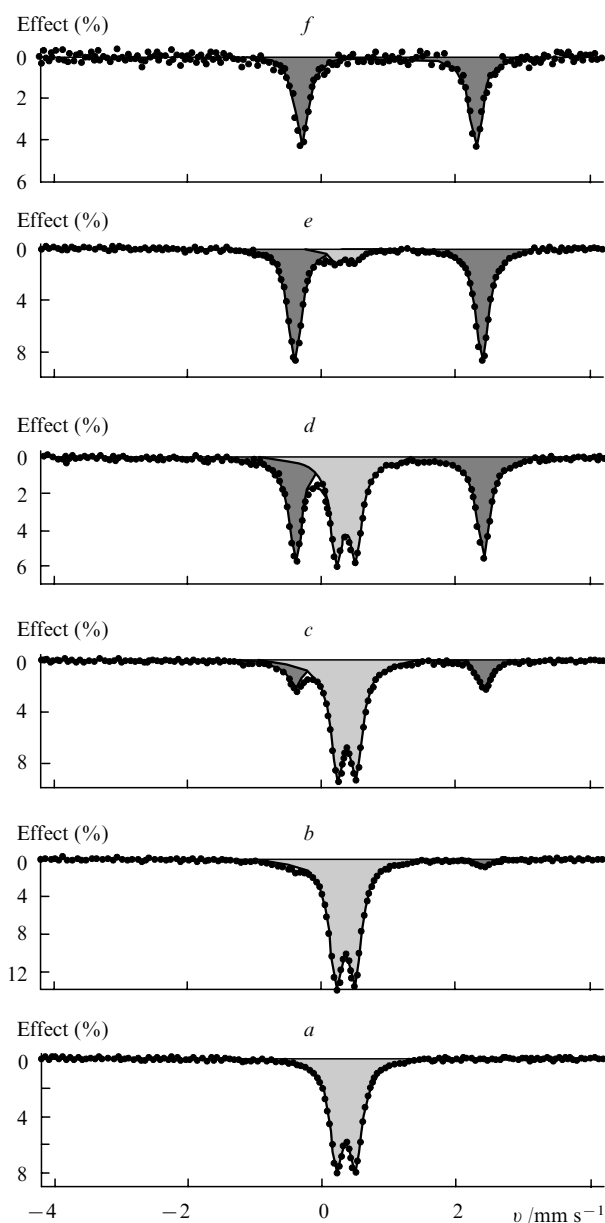


Figure 7. Mössbauer spectra of $[\text{Fe}(\text{phen})_2(\text{NCS})_2]$ measured at different temperatures. The subspectra corresponding to iron atoms in the low-spin and high-spin states are bright and dark shaded, respectively. Temperature /K: 77 (a), 180 (b), 184 (c), 186 (d), 188 (e), 300 (f).

the parameters corresponding to a pure HS state of $\text{Fe}(\text{II})$ ($\delta \approx 1 \text{ mm s}^{-1}$ and $E_Q = 2.6 \text{ mm s}^{-1}$) while the spectrum at 77 K (Fig. 7a) exhibits a single doublet with the parameters corresponding to pure LS state ($\delta \approx 0.35 \text{ mm s}^{-1}$ and $E_Q = 0.25 \text{ mm s}^{-1}$). The spectra obtained in the temperature range 180–188 K exhibit two quadrupole doublets corresponding to two spin states (HS and LS). As the temperature decreases, the proportion of $\text{Fe}(\text{II})$ atoms in the HS state decreases and in the LS state increases. Transition from one state to the other occurs jumpwise in a narrow temperature range (180–188 K).

Spin transitions in $\text{Fe}(\text{III})$ complexes were studied by measuring the magnetic susceptibility using Mössbauer spectroscopy.^{91–93} At present, Mössbauer spectroscopy is employed in studies of spin transitions under the action of electromagnetic radiation, in magnetic field and under pressure.^{94–96}

Recently, the emphasis in structural studies of tin compounds has been placed on determination of the charge states and possible crystallographic positions of tin atoms.^{97–99} The possibility of

simultaneous determination of the chemical shift and quadrupole splitting allows Mössbauer spectroscopy to be used in studying the structure, reactivity and mechanisms of transformations of organotin compounds (see Refs 100–103).

VIII. Mössbauer spectroscopy and the studies and monitoring of corrosion and catalytic processes

The first chemical application of Mössbauer spectroscopy was the study of iron oxides as corresponding corrosion products. Qualitatively, the phase composition of corrosion products can be established by comparing the parameters of Mössbauer spectra with the parameters of the reference spectra of artificially synthesised oxides and hydroxides. Comprehensive information on the structure, magnetic properties and Mössbauer parameters of iron oxides, hydroxides and ferrihydrides was reported by Murad and Johnston.¹⁰⁴ The advantages of Mössbauer spectroscopy as a method of investigation of corrosion processes are as follows:

- uniqueness of information on the chemical and structural transformations during corrosion (in many cases different phases can be identified based on the spectral pattern);
- minimum requirements for sample preparation for analysis and studies;
- possibility of *in situ* studies in aggressive atmosphere and in aggressive liquids;
- possibility of layer-by-layer and phase analyses under coating (thickness of the layers under study can vary over a very wide range);
- the same types of contributions of X-ray amorphous and ultradisperse substances to the Mössbauer spectrum (similar to the contributions of well-crystallised compounds).

Owing to the advantages listed above, Mössbauer spectroscopy has found wide application in studies of corrosion processes, such as corrosion in gases,^{105–109} in water and aqueous solutions,^{110–112} in aggressive media,¹¹³ in studies of inhibition and passivation,^{114–116} internal oxidation and electrode reactions. The availability of Mössbauer spectroscopy also allows it to be employed in solving problems of analytical control, such as monitoring of corrosion of bridges^{117,118} and ship hulls,¹¹⁸ thermal and nuclear power plant circuits,^{117,119,120} etc. Here, the use of Mössbauer spectroscopy made it possible not only to determine the phase composition of oxide films that grow on the surface of pearlitic steels contacting the aqueous phase but also establish the interrelation between different forms of iron existing in the aqueous phase and the compositions of the films grown on the steel surfaces.^{119,120} Using Mössbauer spectroscopy, it was shown that the quality of protective corrosion films on the steel surfaces can be improved by targeted choice of the composition and structure of the dissolved iron compounds involved in film formation.^{119,120}

Mössbauer spectroscopy is a highly informative method of research on such surface phenomena as the catalytic activity, dynamics and chemical state of atoms in highly disperse particles, resins, zeolites, on the surface of sorbents and on surface-modified materials.^{17,121} The possibilities of using Mössbauer spectroscopy in studies of nanoclusters and nanocluster systems have been considered.¹²²

Mössbauer spectroscopy is employed in production of heterogeneous catalysts and in their characterisation, in analysis of the chemical state of the catalyst surface, in analysis of chemisorption products and in the course of catalyst operation. The use of X-ray diffraction methods in studies of real catalysts is complicated by the fact that catalysts are ultradisperse particles. Mössbauer spectroscopy is free from this limitation, which makes it possible to obtain information on the size and distribution of catalytic particles over the catalytically active phase.

Most often, solid catalysts comprise an active component coated on a support. The latter operate various functions, namely, provide the largest surface area to be coated with the active component, stabilise an unstable structure and interact, through

electron exchange, with the active component, thus forming a unique catalytic system. If the active component of a catalyst includes atoms with Mössbauer nuclei, information on the oxidation state of these atoms can be obtained from the chemical shift in the Mössbauer spectra. For instance, Mössbauer spectroscopy data show that iron supported by zeolite LTL is more catalytically active than iron supported by SiO_2 , Al_2O_3 , C and MgO .¹²³ The effect of the annealing temperature on the state of ^{191}Au atoms for two types of catalysts, Au/TiO_2 and $\text{Au/TiO}_2/\text{SiO}_2$, was studied,¹²⁴ as well as the mechanism of low-temperature oxidation of CO using $\text{Au/Fe}_2\text{O}_3$ as catalyst.¹²⁵ Recently, there has been new interest in studies of tin-containing catalysts. For instance, ^{119}Sn Mössbauer spectroscopy was employed to study the catalytic properties of the $\text{Pd-SnO/Al}_2\text{O}_3$ and Pd-SnO/SiO_2 systems designed for water denitration.^{126–128}

IX. Conclusion

Summing up, it should be noted that the examples given above do not exhaust the list of analytical applications of Mössbauer spectroscopy that can be found in special publications on the subject (see above). But it is almost impossible to draw a line between applications of Mössbauer spectroscopy in scientific research and in chemical analysis, because distinctions between these fields are rather conditional. Here, the method remains the same, the main goals being different. The results of basic research into outworld can appear to be in demand for chemical analysis after a very short time they have been obtained. For instance, information on the mechanisms of corrosion processes is necessary for control of technological processes. Therefore, in this review we deliberately do not draw this line. The examples given above illustrate the main avenues of applications of Mössbauer spectroscopy in chemistry, mineralogy, biology and materials science. Undoubtedly the list of examples will be appreciably extended in the future. Here, objects in which the Mössbauer effect was observed for the ^{57}Fe isotope were chosen to be the main part of illustrative material. This can be explained by not only high abundance of iron-containing objects (see above) but also the fact that in the last decade the vast majority of studies ($\sim 90\%$) were carried out with this isotope and therefore they are best to exemplify the range of analytical applications of Mössbauer spectroscopy. The next place is occupied by ^{119}Sn Mössbauer spectroscopy studies with $\sim 6\%–7\%$ of the total number of publications. A total of $3\%–4\%$ of the overall number of communications falls on the studies with other isotopes.

In connection with advances made in the field of excitation of nuclear resonance levels using synchrotron radiation one can hope that this will open new prospects for applications of nuclear γ -resonance for analytical purposes.^{129,130} First, the use of nuclear resonant scattering of synchrotron radiation eliminates problems associated with preparation of Mössbauer sources, especially short-lived ones. Second, auxiliary equipment on facilities for nuclear resonant scattering of synchrotron radiation makes it possible to carry out measurements in a wide range of temperatures, pressures, magnetic fields, in high vacuum, etc., and thus obtain a greater body of information on the object analysed. Particular information on great potential of nuclear resonant scattering of synchrotron radiation for obtaining analytical information can be found in recent literature.^{131–135}

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^a — *Phys. Solid State (Engl. Transl.)*

^b — *J. Exp. Theor. Phys. (Engl. Transl.)*

^c — *Moscow Univ. Bull. (Engl. Transl.)*

^d — *J. Struct. Chem. (Engl. Transl.)*

^e — *J. Anal. Chem. (Engl. Transl.)*

Analytical chromatography. Methods, instrumentation and applications

Ya I Yashin, A Ya Yashin

Contents

I. Introduction	329
II. Advances in the theory and general methodology	330
III. Development of new sorbents and instruments for chromatographic studies	330
IV. The main advantages of analytical chromatography	332
V. Chromatographic instrumentation	334
VI. Major application fields of analytical chromatography	335
VII. Conclusion	338

Abstract. The state-of-the-art and the prospects in the development of main methods of analytical chromatography, viz., gas, high performance liquid and ion chromatographic techniques, are characterised. Achievements of the past 10–15 years in the theory and general methodology of chromatography and also in the development of new sorbents, columns and chromatographic instruments are outlined. The use of chromatography in the environmental control, biology, medicine, pharmaceuticals, and also for monitoring the quality of foodstuffs and products of chemical, petrochemical and gas industries, etc. is considered. The bibliography includes 153 references.

I. Introduction

In the end of the 20th–beginning of the 21st century, analytical chemistry constantly faced the problems of the on-line environmental control, the monitoring of the quality and safety of foodstuffs and beverages and the quality and identity of drugs, as well as the problems of global safety associated with the destruction of chemical weapons, the prevention of terrorists' threats by the timely control over toxic agents and explosives in airports, railway stations and other crowded places and the detection of strong drugs. Chromatographic techniques played the key role in the solution of these problems.

Chromatography was discovered by the Russian botanist M S Tsvet in 1903.¹ In addition to being the pioneer of this method, he also developed in detail the methodological fundamentals of chromatography. Suffice it to say that Tsvet examined more than 100 different adsorbents. The procedure of chromatographic analysis he proposed was used for 50–60 years virtually without changes. His chromatographic columns were highly efficient. He also was the first to demonstrate the high effectiveness of multicolumn versions of chromatography. In 1931, R Kuhn, A Winterstein and E Lederer² repeated, in effect, the Tsvet's experiments and convinced in their great potential. Since

that, the rapid spread of the chromatographic techniques in European countries has begun.

In the first 50 years, chromatography was used either for the separation and isolation of pure substances or as a research method. Its wide use as an analytical technique started only in the second part of the 20th century.

In the period from 1937 to 1972, fourteen Nobel Prizes were awarded for the studies in chemistry, biology, physiology and medicine with chromatography as the key method. Undoubtedly, chromatography has contributed to the progress in many fields of science, technology and industry; this is why it is ranked among 20 outstanding discoveries of the twentieth century that had the greatest impact on the mankind life.

A combination of chromatographic techniques allows one to solve most analytical problems. Gases and volatile substances are well determined by gas chromatography; high-molecular compounds can be determined by high-performance liquid chromatography (HPLC); mixtures of ions (both cations and anions) are separated by ion chromatography and ion-pair chromatographic techniques and also by capillary electrophoresis; the separation of macromolecules (polymers, biopolymers) is carried out by the gel-permeation and exclusion chromatography; for the separation of optical isomers, the methods of chiral chromatography were developed, while the analysis of microparticles uses the methods of force-field fractionation.

The progress in the major chromatographic techniques (gas, liquid, ion chromatography) was very rapid. The literature contains numerous publications that describe the state-of-the-art and the prospects in the development of chromatographic techniques,^{3–5} the reviews devoted to the 20th anniversary of HPLC,⁶ the 25th anniversary of ion-exchange chromatography,⁷ the 30th anniversary of affinity chromatography,⁸ 40 years of gas-chromatographic instrumentation industry,⁹ 90 years of chromatography,¹⁰ 100 years of chromatography.^{11–13} The constant evolution of chromatographic methods was also surveyed.^{14–16} The place of chromatography among other analytical methods was discussed.¹⁷

The present review briefly analyses the most remarkable advances achieved over the past 10–15 years in the theory and general methodology of chromatography as well as in the development of new sorbents and instruments for chromatographic studies.

Ya I Yashin, A Ya Yashin Research Technical Centre 'Khromatografiya', Research and Industrial Association 'Khimavtomatika', ul. Sel'skokhozyaistvennaya 12a, 129226 Moscow, Russian Federation. Fax (7-495) 181 14 02, tel. (7-495) 181 53 27, e-mail: yashinchrom@mtu-net.ru (Ya I Yashin)

Received 19 September 2005

Uspekhi Khimii 75 (4) 366–379 (2006); translated by T Ya Safonova

II. Advances in the theory and general methodology

At present, the main efforts in the field of chromatographic theory are directed towards the problems associated with the selectivity of separation. First of all, the relationship between the structure of molecules and their retention on sorbents of different chemical nature is studied. Attempts are undertaken to develop a retention theory that would be general for the gas, liquid and supercritical fluid chromatographic techniques and also to advance the methods of theoretical modelling. Recently, the geometric factor was invoked for the enhancement of the selectivity of chromatographic separation, which involves the use of cyclodextrins, crown ethers, liquid crystals, molecular sieves, *etc.*

The degree of resolution R in chromatography is determined by the relationship

$$R \simeq \frac{1}{4} \left(\frac{\alpha - 1}{\alpha} \right) \left(\frac{K_e}{1 + K_e} \right) \sqrt{N},$$

where α is the separation factor equal to the ratio of the adjusted retention times for the separated substances, K_e is the retention factor equal to the ratio of the net retention volume to the free column volume, N is the number of theoretical plates. The comprehensive theory of elution made it possible to design columns with the efficiency close to the theoretical one (for both gas and liquid chromatography). Especially high efficiency is characteristic of the capillary versions of chromatography. Taking the average efficiencies (the number of theoretical plates per metre, t.p. m⁻¹) of packed columns to be 1.5×10^3 (for GC) and 5×10^4 (for HPLC) and the efficiency of capillary columns to be 4×10^3 (GC), 3×10^5 (HPLC) and $> 1 \times 10^6$ (capillary electrophoresis and capillary electrochromatography), it is possible to assess the maximum separation potential of columns in chromatography. The packed columns in GC allow only mixtures with $\alpha > 1.05$ to be separated, while capillary columns are capable of separating mixtures with $\alpha > 1.005$ in GC and $\alpha > 1.003$ in capillary electrophoresis.

The studies of the retention mechanism in the reversed-phase chromatography on bonded phases are carried on. For this purpose, spectral methods are invoked. A very promising direction is the optimisation of separation by using expert systems, which includes the optimisation of gradient elution. Considerable progress was achieved in the theory of separation of optical isomers (in both gas and liquid chromatography).^{18, 19}

The development of the theory of chromatography under critical conditions for the gel-filtration method is a considerable step forward.²⁰ Advances have been made in the establishment of a link between the retention parameters and the biological and chemical activity of molecules.²¹ This offers much promise in the field of pharmaceuticals at the quest for new drugs.

In recent years, the effect of the temperature on the retention in HPLC was studied, which led to the development of the high-temperature HPLC characterised by high resolution and fast performance. The elaboration of heat- and hydrolysis-resistant polymeric sorbents for this chromatographic version is in progress. At present, instruments are being developed that would allow the programmed control over the temperature in this method.[†] Of great importance is the optimisation of separation with simultaneous variations in the temperature and the eluent rate.²⁵

Databases containing retention indices in HPLC in which nitroalkanes and alkylbenzenes are used as standard substances are compiled.²⁶

The effect of the electric field on the retention and elution of compounds in the columns packed with carbonaceous sorbents was studied,²⁷ as well as the effect of the magnetic field on the retention in columns packed with magnetic particles.²⁸

[†] For the first application of high-temperature chromatography (at 200 °C) for analytical purposes, see Refs 22–24.

III. Development of new sorbents and instruments for chromatographic studies

1. Gas chromatography

The major achievements in GC include the synthesis of stable sorbents with chemically bonded (immobilised) phases for packed and capillary columns and the development and application of capillary columns of relatively large diameters (0.32 and 0.53 mm) and high capacities that contain bonded liquid-phase films with a thickness of up to 5 μ m (and even up to 16 μ m)²⁹ and also of porous layer open tubular columns PoraPLOT with a fixed adsorption layer of silica or alumina, zeolyte, carbonaceous sorbents and porous polymers.³⁰

For such stable columns, the databases (libraries) of the retention parameters can be created to help the identification of unknown components in a mixture. A combination of these databases with those of mass spectra allows valuable information to be retrieved.³¹ By and large, the development of stable chromatographic columns resulted in the higher reliability and accuracy of the chromatographic analyses. Determination of microimpurities on capillary columns can be made using the methods that allow introducing large samples into the columns (on-column injection, cryofocusing, sampling with the solvent blow-out, *etc.*).³² The electronic control over the carrier-gas rate and the pressure was beneficial for the stable operation of chromatographs. This allowed an automated programme for maintenance of the retention time upon changeover of columns to be developed.³³

Recently, the analytical practice was supplemented with poly-capillary columns,[‡] which allow quick separation of mixtures to be carried out without programming the column temperature.³⁴ The use of adsorption polycapillary columns was documented.³⁵

2. Liquid chromatography

The recent progress in analytical liquid chromatography was associated with the development and the use of methods of high-performance capillary chromatography that combines the chromatographic and electrophoretic separation methods.³⁶ It is due to the coupling of various methods of liquid chromatography and capillary electrophoresis that the nucleotide sequence in DNA was decoded and the programme 'Human genome' was completed.³⁷

The potentials of liquid chromatography are substantially extended with the introduction of chiral,³⁸ immunoaffinity,³⁹ high-temperature⁴⁰ and perfusion⁴¹ chromatographic techniques. The quick chromatographic analysis of proteins on non-porous particles deserves attention.⁴²

The active development of new highly stable and selective sorbents based on dioxides of zirconium and titanium, porous polymers and carbonaceous adsorbents, which are stable over the whole pH range, is in progress.⁴³ For HPLC, a wide spectrum of sorbents are developed and manufactured. Dozens of companies all over the world produce more than 300 sorbent types. Most often (in 70% of cases), HPLC columns are packed with silica gels both pure and grafted with non-polar and polar groups (their fraction is 70%). Styrene–divinylbenzene copolymers, polymethacrylates, celluloses, *etc.* are used less often (20%), as well as porous carbonaceous sorbents and porous oxides of titanium and zirconium (4%) and alumina (1%).

The reversed-phase HPLC version, which employs silica gel sorbents with immobilised alkyl groups (the alkyl chain length varies from C₁ to C₃₄, C₁₈ and C₈ being the most common), finds wide application in the analytical practice (more than 70% of chromatographic analyses are carried out using this LC version).

Depending on the synthetic method, the C₁₈ sorbents can be either monomeric or polymeric. Polymeric C₁₈ sorbents are synthesised from trifunctional silanes in the presence of water, while monomeric sorbents are prepared from monofunctional

[‡] The discovery by Novosibirsk scientists [USSR P. 2986181 (1980)].

silanes. In certain cases, particularly, in the separation of complex mixtures of isomers, polynuclear aromatic hydrocarbons, the polymeric C_{18} sorbents are preferred. The retention capacity and the selectivity of monomeric C_{18} with respect to non-polar and weakly polar compounds depend on the number of immobilised alkyl chains (or on the total content of carbon per the sorbent mass unit, which varies from 8% to 20%). Small percentage of carbon leads to the small sorption capacity, fast separation and the rapid establishment of the equilibrium during the gradient elution.

However, silica-gel-based sorbents with immobilised alkyl groups have many drawbacks. They are unstable in acidic and alkaline media, *viz.*, their Si—O—Si bonds are hydrolysed at pH < 3 and silica gel is dissolved at pH > 10 (especially at high temperatures). These sorbents are non-selective with respect to the separation of polar compounds and isomers, while the characteristics of basic compounds determined on these sorbents substantially depend on the purity, geometry and chemical nature of silica gels as well as on the method used for the immobilisation of alkyl groups, *etc.*

In recent years, great efforts are made to overcome these drawbacks. First of all, the manufacturing of original silica gels is modernised. The production of special grade silica gels (containing minute amounts of heavy metals) with spherical particles, the composition of which remains invariant from batch to batch, is organised. Unfortunately, not all hydroxyl groups in silica gels are completely substituted. The residual hydroxyl groups can take part in parasitic interactions with small polar molecules, giving rise to asymmetric peaks. It was proposed to block the OH groups with bulky isopropyl or isobutyl groups (the sorbent Zorbax Stable Bond). It is also possible to block hydroxyl groups by bonding the silica gel with bidentate reagents where two neighbouring alkyl groups are linked by a bridge of 3–4 methylene groups. These bridges shield the OH groups, making silica gels much more stable and capable of operating even at high pH (Zorbax Extend- C_{18}). For the sorbents based on silica gels that contain immobilised alkyl groups, the selectivity with respect to polar compounds can be enhanced by modifying their alkyl chains with polar groups, particularly, carbamide groups.

Silica gels with the average pore size of 80, 100 and 120 Å are used in the separation of low-molecular compounds, those with pores of ≥ 300 Å are applied for the separation of high-molecular compounds and biopolymers. Thus, a silica gel modified with C_{30} -alkyl groups was used for the separation of polynuclear aromatic compounds, oligonucleotides, fullerenes and alkylbenzenes.

Among other sorbents applied in the reversed-phase chromatography, the polyethylene glycol-based sorbents, which are used in the separation of phenolic compounds, deserve attention, as well as the perfluorinated sorbents for the analysis of halogen-containing compounds.

Polymeric sorbents based of poly(divinylbenzene) with 500-Å and 1000-Å pores were proposed (Jordi).

Today, hundreds of sorbent types are manufactured. To choose a sorbent for reversed-phase chromatography, different estimation procedures were developed.

The development of columns for turbulent chromatography should be assigned to the achievements of recent years. In columns 1-mm in diameter packed with 50- μ m particles, high-velocity flows are employed; large molecules of proteins are not retained, while small molecules have time enough to diffuse into pores and are retained.

In the recent decade, considerable progress was achieved in the synthesis of new types of sorbents and the construction of columns for HPLC. Particularly, sorbents for perfusion chromatography and monolithic columns with a unified porous block based on polymeric materials or silica gels were developed.

The first application of perfusion chromatography dates back to 1990; its theory was developed later. Perfusion chromatography is conventionally used in the preparative isolation of substances (specifically, proteins) in their pure state and, to a

lesser extent, for analytical purposes (particularly, for the analysis of food proteins). Perfusion columns are considered as intermediate between the conventional packed columns and monolithic ones. In perfusion columns, the eluent flows through the sorbent grains rather than around them as in conventional packed columns. In perfusion chromatography, styrene–divinylbenzene copolymers are used as the sorbents. Such sorbents have the shape of beads ~ 20 μ m in diameter with two kinds of pores, namely, large pores (6000–8000 Å), along which the eluent percolates through the sorbent, and diffusion pores (800–1500 Å), through which the substances easily penetrate into the sorbent. Due to the enhanced mass transfer in perfusion columns, high eluent rates can be used, which reduces the separation time. This is especially important for large molecules. At present, perfusion sorbents are produced for various types of chromatography, namely, for reversed-phase, normal-phase, ion, hydrophobic and affinity versions.

In monolithic columns, the sorption layer represents a continuous rigid porous rod. Polystyrene, styrene–divinylbenzene copolymers, polyacrylates, polymethacrylates (PMA), poly(glycidyl methacrylate), poly(ethylene dimethacrylate), *etc.* are used as the materials (Table 1). Monolithic columns of large diameters (> 5 cm) are manufactured for preparative purposes. Special monolithic columns are developed for the separation of enantiomers as well as for polypeptides and polynucleotides. A new generation of monolithic columns based on silica gels of the Chromolith type were developed. In 2001, a series of analytical monolithic columns (Chromolith Performance RP-18e, Chromolith Flash RP-18e, *etc.*, Merk, column size 100 $\times$ 4.6 mm, 50 $\times$ 4.6 mm, 25 $\times$ 4.6 mm) was rewarded with a gold medal at the Pittsburg Conference as the best product. These columns can operate at high eluent flow rates without sacrifice in separation, moreover, the input pressure is substantially lower as compared with packed columns. Chromolith RP-18e columns are suitable for the separation of acidic, basic and non-polar compounds.

Table 1. Monolithic chromatographic columns used in reversed-phase chromatography.

Name	Shape	Manufacturing company	Material
CIM-Disk	disk	BIA Separations	PMA and PS
CB Silica Plate	"	ConChrom	silica gel
Onyx	cylinder	Phenomenex	silica gel
SWIFT	"	ISCO	PMA and PS
Chromolith	"	Merck	silica gel
Monoliths	"	LC Packing	PS

For the sorption of only one type of molecules or a group of related molecules, the sorbents with molecular-size pores (SMSP) were developed. The major method of SMSP preparation is polymerisation of methacrylic acid or ethylene dimethacrylate. These selective sorbents are applied for the separation and preconcentration (such separation relies on the principle of molecular recognition). They selectively bind non-polar super-toxic agents, particularly, 2,3,7,8-tetrachlorodibenzodioxine, and are well suited for the selective concentration of noxious substances (*e.g.*, pesticides), as well as for the concentration and separation of medicinal drugs. Special SMSPs allowed successful separation of phenylalanine and tryptophane.

A template technology for the production of macroporous carbon sorbents with the surfaces resembling that of graphitised thermal carbon black was developed. Macroporous 5- μ m silica gel beads were used as the templates. The pores in such particles were filled with a phenol–formaldehyde polymer, after which the polymer was carbonised by heating to 1000 °C in an inert medium so that the pores turned out to be filled with carbon. Then, silica gel was dissolved in 5 M NaOH to produce a macroporous carbon sorbent, a mirror replica of the porous silica gel. Unfortunately, in

this stage, the carbon sorbent contained too small pores (measuring 30 Å), which were hardly suitable for HPLC, and also had the amorphous surface (specific surface area of $\sim 400 \text{ m}^2 \text{ g}^{-1}$). Graphitisation at temperatures above 2000 °C led to the total restructurisation of the carbon sorbent, particularly, to the disappearance of micropores and the formation of a uniform crystalline surface. Upon the graphitisation, only those pores retained that were present in the original silica gel. Fractionation was the final technological step.

The commercially produced sorbents called 'Hypercarb' (Shendon) have the specific surface of $\sim 120 \text{ m}^2 \text{ g}^{-1}$, the average pore diameter is $\sim 250 \text{ Å}$, the volume of pores amounts to 75% and the particle size is 5 or 7 μm . This sorbent is stable throughout the pH range (0–14), it is neither dissolved, nor hydrolysed, nor swelled in the solvent and withstands pressures up to 400 atm. Columns packed with Hypercarb are highly efficient, *viz.*, up to 60 000 theoretical plates.

At present, the Hypercarb sorbent is widely used for the separation and the analysis of different mixtures, namely, aromatic compounds, various pharmaceuticals, cations and anions, as well as structural isomers. Hypercarb has no drawbacks typical of the C_{18} sorbent in reversed-phase chromatography; particularly, polar compounds are well retained in Hypercarb-packed columns. For example, the retention factor is 1.8 for phenol, 2.35 for resorcinol and 2.7 for 1,3,5-trihydroxybenzene. The latter two compounds could not be separated on the C_{18} column. In addition, Hypercarb can be used for the separation of carbohydrates and compounds containing carboxyl and amino groups.

In recent years, size-exclusion chromatography was actively developed, which was favoured by the introduction into the chromatographic analysis practice of Sephadexes, *i.e.*, dextran gels cross-linked with epichlorohydrin. Sephadexes are extensively used in medicine.

To date, the HPLC techniques are actively used in proteomics,⁴⁴ in the metabolism studies,⁴⁵ as well as for the determination of the components of a single cell.⁴⁶

3. Ion chromatography^{47,48}

The main achievements of ion chromatography include the development of fast monolithic columns for superfast separation of substances, particularly, inorganic anions (H_2PO_4^- , Cl^- , NO_2^- , Br^- , NO_3^- , ClO_3^- , I^- , SO_4^{2-}) and columns for the simultaneous separation and detection of anions and cations; synthesis of sorbents for micropacked and capillary columns; the extension of the array of detection systems used in ion chromatographs (up to 10 types), particularly, the development of pulsed amperometric detectors for the determination of carbohydrates, amino acids, biogenic amines and alcohols; the development of the eluent generator (the add-only-water system) and a 10-port valve for the analysis of samples with widely different concentrations; the use of non-metallic materials (ceramics, PEEK plastics, sapphire, PTFE, *etc.*) in pumps and liquid tracts in ion chromatographs; the introduction into practice of a 'heart-cut' system for the partial disposal of the sample to prevent its entering into the column; the increase in the sensitivity and stability of detection systems in the determination of ions down to the ppt level (1 ppt = $1 \times 10^{-10}\%$).

4. Thin-layer chromatography

Conventional thin-layer chromatography (TLC) represents a popular, simple and cheap chromatographic technique used for the detection and determination of different classes of substances.^{49–51} In TLC, the separation is usually carried out on glass, metal or plastic plates measuring 100 × 100 mm and covered with an adsorbent layer 50–300 μm thick and containing 3–15 μm grains. At present, the following four types of plates are used most often: classical, high-performance, microplates and preparative.

Silica gels as such and containing immobilised alkyl groups, alumina, cellulose, cyclodextrins, Florisil (magnesium silicate), inorganic ion-exchangers, *etc.* are used most often as the adsorbents. The main advantages of TLC include the simultaneous

parallel separation of several samples (up to 10 and more), high efficiency, the possibility of two-dimensional separation and the fast and cheap determination. Yet another positive feature is the possibility to observe the separation process, in particular, see the remainders of a non-soluble sample at the application point. The drawbacks of TLC include the exposedness of the separation plates to atmosphere, which may result in the decomposition of easily oxidisable and hydrolysable compounds.

The detection of spots on a plate involves the use of different methods including mass spectrometry, Raman spectrometry, spectrophotometry with diode matrices, plasma-ionisation detectors, fluorescence indicators. Electrochemical detection is also used.

In recent years, the TLC techniques were constantly developed and improved. New TLC versions were proposed, namely, polyamide, thin-film, high-performance, rotation, two-dimensional, micellar, flow-through, *etc.*^{52,53} Densitometers were developed for the quantitative TLC determination of substances. Chiral plates are used for the separation of optical isomers.

The standardisation of TLC procedures, namely, pretreatment of adsorbents, preparation of plates, the processing of the results of separation favoured the introduction of TLC into the wide practice of analytical laboratories in many industrial fields.

IV. The main advantages of analytical chromatography

According to Zolotov,⁵⁴ chromatography pertains to the hybrid analytical methods. In chromatographs, the analysed mixture is preliminarily separated on a column due to the different sorption ability of the mixture components, then, at the column outlet, a sensitive element, *viz.*, a detector, registers each of the separated components.

Insofar as the separation capacity of modern chromatographic columns is extremely high (tens and even hundreds of components of a mixture can be separated), the modern chromatography has no rivals in the analysis of complex natural and industrial multicomponent mixtures. In principle, it allows the separation of any mixtures of molecules including all kinds of isomers, particularly, enantiomers, to be performed. However, chromatography has to pay a price for this advantage, namely, this analytical method is indirect rather than direct. The point is that the initial concentration of a substance in the original mixture by no means remains unchanged. Following the injection to the chromatograph, a component is diluted with the eluent and then is spread over the column due to diffusion and kinetic factors. At the outlet, the detector measures a concentration different from the initial one. This situation calls for the calibration in order to establish the relationship between the initial concentration of a substance and that at the outlet from the column.

Yet another peculiarity of analytical chromatographic techniques is their periodicity.

Let us consider the advantages of chromatography over other analytical methods.

1. Versatility and high separation capacity

Chromatographic methods allow virtually all kinds of mixtures to be separated and analysed.[§] Modern chromatographic techniques exhibit high separation capacities. They make it possible to separate multicomponent mixtures including complex mixtures formed by all kinds of isomers and also certain isotopes and isotopically substituted compounds.

Gas chromatography allows more than a thousand of components in gasoline fractions to be separated from a single injection; two-dimensional high-performance TLC makes it possible to separate hundreds and even thousands of components; capillary

§ It is evident that in this case only those mixtures can be analysed that can be separated in principle.

electrochromatography allows the separation of more than a thousand of proteins (the majority of scientists working in the proteomics field are confident that coupling of HPLC with tandem mass spectrometry would provide a rapid breakthrough in proteomics).

2. Low detection limits (high sensitivity)

Among the advantages of chromatography is its compatibility with almost all analytical methods known. However, this cannot be the grounds for the comparison of chromatography with other modern analytical methods, because chromatography employs all the achievement of these methods. At the same time, it is within the latter methods that the sensitive flow-through cells were developed specially designed for the chromatographic applications and the procedures were modernised to fit chromatographic techniques.

For chromatographic techniques, various detection systems, both versatile and selective (specific) were developed. Table 2 shows the detectors used most often in gas chromatographs. In addition to those listed in the table, the Hall electrolytic, chemiluminescence, infrared, fluorescence, helium ionisation, radioactive and ultrasonic detectors are used, as well as densitometers. In total, more than 50 types of detectors are known. The most sensitive of them make it possible to determine impurities at a level of $10^{-5}\%$ – $10^{-7}\%$ without preconcentration.

Selective detectors have a great advantage in the determination of impurities in complex mixtures. It is possible to provide the conditions where the impurities would be determined, while the basic substances in the mixture would not, for instance, in the determination of chlorine-containing organic pesticides in the environment by means of an electron-capture detector.

In HPLC, the detection schemes based on almost all determination methods are used. Table 3 shows the detectors used in high-performance liquid chromatographs. Under favourable conditions, the electrochemical and fluorescence detectors allow determining impurities at a level of pico- or femtograms (10^{-12} – 10^{-15} g) without preconcentration.

Unfortunately, even most sensitive detection systems fail to determine microamounts of certain environmental pollutants, for example, supertoxicants. In this case, the methods of preliminary concentration of samples are used, which makes it possible to reduce the detection limits by two–four orders of magnitude and determine certain contaminants, *e.g.*, dioxins, at the ppt level.

In the past decade, the interest in the concentration methods increased [they were the subject of a monograph⁵⁵ and several reviews (*e.g.*, see Refs 56–59)]. The conventional methods of concentration are modernised, new methods are proposed and new instruments are developed.

Earlier, the liquid–liquid extraction has been used for the preconcentration; however, since this method required very expensive special-grade solvents and sometimes did not provide the complete extraction, which necessitated the regeneration or utilisation of great amounts of solvent wastes, its current application in the classical version progressively decreases. Today, the following new methods of liquid extraction are used: the extraction with small amounts of solvents (merely several millilitres) in a special vessel; the extraction with small amounts of solvents at elevated pressures and temperatures under dynamic conditions (the instrumentation resembles that used in liquid chromatographs); the extraction with a single drop of an organic solvent in water; the extraction with superhot water[¶] under elevated pressure (the dynamic version is possible). In the latter case, the utilisation presents no special problems, because water is 'friendly' to the environment.

At present, the solid-phase extraction occupies the first place in the popularity, because this provides more efficient (nearly 100%) extraction of microcomponents, makes the automation of the preconcentration procedure possible and allows direct coupling with chromatographs in the on-line mode. Various polymeric, carbonaceous and inorganic sorbents (polar, non-polar and ion-exchange) were developed for the solid-phase extraction.⁶⁰ Many companies manufacture filters of large diameters and 96-cartridge kits for performing concentration from large volumes.

The determination of impurities in aqueous media effectively employs the solid-phase microextraction, *i.e.*, the preconcentration on a sorption-layer-coated rod, which is drawn out from the tip of a special syringe. In those cases where selective solid-phase extraction is required solely for the determination of a certain class of compounds or even a single compound, the methods of ion-pair⁶¹ and immunoaffinity⁶² solid-phase extraction are used. In recent years, technologies for the synthesis of porous polymers with molecular-scale pores of fixed sizes have been actively

¶ High temperatures increase the solubility of non-polar compounds in water.

Table 2. Technological characteristics of detectors used most frequently in GC.

Detector	Detection limit /g s ⁻¹	LDR ^a	Detector type	Determined compounds
Flame-ionisation (FID)	2×10^{-12}	10^7	selective	organic compounds ionisable in the hydrogen flame
Heat conductivity (DHC, katharometer)	4×10^{-10} (see ^b)	10^6	universal	all compounds differing in heat conductivity from that of the carrier gas
Electron-capture (ECD)	1×10^{-14}	10^3 – 10^4	selective	mainly organohalogen compounds
Photoionisation (PID) ^c	2×10^{-12}	10^7	"	all compounds with ionisation potential below 10.7 eV
Thermoionic (TID)	4×10^{-13} (for N), 2×10^{-13} (for P)	10^4	"	heterocyclic compounds containing N and P atoms
Flame-photometric (FPD)	2×10^{-11} (for S), 9×10^{-13} (for P)	10^3 10^4	specific	S- and P-Containing compounds
Atomic-emission (AED)	2×10^{-11} – 1×10^{-13}	10^4	universal	all compounds containing 12 basic elements (H, C, O, S, N, P, <i>etc.</i>)
Mass spectrometric (MSD) ^d	1×10^{-9} – 1×10^{-11}	10^5	"	all compounds

^a LDR is linear dynamic range; ^b in g ml⁻¹; ^c UV radiation; ^d identifies a compound from its mass spectrum.

Table 3. Technological characteristics of detectors applied in HPLC.

Detector	Detection limit /mol litre ⁻¹	Selectivity	Advantages and drawbacks
Coulometric	10 ⁻¹¹ –10 ⁻¹²	high	three-dimensional signals can be recorded; complete oxidation or reduction of the determined substance
Amperometric	10 ⁻¹⁰ –10 ⁻¹¹	"	low cost; selectivity with respect to electroactive compounds
Mass spectrometric	10 ⁻¹⁰	very high	allows identification of unknown compounds; high cost
Fluorescence	10 ⁻⁷ –10 ⁻¹⁰	high	many mixtures should be derivatised; high cost
Chemiluminescence	10 ⁻⁷ –10 ⁻¹⁰	very high	high cost; limited application (only for N- and S-containing compounds)
Spectrophotometric with diode arrays	10 ⁻⁶ –10 ⁻⁷	high	possibility of recording three-dimensional signals; high cost
Spectrophotometric	10 ⁻⁵ –10 ⁻⁷	low	low cost, versatility
Light-scattering-based	10 ⁻⁴ –10 ⁻⁵	"	versatility
Refractometric	10 ⁻⁵	"	versatile detector very sensitive with respect to the temperature and eluent rate variations

developed, aimed at the extraction of the molecules with dimensions corresponding to the pore sizes.

The supercritical fluid extraction is a very promising method;⁶³ however, its instrumentation is very expensive. The supercritical fluid extraction utilises substances at the temperatures and pressures above the critical points. Carbon dioxide is used most often. The potential prospects of the application of the extraction with supercritical CO₂ in the recycling of nuclear fuel wastes were demonstrated.

The preconcentration of light admixtures from solutions is carried out most often by gas (head-space) extraction, which is adequately automated. The method itself and its instrumentation are constantly improved. In particular, the procedure of gas extraction at high temperatures and coupling of gas extraction with solid-phase microextraction were developed as well as other procedures.⁶⁴ Among the dynamic versions of extraction, mention should be made of the purge-and-trap methods⁶⁵ and also the membrane extraction,⁶⁶ which allows the continuous isolation of microcomponents from the flows.

3. Reproducibility of determination and express separation

Modern chromatographs make possible achieving good reproducibility of measured quantities. For the best instruments, the relative standard deviation of the retention parameters on capillary columns can reach record-breaking values, *viz.*, 0.1% and even 0.01%.

For ordinary chromatographs, the root-mean-square deviation of retention parameters and peak heights and areas lies normally within 1%–3%. For the determination of microimpurities, these values are, naturally, larger.

Chromatographic techniques are used most often for the determination of microcomponents (10⁻¹%–10⁻¹⁰%). For the impurity contents within 10⁻¹%–10⁻⁵%, the relative standard deviations of commercial chromatographs are quite comparable with those provided by other methods.

Most often, the duration of separation and determination is within 5–30 min. In this period, tens and even hundreds of substances are separated and determined. Recalculated per a single substance, the analysis is in the range of minutes. At present, the methods for rapid separation, which allow several dozen of components to be separated in two minutes, are developed for GC, HPLC, TLC and capillary electrochromatography.^{67–70}

V. Chromatographic instrumentation

The advances of analytical chromatography are largely associated with the modernisation of the chromatographic instrumentation. The wide distribution of one or another chromatographic technique in the analytical practice was closely related with the commercial production of the corresponding chromatographs. Thus the development by Moore and Stein in 1956 of an amino acid analyser based on ion-exchange chromatography, post-column derivation and photometric detection gave impetus to its wide application in the analysis of amino acid mixtures. The commercial production of gas chromatographs in many countries in 1955–1960 determined the boom in the application of gas chromatography in numerous fields of science and technology. The development in 1965–1970 of high-pressure pumps, flow-through liquid detectors, columns packed with stable fine-grain sorbents and other parts of modern liquid chromatographs made it possible to convert the classical liquid chromatography into a rapid high-performance technique that meets the analytical goals.

In the end of the 20th century, the chromatographic instrumentation represented an individual, sufficiently large industrial branch. Hundreds of companies all over the world produced different types of chromatographs and accessories for the total sum of above USD 10 billions.

The chromatographic instrumentation has reached a very high level; the control over the analysis and the processing of its results are carried out on the basis of microprocessors, most procedures are automated. These instruments employ the latest achievements of electronics, fine mechanics, pneumatics, planar technology and optics.

The commercial production of gas chromatograph–mass spectrometers (GC-MS) is the major achievement in chromatographic instrumentation. Recently, mass spectrometers have occupied a prominent place among detectors for gas chromatographs, they are constantly modernised and their cost decreases. Annually, 3000–3500 such detectors are sold, 80% of which are quadrupole and the other are equipped with ion traps. Their considerable part (above 25%) are used in the environmental control.⁷¹ Table 4 shows the major types of gas chromatographs, which include analytical laboratory instruments, industrial, portable, preparative and multidimensional chromatographs, chromatographs as the gas analysers, GC-MS, GC-IRS and radiochromatographs.^{1, 72}

Table 4. Basic types of gas chromatographs.

Basic types of chromatographs	Functions	Advantages, specific features
Laboratory	for stationary laboratories	wide set of accessories and options
Industrial, automatic	for monitoring industrial processes	in most cases, explosion-proof construction
Two-dimensional, multi-dimensional	for complete separation of complex multicomponent mixtures	separation on twin columns of different selectivity
Chromatographs mass spectrometers	for identification of already separated compounds	quantitative and qualitative analysis of unknown mixtures
Compact	for mobile and stationary laboratories	economy without reducing analytical characteristics, low weight (10–25 kg)
Portable, mobile, field	for on-the-site analysis	high rate analysis with autonomous power and gas supply, low weight (5–15 kg)
Chip-based microchromatographs (silicon-based technology) personal, pocket-size	the same	rapid analysis, complete autonomy, small weight (0.2–3 kg); used only for simple tasks
Special microchromatographs	for space studies	automated analysis, shock- and shake-resistant

To extend their analytical potential, the gas chromatographs are also equipped with sets of additional options, namely, instruments for the sample preconcentration (units for solid-phase, solid-phase micro-, supercritical and gas extraction, systems for purge-and-trap, *etc.*), supplemental sampling systems (autosamplers, cryofocusing systems, gas valves), facilities for the pyrolysis, pre- and postcolumn derivatisation (*e.g.*, methanators, *etc.*).

The main achievements involve the development of portable field chromatographs,⁷³ portable industrial devices in the explosion-proof versions, thermostats with new methods of heating (microwave, IR-radiation), instruments with the temperature programming facilities for the direct heating of columns, new methods and instruments for feeding large samples into capillary columns (cryofocusing, solvent blow-out, programmed heating, on-column introduction), and also the development and introduction into analytical practice of large-diameter (0.53 mm) capillary columns with thick bonded layers of stationary phases (up to 5 μm) and capillary adsorption columns with layer thickness of up to 10–20 μm of the PoraPlot type,^{74,75} the use of electronic control over the gas flow rate and pressure, *etc.*

The development of instruments for the analytical liquid chromatography started 15 years later than that for gas chromatography; nonetheless, its current production and market exceed those of gas chromatographs. Among liquid chromatographs, mention should be made of high-pressure liquid chromatographs (closed systems), gradient, isocratic, ion, exclusion, microcolumn, counter-current, multidimensional and high-temperature chromatographs, instruments for HPLC-MS, *etc.* (nearly 20 types of instruments). Commercial liquid chromatographs can be equipped simultaneously with several detection systems, *viz.*, optical, electrochemical, fluorescence, mass spectrometric, elemental, gas-chromatographic, immune, *etc.* The lowest detection limits (below several femtomoles or attomoles) are typical of electrochemical (coulometric and amperometric) liquid chromatographs.

Special mention should be made of the development of chromatographs for HPLC-MS. This method is actively developed since 1990. At present, sufficiently reliable and sensitive systems based on the electrospray ionisation at ambient pressure are developed, which are suitable for wide analytical application. The 2001 Nobel Prize was awarded for the development of these systems and their use in biochemical studies. The HPLC-MS technique has found the wide application in pharmaceuticals, medicine, in the analysis of herbs, in biology and biotechnology (particularly, in proteomics). As the mass analysers in HPLC-MS,

the quadrupole, ion, time-of-flight, magnetic (sector), and other traps are used.^{71,72}

VI. Major application fields of analytical chromatography

Undeniably, the chromatographic methods occupied the leading position among other analytical methods in the past decade.⁷⁶

According to publications of the last 20 years, gas chromatography was largely applied for the analysis of environmental objects (12.5%), foodstuffs and beverages (10%), medicinal drugs (10%), for clinical studies (4%), in forensic medicine (3.5%) and for the determination of enantiomers (2.5%). Moreover, it was widely used in the gas, chemical and petrochemical industries, although only few publications were devoted to these issues.

The detection and identification of biological compounds (in particular, amino acids, proteins, lipids, carbohydrates, vitamins, steroids, *etc.*) is the main application field of HPLC (> 50% publications). Among the other application fields, mention should be made of the analysis of medicinal drugs (16%) and the products of chemical and petrochemical industries (more than 10%), the separation and determination of enantiomers (5.5%), the analysis of inorganic compounds (mainly the determination of anions and cations by the ion technique), the analysis of foodstuffs and beverages (4.5%), in the environmental control (3%), clinical analyses (2.8%) and in toxicology (1.3%).

At present, there are virtually no fields in industry, science and technology that do not apply chromatographic techniques. Here, we list the most important advances achieved with the use of chromatographic methods:

- decoding of the human genome;
- separation of multicomponent protein mixtures for the proteomics purposes;
- analysis of the components of a single cell;
- studies in the field of pharmacokinetics (studies of the effect of drugs on the human organism);
- early recognition of diseases (detection and identification of biochemical markers);
- separation of optical isomers, analysis of the enantiomeric purity of medicinal drugs;
- doping-control of sportsmen;
- forensic and medical tests, detection of drugs;
- environmental control, which includes the monitoring of supertoxicants (dioxins, polychlorinated biphenyls, polynuclear aromatic compounds at the ppt level);

— purity control of foodstuffs and beverages, including the detection of most dangerous mycotoxins, nitrosamines, pesticides, *etc.*;

— studies of the components in smells and aromas of foodstuffs and beverages;

— analysis of natural gas, gas condensate, gasoline, kerosene, mineral oils and crude oil; simulation of oil distillation;

— separation and determination of metal ions, including transuranic ions;

— complete analysis of the polluted urban atmosphere;

— determination of Freons in the stratosphere;

— detection and identification of insect pheromones;

— analysis of atmospheres and soils of other planets (Venus, Mars and Moon);

— studies of isotopically substituted compounds.

Below, some of these achievements are discussed in detail.

1. Environmental analysis^{77–81}

Gas chromatography coupled with mass spectrometry is used for the detection and quantitation of organic impurities in the atmosphere of large industrial cities. The impurities are first concentrated on non-polar sorbents that do not retain moisture, then, desorbed and collected at the top of a capillary column (cryofocusing), separated with temperature programming and, finally, detected and identified using a mass spectrometric detector.

Harmful gases in the atmosphere (NO_2 , SO_2 , SO_3 , HCl , HF , Cl_2 , NH_3 , *etc.*) are determined using gas and ion chromatographs. Petrochemicals, being the abundant contaminants of water and soil, are determined most often using certified HPLC methods. Residual pesticides in the environment are determined in most cases by GC, HPLC and TLC techniques. Thousands of analyses are carried out at plant protection stations, veterinary laboratories and various environmental centres.

Carcinogens, namely, certain chlorine-containing organic compounds[†] and aromatic compounds, phthalates, polyamines, *etc.*, are the most hazardous environmental pollutants. Their detection and quantitation in water, air and soil involves most often the use of GC and HPLC techniques. For example, polynuclear organic compounds (*e.g.*, 3,4-benzopyrene) are determined in water and soil by HPLC, while benzene, toluene, ethylbenzene and xylenes in the urban atmosphere are determined by means of GC equipped with photoionisation detectors. Phenol and its derivatives can be determined at the MPC level with a liquid chromatograph 'TsvetYauza' equipped with an amperometric detector. This instrument was also used for the determination of cyanide ions in drinking water.⁸¹

All major anions in drinking water are determined using ion chromatography (in 10–15 min at a level of $1 \times 10^{-4}\%$ – $1 \times 10^{-5}\%$), while volatile chlorine-containing organic compounds are determined by the GC method combined with head space analysis. Ion chromatography is also used in the determination of nitrates and heavy metals in water and soil.

2. Quality control of foodstuffs and beverages

The quality and safety control of foodstuffs is at present among the topical problems of analytical chemistry. In certain sense, it is even more important that the problem of environmental control, because, according to scientists, more than 70% of toxic impurities get into a human organism with food, 20%, with water and 10%, with inspired air.⁸² In addition to technological contaminants that get into foodstuffs through soil, water and air, the foodstuffs can also contain natural contaminants that either are formed during their improper storage, due to failures in the food

processing technology or get into them through the wrapping, *etc.*^{83, 84}

Currently, the safety of people (especially in Russia[‡] largely depends on the cleanness and quality of foodstuffs, spirits and non-alcoholic beverages, because many contaminants possess carcinogenic, mutagenic, teratogenic and immunosuppressive properties. In addition to direct poisoning, the contaminated foodstuffs can reduce the immunity and cause hereditary changes. In some cases, they can directly cause diseases (allergic, oncological, cardiovascular, *etc.*) as a result of the changes in the biochemical reactions in the organism.

The monitoring of the foodstuff quality often involves using chromatographic techniques.^{85, 86} The latter are used to control the quality and freshness of foodstuffs, determine the technological and natural contaminants, reveal counterfeit foodstuffs and determine synthetic dietary supplements and residual veterinary drugs in meat (Table. 5).

Table 5. Main applications of chromatographic techniques in the food-stuff monitoring.

Analysis goal	Determined compounds	Ref.
Determination of nutrition validity of products	food proteins	87
	amino acids	88
	lipids	89
	organic acids	90
	carbohydrates	91
	vitamins	92
Determination of impurities in foodstuffs	carotenoids	93
	pesticides	94
	mycotoxins including:	95
	aflatoxins	96
	patulin	97
	ochratoxins	98
	fumonizins	99
	zearalinon	100
	nitrosoamines	101
	polynuclear aromatic hydrocarbons	102
	dioxins	103
Determination of dietary supplements	biogenic amines	104
	antioxidants	105
	synthetic dyes	106
	sweeteners	107
	aromatisers	108
Determination of residual veterinary drugs in foodstuffs	bitter substances	109
	antibiotics (tetracycline, <i>etc.</i>)	110
	sulfamide drugs	111
	hormones	112
	anabolic steroids	113
	cytostatin	82

A new direction, the enantioselective analysis of food components, has appeared, which, based on the ratio of optical isomers of amino acids, hydroxy acids, *etc.*, makes it possible to infer whether a given foodstuff is natural or contains synthetic substitutes and additives. For instance, the development of a procedure of gas chromatographic separation and analysis for all fatty acid isomers has forced the manufactures to reduce several-fold the content of *trans*-isomers of unsaturated acids in margarine.

[†] Chlorine-containing organic compounds (polychlorobiphenyls, dioxins, *etc.*) are among twelve most dangerous contaminants.

[‡] In recent years, the counterfeit foodstuffs and beverages (butter and vegetable oil, mineral water, juices, wine, brandy, vodka, *etc.*) became more frequent. The spread of retail trade has resulted in the improper storage of foodstuffs (without refrigeration) and their delivery at long distances in poorly equipped vehicles.

3. Early recognition of diseases by determination of biological markers

The successful curing of various dangerous diseases depends on their early recognition. Many diseases can be recognised by their markers, *i.e.*, substances contained in biological fluids and expired air.

Most often, the markers represent low-molecular biologically active compounds, namely, nucleosides, nucleotides, catecholamines, hydrocarbons, amino acid derivatives (*e.g.*, homocysteine, *etc.*), steroids, carbohydrates, indoles, porphyrins, organic acids, vitamins, *etc.*¹¹⁴ Large molecules, for example, proteins and lipids, can also be the markers.

Chromatographic techniques allow many biochemical markers to be determined at the level of 10^{-9} – 10^{-15} g (depending of the preconcentration and detection techniques used).^{115, 116} The large volume of available information (due to the possibility of the separation and determination of tens–hundreds compounds per cycle), the low detection limits,[§] the reliable instrumentation, the automated analysis that provides the complete test report, the data storage in the PC memory, the versatility (a single chromatograph can be used for carrying out numerous tasks), the preferential use of non-invasive samples (urine, saliva, tears, sweat, hair, expired air, *etc.*) make the chromatographic techniques irreplaceable in the analysis of markers.

GC and HPLC are the techniques used most often for the analysis of markers.

Naturally, the markers of dangerous, particularly, oncological diseases attract the keenest attention (Table 6).

Here, we consider the diagnostics of oncological diseases, namely, breast and lung cancer.

Table 6. Biochemical markers of oncological diseases.

Disease to be recognised	Disease markers	Ref.
Breast cancer	(1) modified nucleosides (1-methyl-guanosine, 2-methylguanosine, pseudouridine, 5,6-dihydrouridine) in urine (2) polyamines (spermine, spemidine, putrescine, cadaverine) in urine	117–119
Lung cancer	hydrocarbons(n-butane, n-pentane, n-heptane, 2-methylhexane, 3-methylhexane, 4-methyloctane, 5-methyldecane, 3-methyltridecane, 7-methyltridecane) in expired air	120
Malignant melanoma	cysteine and indole derivatives in urine	121
Ovarian carcinoma	polyamines in urine	119, 122
Oestrogen-initiated tumours	4-hydroxyoestradiol in urine	123
Carcinogenic diseases	5-hydroxyindoleacetic acid in urine	124
Cancerous growth (children)	fucose in urine	125
Neuroblastoma (children)	homovanillic acid and vanillyl mandelic acid in urine	126
Pheochromocytoma	catecholamines (adrenaline, nor-adrenaline and dopamine) in blood plasma or urine	127

§ Due to the low detection limit, only small amounts of biological samples are required for the analysis (often, several microlitres).

The specialists at the American Oncological Centre who studied the possibility of early recognition of cancer based on biological markers have found that high concentrations of modified nucleosides in the blood of oncological patients points to the presence of a tumour. Such an analysis allows the disease to be recognised at the earliest stage. The determination of nucleosides in urine can be performed with the use of HPLC. The results of the analysis of urine samples of 62 women suffering breast cancer (reliably confirmed) and 100 healthy women were described.¹¹⁹ Their statistical processing confirmed the higher diagnostic value as compared with the analyses that used conventional markers of breast cancer, *viz.*, CEA and CA 15-3. The sensitivity and selectivity of the diagnostics from the analysis of modified nucleosides exceed 80%. The examination of the transformed nucleosides allows certain types of leukaemia, lung and brain cancer to be recognised.^{117–119}

The prospects of the early recognition of lung cancer are associated with the analysis of expired air.¹²⁰ The air expired by the patients suffering lung cancer was found to contain higher concentrations of alkanes and methylalkanes such as n-butane, n-pentane, 3-methyltridecane, 7-methyltridecane, 4-methyloctane, 3-methylhexane, heptane, 2-methylhexane and 5-methyldecane. These hydrocarbons were present at the level of nano-(pico)moles; hence, their determination should involve their preconcentration on special adsorbents that do not absorb moisture. The chromatographic method of the diagnostics based on the analysis of the expired air has advantages over other methods due to its safety, low cost and high selectivity. Therefore, it was proposed for the early initial screening of oncological patients.

4. Pharmaceutical and pharmacological applications

The major application fields of chromatography in the analyses and examination of medicinal drugs (pharmaceutics) and also in the determination of drugs in biological fluids (pharmacology) are as follows:

- pharmacopeia control over the quality of drugs;¹²⁸
- monitoring of impurities in drugs;¹²⁹
- studies of the stability of drugs;¹³⁰
- analysis of medicinal herb extracts;¹³¹
- analysis of drugs based on the herbs used in traditional Chinese medicine;¹³²
- application of the LC-MS technique in the development of new drugs;¹³³
- application of supercritical fluid chromatography for the separation of drug enantiomers;¹³⁴
- the use of HPLC for the separation of drug enantiomers;¹³⁵
- the use of HPLC in pharmaceutical industry;¹³⁶
- determination of natural phenolic compounds in plants (flavonoids, hydroxy acids, natural dyes, *etc.*);^{137–140}
- analysis of drugs in the doping control;¹⁴¹
- clinical pharmacy;¹⁴²
- chromatography in pharmacokinetics;¹⁴³
- toxicologic analysis;¹⁴⁴
- binding of drugs in the organism.¹⁴⁵

The use of chromatography in pharmaceutics was also the subject of monographs.^{146, 147}

High-performance liquid chromatography is the main method used in the analysis of medicinal drugs at pharmaceutical factories. Ion chromatography is widely used for the determination of ions in drugs, of anions and cations in special-grade water and water used for injections. Ion chromatography coupled with a pulsed amperometric detector allows mono-, di-, tri- and polysaccharides, alcohols and free acids to be determined (without preliminary derivatisation). Gas chromatography is used in the analysis of solvent residues that can be present in pharmaceutical products.

5. Chromatographic methods for the analysis of natural gases, gas condensates, mineral oils and crude oil

Chromatography is widely used in the gas, oil and oil-refining industries.^{148–151} Analyses are carried out at all stages, *viz.*, during the geological survey of gas and oil areas, gas and oil production, piping, at different stages of technological processing and, ultimately, for monitoring the finished products. Moreover, the chromatographic techniques are used for the monitoring of pollution of the environment (soil, water, air, bottom sediments, *etc.*) with mineral oils.

Modern high-performance capillary columns make it possible to completely separate the gasoline fractions into components (200–1000 components in a single sample). These analyses cannot be accomplished by other methods.

Chromatographic techniques (GC, HPLC, ion, gel-filtration chromatography) are used for the monitoring of natural and accompanying petroleum gases, gas condensates, gasoline and kerosene fractions, diesel fuel, lubricating oils, oil heavy fractions, pyrobitumen and even crude oil. The methods of the analysis of natural gases and different fractions of mineral oils are specified by the Russian State Standards (GOSTs).

Chromatography makes it possible to determine both individual (component-after-component) and group compositions; to simulate the distillation of petroleum and its derivatives according to their boiling points; to assess the environmental characteristics of petroleum derivatives, in particular, determine the benzene content, the total sulfur and nitrogen contents and the concentrations of heavy metals and polynuclear aromatic compounds.

High-performance liquid chromatography allows one to easily perform the 30-min separation of petroleum into the following four fractions: asphaltenes, saturated hydrocarbons, aromatic hydrocarbons and polar compounds. After such a grouping, the separation of saturated, aromatic and polar compounds into individual components is possible. The group type separation (to paraffins, naphthens and aromatic compounds) of gasoline is carried out on 13X-zeolite-packed columns, whereas their separation into individual components is accomplished on capillary columns. The chromatographic separation of oxygenates in gasoline is performed using a flame ionisation detector, which is selective with respect to oxygen-containing compounds. The operation of the detector is based on the conversion of oxygen-containing compounds into methane, which allows one to avoid the effect of the hydrocarbon background and determine oxygenates at the trace level.

Multidimensional gas chromatography[¶] is used for the separation of complex multicomponent mixtures in petrochemistry and also for the determination of the hydrocarbon content of natural and accompanying gases. The increase in the gas cost places more stringent requirements upon the reliability of the natural gas analysis, which is necessitated by the interpayments between the oil-production, oil-delivery and oil-consumption companies.

Chromatography plays the exceptionally important role in the chemical, pulp and paper and many other industrial fields. It is used, first of all, to exercise technological control (analyses at all technological stages) and maintain the optimum conditions and, secondly, to analyse rough materials, finished products and wastes. The technological control at hundreds of Russian plants involves the use of more than 50 thousand gas chromatographs. Thousands of gas, liquid and ion chromatographs are constantly operated at the laboratories and centres of Gosepidnadzor (State Sanitary and Epidemiological Control), environmental control committees and centres, toxicological laboratories, organisations such as Vodokanal, laboratories of Goskomgidrometeotsentr (State Hydrometeorology Centre), veterinary laboratories, plant

protection stations and the laboratories of forensic and medical examination, *etc.*

In recent years, the role the chromatography plays in power engineering increased, namely, it is used for the determination and evaluation of the calorific power of gases and in the analysis of pollutant emissions. Ultimately, chromatography finds application in archaeology and art (for studying old paints, varnishes, coatings, *etc.*).

Chromatography surpasses other analytical methods in the number of publications. More than 300 thousand books, reviews and papers were published (including 110 thousand on the liquid column chromatography, 65 thousand on the gas chromatography, 65 thousand on the planar chromatography and about 50 thousand on the capillary and planar electrophoresis.).

VII. Conclusion

In summary, we outline the main directions in the development of chromatography.

Upgrading the selectivity of separation due to the development of new sorbents. In GC, this is the synthesis of new liquid phases with bi- or trifunctional groups, the development of adsorption capillary columns of the PoraPlot type of different chemical nature, the use of the geometric factor for the increase in the selectivity. In HPLC, this is the synthesis of reversed-phase sorbents that contain immobilised polar groups in alkyl chains and also sorbents with molecular-size pores for the retention of molecules of both single and related types, the use of Hypercarb carbonaceous sorbents based on porous graphitised carbon black to enhance the selectivity of the separation of isomers.

Enhancement of the column efficiency due to the changeover to capillary columns. At present, more than 60% of studies are carried out with the use of capillary columns. The share of micropacked, capillary, and nanocolumns in HPLC has substantially increased. In capillary electrochromatography, the separation is carried out exclusively on capillary columns. In GC, HPLC and capillary electrochromatography, the efficiency of columns exceeds one million of theoretical plates.

The development of new rapid separation methods. In GC, the high separation rate is achieved due to the decrease in the column volume and also due to the high-gradient temperature changes (up to 1800 deg min⁻¹). Dozens of components can be separated in a minute. In HPLC, the high separation rates are achieved by using columns packed with fine non-porous particles (measuring 1.0–1.5 µm), monolithic columns and columns with perfusion sorbents and turbulent flows.

Miniaturisation of instruments is the common trend of all chromatographic techniques. The most significant progress is observed in GC, HPLC and ion chromatography. Portable field chromatographs, hand-held devices, and also chip-based instruments are developed.

Improvement of microprocessor programmes for the analysis-data processing and the control over the chromatograph parameters. Attention is drawn to the computer-assisted processing of the results of chromatographic analysis. The systems for recording, processing and storage of chromatographic information are constantly renewed and refined. The number of publications on the simulation of chromatographic processes increases, particularly, the publications devoted to the use of neural networks and the linear and non-linear regression analysis for the simulation and optimisation of these processes. The chromatographic databases are constantly replenished.

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^a — *J. Anal. Chem. (Engl. Transl.)*

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^d — *Mendelev Chem. J. (Engl. Transl.)*

Organic reagents in spectrophotometric methods of analysis

S B Savvin, S N Shtykov, A V Mikhailova

Contents

I. Introduction	341
II. Individual organic reagents	341
III. Modified organic reagents	342
IV. Immobilised organic reagents	344
V. New classes of organic reagents	345
VI. Conclusion	346

Abstract. The role of organic, in particular, complex-forming, reagents in the formation and development of spectrophotometric analysis is discussed. The prospects for the use of organic reagents in modern analytical methods are considered; the attention is focused on modified and immobilised reagents, receptor molecules and on the use of nonaqueous and organised media. The bibliography includes 170 references.

I. Introduction

For many years, organic reagents play an important role in the chemical and physicochemical methods of analysis. They are employed for qualitative or quantitative determination of chemical elements and compounds (both organic and inorganic), as well as for separation, concentration, masking and other auxiliary operations that precede or accompany the analysis.

Theoretically, the possibilities of design of new organic compounds for analytic purposes are boundless; however, in practice only several dozens of classes of chemical compounds are effective as organic reagents.¹ The requirements for the organic reagent are dictated by the analytical method used.

The reagent for the determination of metals should, first of all, contain a proper functional analytical group that enables its interaction with the determined element and subsequent observation of the respective analytical signal. Currently, several tens of such functional analytical groups are known and documented.^{2,3}

The determination of organic compounds requires that the reagent molecule contained specific groups able to react with functional groups of determined compounds (hydroxyl-, carbonyl-, halogen-, sulfur-, nitrogen-containing) with the formation of intensely coloured or luminescent products. Reactions used for the determination of functional groups differ considerably from those used for inorganic ions. In particular, the nature of the

molecular core (aliphatic or aromatic) is important. Besides that, the course of many reactions depends substantially on the media and the reactions are not often sufficiently selective.

New problems that the chemical methods of analysis encounter with have stimulated wider studies of organic reagents. Novel directions have appeared, that are associated with the modification and immobilisation of the conventional organic reagents, as well as with the use of non-aqueous, water – organic and organised media. The variation of conditions of the analytical reactions, *viz.*, the control over the reaction rates and solvation processes, changes in the solubilities or hydrophobicity of the reactants, utilisation of solid matrices, is becoming more and more popular.

There are also completely new directions dealing with the use of receptor molecules and reagents based on the principles of supramolecular chemistry, host – guest interaction mechanisms, as well as immune reactions with organic and bioorganic compounds. Some organic compounds act as reagents in excited states; reagents that form π -complexes with analytes, bacteria and micelles (vesicles), *etc.* are also known.

At present, organic reagents are widely used not only in spectrophotometry^{2–10} and luminescence analysis,^{11,12} but also in atomic absorption^{13–16} and atomic emission spectrometry,¹⁷ inverse voltammetry,^{18–21} in the methods based on the use of ion-selective electrodes²² and different chemical sensors,²³ in the kinetic,^{24,25} flow-injection²⁶ and tracer analysis,²⁷ in capillary electrophoresis,²⁸ and in liquid²⁹ and gas chromatography.³⁰ As usual, organic reagents play a crucial role in titrimetry,^{31,32} extraction^{33,34} and many other methods of determination, separation and preconcentration.^{35–37} Comprehensive textbooks^{38,39} on the use of organic reagents in the inorganic analysis have been published.

In the present review, we discuss the role of organic reagents (mostly, complex-forming) in the spectrophotometric analysis and consider the perspectives of their use in modern analytical methods.

II. Individual organic reagents

In the first third of the 20th century, a new scientific direction based on the application of chelating reagents, mostly organic, in chemical analysis emerged at the joint of organic, inorganic, coordination and analytical chemistry. The concept of functional analytical groups was formulated, the effects of substituents (called later the analytical active groups) in the reagent molecules were studied, and the general conditions of formation of stable complex compounds were revealed.

S B Savvin, A V Mikhailova V I Vernadsky Institute of Geochemistry and Analytical Chemistry, Russian Academy of Sciences, ul. Kosygina 19, 119991 Moscow, Russian Federation. Fax (7-495) 938 20 54, tel. (7-495) 137 28 78, e-mail: zubor@geokhi.ru (S B Savvin)

S N Shtykov Department of Chemistry, N G Chernyshevskii Saratov State University, ul. Astrakhanskaya 83, 410012 Saratov, Russian Federation. Fax (7-8452) 27 14 91, e-mail: shtykov@info.sgu.ru

Received 14 May 2005

Uspekhi Khimii 75 (4) 380–389 (2006); translated by I S Neretin

In the next years, organic reagents have acquired wider applications in different analytical methods. New more efficient reagents were synthesised and exploited, *viz.* oxine (8-hydroxyquinoline), dithizone (1,5-diphenylthiocarbazone), cupferron (*N*-nitroso-*N*-phenylhydroxylamine ammonium salt), dialkyldithiocarbamates, arsenazo I [sodium 2-(2-arsenophenylazo)-1,8-dihydroxynaphthalene-3,6-disulfonate], 1,3-diketones. Theoretical concepts on the mechanisms of their action were developed. It can be said for sure that Russian science has made a major contribution to the development of theory and practice of the use of organic reagents in the analytical chemistry.⁴⁰

In the 1950–1980's, complexones,³¹ the reagents of the triphenylmethane^{4–7,41} and fluorone⁴² series, antipyrin derivatives,⁴³ mono- and bis-azo compounds, for example, arsenazo III,⁴⁴ acquired a broad use in the photometric analysis. Hydroxyflavones, hydrazones and Schiff bases were often used in the fluorimetric analysis, whereas rhodamines, in the version with extraction.

In the last two decades, heterocyclic mono-azo compounds,^{45,46} including both the well-known 1-(2-pyridylazo)-2-naphthol (PAN), 4-(2-pyridylazo)resorcinol (PAR) and 4-(thiazol-2-ylazo)resorcinol (TAR), and especially halogenated heterocyclic compounds began to play an important role in the photometric analysis. Extremely high molar extinction coefficients of the latter [often reaching $(1.0–1.5) \times 10^5$], contrast ranges and higher selectivity as compared to PAN and PAR are their main advantages. Complexes of water-soluble analogues of natural porphyrins also possess high molar extinction coefficients.⁴⁷ Besides, new principles of the reagent design were developed, using the concept of functional analytical group duplication. In particular, the series of bis-azo compounds of the arsenazo III group has been considerably broadened.

The unusually high apparent molar extinction coefficients [$\epsilon_{\text{mol}} = (1–10) \times 10^5$] were obtained in the flotation of ionic pairs of organic reagents (Rhodamine 6G, Crystal Violet, Methylene Blue, *etc.*) with analytes.⁴⁸ The highly sensitive kinetic and catalytic methods for the determination of metal ions, anions and organic compounds in photometric and fluorimetric versions, are very promising.^{49–51} A number of works on the determination of different anions with the use of organic reagents that have been analysed in detail in a fundamental review,⁵² should be specially noted. Many of the above-mentioned applications of organic reagents for the analytical purposes have been discussed.⁵³

Quantum-chemical methods for the calculation of the characteristics of the coloured compounds gained further development. An attempt was made of quantum-chemical design of photometric reagents with optimal characteristics.⁵⁴

However, it is obvious that the synthesis of many novel organic reagents for the determination of metal ions will not give considerable benefits. At present, diverse modifications of the known organic reagents by complication of their chemical structures or changes in the media properties where the analytical reaction is carried out, are becoming popular. In particular, non-aqueous and water–organic media, as well as organised media, are used more and more widely.

III. Modified organic reagents

1. Types of modifications of organic reagents

There is still no clear definition of a modified reagent. One can consider the modification as the purposeful change in the properties not related to the formation of new in principle chemical compounds. According to this definition, a chemical compound with an additional substituent is a new organic reagent. It can be similar to the prototype reagent in its chemical and analytical properties (*e.g.*, in the selectivity, provided that the functional groups were not affected), but cannot be considered as the modified reagent.

On the other hand, different salts, ionic and other associates of organic reagent with other organic and inorganic compounds

formed due to electrostatic or hydrogen bonds or hydrophobic interactions, can be regarded as modified organic reagents. Solvates (adducts) involving the organic solvent molecules also fall in this category. In our view, the solubilisation of organic reagents in various types of nanosized organised systems, which serve as the nanoreactors in analytical reactions, is also a kind of modification.

One of the main features of the modified reagent, according to our definition, is the reversibility of the modification, so that upon changes in the conditions, *e.g.* upon acidification or dilution of the solution or change in the solvent, *etc.*, the reagent dissociates into the starting components.¹ It is noteworthy that the modification of organic reagents has long been employed, especially for their hydrophobisation upon formation of neutral ion associates. However at present, diversification of the modification pathways and the use of this approach in the routine analysis is in progress. Several examples of analytical systems where, in our view, the authors deal with the modified organic reagent, are discussed below.

2. Modification upon association of organic reagents

This type of modified organic reagents comprises different associates, *viz.* associates of the initial organic reagent with its counterion (ion associates or pairs), associates of an acidic organic reagent with a base (amine or amide) or of a basic organic reagent with a proton donor (see, for example, Ref. 55). In 1954, it was proposed⁵⁶ to use organic co-precipitants to concentrate elements from very dilute ($1:10^{10}$ and more) solutions. The use of large molecules as organic co-precipitants and for the determination of trace amounts of elements proved beneficial. Different types of co-precipitants were found. The mechanism of their effect is described in the original works, reviews and monograph (see, for example, Refs 56–58).

Let us limit ourselves to the consideration of the mechanism of co-precipitation of ionic associates, poorly water-soluble and containing an extended hydrophobic organic fragment. It is known that the majority of organic reagents that form complexes with precipitated metal ions contain sulfo, carboxy, and other negatively charged groups. Their effect on the solubility can be levelled by formation of a salt or an ion associate with a 'heavy' hydrophobic organic cation. In this case, it is pertinent to consider this as a modification of the respective organic reagent by organic cations, since it is the salt or ion associate that serves as the ligand for the metal ion. Other versions are also possible, for example, precipitation of actinides by the arsenazo-type reagents and the precipitate of diphenylguanidinium anthracene- α -sulfonate,^{57,58} precipitation of thorium by SPANDS [sodium 2-(*p*-sulphophenylazo)-1,8-dihydroxynaphthalene-3,6-disulfonate] and Methylene Blue, and precipitation of rare-earth elements by stilbazo[4,4'-bis(3,4-dihydroxyphenylazo)stilbene-2,2'-disulfonic acid] and so on.⁵⁵

In the 1960–1980's, ion associates were most often employed in extraction systems. The role of reagent modification for the extraction of charged complexes is similar in many aspects to that of counterions in the precipitation reactions, since in both cases charge neutralisation is required for the passage of a complex to another phase (solid or liquid). In the extraction of anionic chelates it is necessary to block sulfo, hydroxy, and other hydrophilic groups by 'heavy' hydrophobic organic (or sometimes inorganic) cations, which thus serve as the modifiers of the original organic reagent. Large hydrophobic organic cations include, *inter alia*, tetrabutylammonium, tetraphenylarsonium, trioctylammonium, and potassium is used as the inorganic cation.³³ The use of diphenyl- and triphenylguanidinium salts as a source of cations and extraction with higher alcohols allowed one to expand this approach onto a large group of complex organic reagents belonging to the family of azo-dyes.⁴⁴

Chelates with multiply charged metal cations can have a positive charge. To compensate it, a sufficiently hydrophobic anion (*e.g.*, tetraphenylborate, naphthalenesulfonate, or acid dye

anions) should be added to the solution.^{34, 55} In any case, it can be said that the anionic or cationic chelates are modified by hydrophobic cations or anions, respectively.

3. Modification upon formation of multicomponent complexes and outer-sphere chelates

The passage from binary to ternary and multicomponent systems is a well known (since the 1950's) approach aimed at improving the analytical characteristics of photometric organic reagents. Hundreds of papers on the so-called mixed-ligand complexes were published in the 1970–1980's; a monograph devoted to this topic appeared, in which the authors propose the term 'hetero-ligand' for such complexes. The interactions between ligands can differ in nature, namely, hydrophobic interactions, stacking interactions, π -bonding, hydrogen bond. On the whole, they lead to the change in the character of complex formation by the original organic reagent.^{55, 59–61} It is believed that the interaction between two ligands gives a new 'compound' reagent, which is more efficient than the original reagents.

Yet another route to the modification characteristic of multicomponent systems is the outer-sphere complexation, which also changes the analytical parameters of the reaction products.^{55, 62} A specific effect of the outer-sphere reagents enhances the differentiating action of organic reagents in respect of metals. Outer-sphere complexes occupy an intermediate position between the inner-sphere complexes and ion associates.⁵⁵

4. Modification of organic reagents caused by changes in the media properties

a. Non-aqueous media

Extensive investigations into non-aqueous solutions, especially in the mid-20th century, has led to their use not only in research studies, but also in the routine chemical analysis. It was found that the properties of organic reagents (protolytic, redox, donor-acceptor, complex forming, tautomeric, solubility, *etc.*) vary dramatically in different solvents, therefore changing the sensitivity, selectivity, contrast and rate of a reaction, and even the end products. Thus, a solvent is not only a medium, but is rather a kind of an active reactant. Its effect on the chemical process is determined primarily by the two principal characteristics, *viz.*, donor-acceptor properties and dielectric permeability. As a result, one can control the process by changing the character of solvation of both the reagent and the element under study.⁶³

However, the change in solvent results in simultaneous changes in both the dielectric permeability and donor–acceptor properties. Therefore analytical chemists have begun to use mixed (non-aqueous and water–organic) solvents. New ways of increasing the selectivity and contrast of metal ion reactions with organic reagents were revealed also in the use of strongly acidic media.⁶⁴

Despite a sufficient progress in the control over chemical processes with the use of such solvents, many problems still remain unsolved. In addition, these media are sometimes unsuitable due to toxicity, strong odour or volatility. Non-aqueous media have certain advantage only in the extraction version of photometric, fluorimetric and atomic absorption methods, because they allow one to unite separation, preconcentration and determination, thus increasing both selectivity and sensitivity of the analysis.

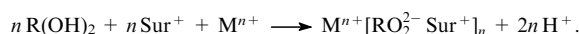
b. Surfactants

A broad class of ionic surfactants can serve as versatile modifiers of physico-chemical properties of chromophore polydentate multifunctional organic reagents of different chemical nature.⁶⁵ It is for this reason that the analytical determination of elements with the use of surfactant-modified reagents considerably exceeds the best known conventional methods in sensitivity, selectivity and contrast. A vast literature on the theoretical aspects and analytical applications of surfactants includes two books^{65, 66} and a number of reviews.^{67–72}

Formation of ion associates is one of the main routes of modifying electronegative or electropositive organic reagents by surfactant ions of the opposite charge. The surfactant ions interact with the analytical active group of the organic reagent, so that no competition with the complexation of the metal ion occurs. This allows creation of many new and more efficient modified organic reagents from the known ones. It is applicable to ionogenic surfactants and chromophore polydentate chelating or, more generally, complex forming reagents.

The best known and the most analytically efficient reagents belong to the following classes: sulfophthalein indicators (Pyrocatechol Violet, Xylenol Orange, Phthalexones), phenolcarboxylic acids of the triphenylmethane series (chromazurol C, eriochromcyanin R, eriochromazurol B, sulfochrom), trihydroxyfluorones (disulfophenylfluorone, salicyl fluorone) and other reagents of the xanthene series (Pyrogallol Red, Bromopyrogallol Red), as well as from some other classes of organic reagents.^{65, 70, 72–78} For the modification of organic reagents with the negatively charged analytically active groups, one should use a long-chain cationic surfactant with no less than twelve carbon atoms in the alkyl chain, *i.e.*, salts of quaternary ammonium bases (for example, cetyltrimethylammonium bromide), alkylpyridinium salts (*N*-cetylpyridinium chloride) and salts of other heterocyclic amines, primary, secondary and tertiary amines that can be protonated in water with the formation of cations.^{65, 70–78}

The basic idea of modification of this type of organic reagents is the concept of formation of ion pairs or ion associates.^{65, 75} The scheme of a reaction of a reagent $R(OH)_2$ containing one functional analytical group and one analytical active group (CO_2H , OH , SO_3H) with a cationic surfactant (Sur) can be written as follows:



Due to the addition of the biphilic surfactant cation with a large non-polar chain to the organic reagent molecule, the associate becomes significantly more hydrophobic than the original more hydrophilic reagent, *i.e.*, the character of the species hydration changes.^{65, 78, 79} As a result, a local decrease in the polarity of the medium occurs in the microenvironment of the organic reagent molecule.⁷² This leads to a decrease in the hydration of the functional analytical group and the bound metal ion, which, in turn, causes the change in protolytic properties of the groups involved in the functional analytical group,^{65, 72} and the increase in the number of adjoining chelating ligands.^{65, 78}

There are at least four features of the complexation with surfactant-modified ligands:^{65, 78} the increase in the number of coordinated ligands in the analytical forms; the multisite interaction of polydentate reagents; activation of complex formation in strongly acidic media; and the increase in the stability of the chelates. A widening of the pH plateau of complex formation to acidic or basic region is sometimes considered as the fifth effect.⁶⁵ These factors ensure the increased sensitivity and selectivity of the reactions in the presence of surfactants. Cationic surfactants in such systems bring into interaction both analytical functional and analytical active groups, *i.e.*, induce multicentre interaction involving the chromophore π -electron system. Thus, the potential of the given reagents can be used to their full extent in order to enhance the contrast of the photometric reaction. In the case of multiply charged metal cations, the number of coordinated ligands increases, which also leads to an increase in the sensitivity of the determination. For instance, in the case of titanium complexation with Pyrocatechol Violet, the molar extinction coefficient of the complex reaches 1.5×10^5 and the contrast of the reaction $\Delta\lambda$ is 250 nm upon modification of the reagent by cationic surfactants.

It should be noted that in the case of a stoichiometric component ratio in the reagent–surfactant system, as a rule, neutral ion associates precipitate. Their solubilisation can be effected by addition of a 2–5-fold excess of the surfactant, which

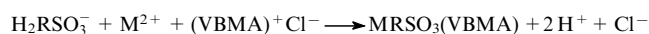
causes surfactant adsorption on the precipitate particles, their charging and dispersion to the virtually molecular level. Such charged particles of ion or chelate associates containing small excess of the surfactant ions, are sometimes called mixed micelles.⁶⁶

c. Water-soluble polymers

Water-soluble polymers are commonly used in chemical technology, for example, in water purification. However, their use in the analytical chemistry has long been limited to the concentration by membrane filtration.^{80, 81} Later it was found⁸² that the modification by water-soluble polymers is an almost versatile way to transform water-insoluble (hydrophobic) organic analytical reagents or dyes into the water-soluble form. The molecular mass of these organic polymeric compounds is usually in the range of 10^4 – 10^5 ; they contain both the hydrophobic chain and the hydrophilic groups incorporating tertiary or quaternary nitrogen atoms.

The mechanism of the interaction of water-soluble polymers with the organic reagents is as follows. Hydrophobic (water-insoluble) organic reagents are solubilised as a result of their hydrophobic interaction with the non-polar carbon skeleton of the polymer molecules.^{65, 83} Since the solubilisation of the neutral organic reagent molecules does not block the cationic centres of the water-soluble polymer, its interaction product with the reagent retains the properties inherent in the original polymer and is also water-soluble. Moreover, if the analytical functional groups of the reagent responsible for the complexation of metal ions are neither blocked by the water-soluble polymer, the modified organic reagent does not lose its chemical analytical properties with retention of the coloration reaction, which determines the analytical value of the organic reagent. In addition, due to the solubilisation and related structuring of water in the close vicinity of the chelate, the stability constant of the complex of the polymer-modified reagent with the metal ion increases, which favours virtually complete binding of the element.

The use of the organic reagent–water-soluble polymer systems, as well as the organic reagent–surfactant systems, broadens the potential of the spectrophotometric analytical methods. For example, the use of organic reagents in the flow-injection analytical methods is limited due to the reagent sorption on the capillary walls and on the other parts of the flow system. Due to higher affinity of the hydrophobic organic reagent to the water-soluble polymer than to the material of the instrument parts, the introduction of water-soluble polymer solves this problem and prevents the organic reagents and their metal complexes from sorption on the working parts of the instrument. The use of water-soluble polymers also broadens the potential of the classical titrimetric analysis due to the use of metal indicators of different nature. For example, a scheme of a reaction of poly[N-(4-vinylbenzyl)trimethylammonium] chloride, (VBMA)⁺Cl[−], with the two-basic reagent H₂RSO₃[−] containing one dissociated sulfo group and doubly-charged metal cation M²⁺ can be written as follows (for one unit of the polymer chain):



The water-soluble polymer–organic reagent–M systems are successfully used for retention and preconcentration (for example, by the membrane filtration method) with the subsequent determination of elements.^{84, 85} Ionenes represent yet another example of charged water-soluble polyelectrolytes used in analysis.⁸⁶

d. Organised micellar media

Organised media differ in principle from the classical homogeneous media described above since they are microheterogeneous. They consist of a solvent and a huge number of ensembles of tens or hundreds of distributed biphilic surfactant molecules or ions. The species in such an ensemble form a nano-sized micellar pseudo-phase (dispersed phase), the properties of which differ sharply from those of the bulk solvent (a dispersion medium),

which produces a reaction medium of a new type, combining the properties of both polar and non-polar media.^{70, 71, 87, 88}

More complex micellar systems can contain two or three components in addition to the surfactant molecules. The examples of surfactant-based micellar systems are represented by direct and inverse micelles, microemulsions ('oil-in-water' and 'water-in-oil'), vesicles, liposomes, lipid membranes, Langmuir–Blodgett films (LBF), liquid crystals and other systems.⁷¹ Micellar systems can also appear on the solid surface being in a contact with the solution in a form of hemimicelles (half-micelles) or adsorption bilayers.⁶⁶

A peculiarity of the nano-sized phase created by an ensemble of surfactant species is that it has virtually no macroscopic analogue.⁸⁹ It is worth noting also that the formation of micellar systems as a result of self-organisation (self-assembly) of surfactant molecules or ions does not include a formation of intermolecular chemical bonds, and is therefore related to supramolecular chemistry, a new section of chemistry that emerged in the last decade of the 20th century.⁹⁰

The microheterogeneous organised media differ in principle from the common homogeneous solutions in that the main feature of the former is the local effect based on the solubilisation of hydrophilic and hydrophobic reagent molecules in the nanoscale volume of the micellar system.^{70, 71, 87, 88} In this case, the change in properties and the reactivities of organic reagents is determined by the change in the state of the medium in their microenvironment (rather than in the entire volume). If the analytical reaction occurs in the nano-sized microphase rather than in the bulk, the former is called a micro- or nano-reactor.^{71, 87, 88}

It was shown that the solubilisation of organic reagents in micelles, microemulsions, LBF or cyclodextrins changes their protolytic,^{91–94} redox⁹⁵ and complexation^{65, 66, 96} properties, as well as the tautomeric transformations.^{94, 97–99} These changes in turn result from changes in the properties of the reaction media (polarity, acidity, dielectric permeability) in the microenvironment of the solubilised reagents and changes in their hydration type.^{72, 100–102} Numerous applications of the organised media for the modification of the organic reagent's properties are summarised in books^{65, 66} and reviews.^{67–71}

IV. Immobilised organic reagents

The term 'immobilisation' of organic reagents on the surface layers or in the bulk of a solid phase (matrix) has come to analytical chemistry from biochemistry. If, as a result, some properties of the compound change (which is the goal of immobilisation in the analytical chemistry), this compound can be considered modified. Thus, it is possible to consider that the immobilisation is a particular case of the modification.

1. Complex-forming sorbents

Complex-forming sorbents are organic or inorganic polymeric compounds with groups or reagents attached in one or another way, which can interact with metal ions or other compounds in the solution.

The mode of attachment can be based on both the sorption of the reagent molecules on the matrix and their covalent binding with the formation of a new polymer containing reactive fragments of the original reagent. It can be said that it is immobilisation of an organic reagent on the solid matrix that occurs in the former case, while in the latter case one deals with the formation of a new polymeric compound.

There are numerous examples of immobilisation of organic reagents on polymeric matrices.^{103, 104} One of the first developed methods was preparation of ion-exchange resins with absorbed reagents.¹⁰⁵ This consisted of common organic reagents containing sulfo or other acidic groups on an appropriate ion-exchange resin. The analytical functional groups in the sorbed reagent molecules do not lose their ability to bind metal ions. A wide range of different materials, e.g., linear and network polymers

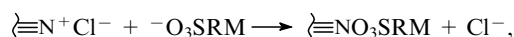
(ion-exchange resins based on styrene and divinylbenzene), polyurethane foams, activated charcoal, other organic and inorganic materials serve as solid matrices. The possibility of using ion-exchange resins in photometry was established¹⁰⁶ and reviewed.¹⁰⁷ A linear coloristic method was proposed for the determination of iron(III) and copper(II) with the use of hydrophobic silica gels with non-covalently immobilised Xylenol Orange or PAN as indicator powders.¹⁰⁸ Luminescent reagents can be immobilised as well, for example, luminol (3-aminophthalohydrazide), Rhodamine B {[9-(2-carboxyphenyl)-6-diethylamino-3*H*-xanthen-3-ylidene]diethylammonium chloride}, while glass, silica gel or organic polymers serve as the inert support.¹⁰⁹ For instance, it was proposed to use immobilised morine for the sorption-fluorimetric determination of zirconium and tin.¹¹⁰ Polyurethane foams also present a considerable interest as sorbents due to their high efficiency in combination with versatility and high chemical and mechanical stability. Methods of concentration and determination were developed for more than 50 chemical elements.^{111–116}

The detection of an analytical signal can be based on direct measurement of light absorption by the organic reagent modified by an ion-exchange resin, as well as on the application of reflectance spectroscopy. The former method called solid-phase spectrophotometry was proposed by Japanese researchers,¹¹⁷ who were the first to establish a linear dependence of the light absorption by the solid phase on the concentration of the element in the initial solution. Different versions of this procedure were developed, including sorption of the metal–reagent complex by the ion-exchange resin and, *vice versa*, preliminary sorption of the reagent and its reaction with the metal in the sorbent phase.¹¹⁸ Since the reagent is the active principle in both cases, it is possible to say that the organic reagent is immobilised on, and modified by, the ion-exchange resin.

2. Ion-exchange membranes

Yet another modern material that is used as a solid matrix is the ion-exchange membrane in a form of a thin film, plate or filter. It was established that the analytical efficiency of organic reagents increases upon immobilisation on such membranes. There are different versions of the practical implementation of this method of preconcentration and determination. Optically transparent membranes [for example, based on poly(vinyl chloride)], impregnated with trioctylamine in order to make them work as ion-exchange resins, are treated with a solution of a complex of a metal with an organic reagent (for example, Nb with PAR). The complex is adsorbed on the membrane and then the optical density is measured in a usual manner (in transmission mode).

As the interaction between the complex and the membrane active groups is mainly electrostatic in essence (formation of a salt or an ion associate), one can say that in such systems, *e.g.*, with polycapraamide membranes, the complex or the reagent incorporated in the matrix is modified (and immobilised). The equation of a reaction for a single unit can be written as follows:



where $\rightleftharpoons \text{N}^+ \text{Cl}^-$ is a membrane polymer chain unit, $-\text{O}_3\text{SRM}$ is an anion of metal complex with the reagent and $\rightleftharpoons \text{NO}_3\text{SRM}$ is a polymer chain unit with an attached complex.

Other applications of membranes are also known.^{119, 120} For instance, a cobalt complex with PAN was concentrated on thin ion-exchange films with subsequent determination of the metal directly in the sorbent phase. A number of reviews is devoted to the use of organic reagents in the sorption spectral methods.^{121–124} Dynamic sorption preconcentration of elements with subsequent spectroscopic study has been surveyed.¹²⁵

V. New classes of organic reagents

1. Receptor molecules

Macrocyclic ethers, the so-called crown ethers, are of considerable interest in many fields of chemistry, in particular, in analytical chemistry.¹²⁶ The molecules of crown ethers represent rings of nine or more atoms, at least three of them being oxygen atoms. 18-Crown-6 with six oxygen atoms in the ring is the most famous. A number of macrocyclic compounds containing secondary, tertiary, pyridinium-type, pyrrolium-type, azomethine, *etc.* nitrogen atoms (azacrown compounds), oxygen and nitrogen (oxazacrown compounds, cryptands), sulfur (thiacrown compounds), oxygen and sulfur (oxathiacrown compounds), nitrogen and sulfur (azathiacrowns) and so on were synthesised. Porphyrins belong to natural macrocycles.

The area of the use of macrocycles in the chemical analysis is extremely wide. They serve as reagents in photometry, in luminescence analysis (in conventional and extraction versions for ion pairs with the dye anion) and flow-injection analysis. They are also used as components of membranes for ion-selective electrodes, in sorption methods (following immobilisation on a surface), liquid and gas chromatography, extractive separation of alkali and alkaline-earth metals as well as radionuclides, *etc.*^{126, 127}

The ability of macrocycles to form more stable complexes with metals with higher selectivity as compared to the acyclic ligands was called the macrocyclic effect.⁹⁰ This effect is caused by the fit of the macrocycle cavity to the size of the metal ion, as well as by the properties of the donor heteroatoms. In addition, a multi-centre and multifunctional ion-to-ligand binding occurs, which forms the basis of the molecular recognition effect, or the host–guest correspondence principle. The multifunctional nature of the interaction is caused by the involvement of electrostatic (ion–ion, ion–dipole, dipole–dipole), donor–acceptor, π – π -stacking, van der Waals and hydrophobic interactions and hydrogen bonding. With account of the enthalpy factor, such systems have much in common with biosystems.

3D Receptor molecules with cavities of definite size, such as cryptands, spherands, cryptospherands, cavitands in a form of a bowl, and also carcerands which have a form of coupled cups are the most efficient as regards both selectivity and the strength of binding to the analyte.^{90, 126}

These receptor molecules exhibit quite unique properties.^{128, 129} One of the spherands forms a stable complex with sodium ions ($\log K_{\text{stab}} = 14.1$) with the $\text{Na}^+ : \text{K}^+$ selectivity of 10^{10} ! A photometric reagent for lithium ions of the torand family changes its colour upon replacement of the protons at the secondary nitrogen atom inside the ring. Molar extinction coefficients of such compounds (*e.g.*, metal porphyrins) are in the range of $n \times 10^5$.

The receptor molecules most widely used in different methods of analysis, separation and preconcentration are cyclodextrins (having the shape of a truncated cone) and calixarenes (having the shape of a basket).⁷¹ The use of cyclodextrins in chemical analysis is reviewed.^{130–135}

An important feature of the receptor molecules is the ability to bind not only metal cations, but also anions^{90, 126, 128} or neutral organic molecules. In the case of organic compounds, the selectivity of receptors is manifested not only with respect to molecules of different sizes and nature, but also with respect to structural, geometrical and optical isomers. The separation and determination of enantiomers of pharmaceutical preparations, amino acids and other biologically active compounds by means of gas-liquid^{130, 131, 134, 135} and liquid^{136–138} chromatography, capillary electrophoresis,¹³⁸ extraction¹³¹ and other methods^{131, 136, 139} with the use of cyclodextrins as a mobile or stationary phase have become a common tool in the analytical practice. Cyclodextrins and calixarenes are widely employed in the luminescence analysis^{130, 133} and in chemical sensors.^{133, 140, 141} A series of receptor molecules for the anion determination were synthesised.¹⁴² Aptamers belonging to the class of oligonucleotides¹⁴³

represent a new type of analytical reagents the action of which is also based on molecular recognition.

2. Miscellaneous new classes of organic reagents

In recent years, the methods of determination of organic compounds both in the common objects (*e.g.*, in liquid media) and in biomaterials, were successfully developed. Enzymes used for the determination of metal ions,^{144, 145} organometallic¹⁴⁶ and organic compounds^{147, 148} both in solution and in the immobilised state are a new type of organic reagents. These reagents exhibit not only high sensitivity allowing the determination of many compounds on the nano- and picomolar levels, but also an extremely high selectivity that is characteristic of all enzymatic reactions. Fluoroimmunoassay based on the use of antigen–antibody interaction in different variants of registration of fluorescence as an analytical signal^{149, 150} is closely related to this group of methods.

Many other organic reagents for determination of organic compounds are known, for example, widely used *o*-phthalaldehyde for primary and secondary amines and thiols,^{151, 152} lophine derivatives (for a review, see Ref. 153) and other reagents (see reviews^{154, 155}). Organic reagents are used for the determination of biological macromolecules,¹⁰ the action of some reagents is based on the formation of charge-transfer complexes,^{156, 157} metal diketonates can be used for the recognition of organic molecules.¹⁵⁸ Carbon tetrachloride can be determined by photochemical reactions.¹⁵⁹ New types of acyclic reagents for metals exhibit surprisingly high selectivity.¹⁶⁰

Yet another method, the potential of which is not highly appreciated, is the determination of some metals and especially organic compounds by organic reagents in excited states. These analytical reactions are based on intra- and intermolecular transfer of excitation energy of molecules solubilised in different organised systems, which favours the concentration and close contact of the reactants. For example, in the widely known multicomponent system Eu(III)–thenoyltrifluoroacetone (TTA)–phenanthroline (or trioctylphosphine oxide)–surfactant, three TTA molecules excite to the singlet state as a result of light absorption, and then pass to the triplet state by intersystem crossing. Due to the relatively long lifetime and high energy of the excited state, the excitation energy is transferred intramolecularly from the TTA to the excited levels of Eu³⁺ (the antenna effect). As a result, the intensity of Eu³⁺ radiation increases virtually by an order of magnitude, and its detection limit drops to 10^{−9}–10^{−12} mol litre^{−1} (Refs 161 and 162).

An additional decrease in the europium detection limit by 1–2 orders of magnitude can be acquired on addition of a second rare-earth ion (for instance, gadolinium, terbium, yttrium), which serves as the intermediate unit in the energy transfer from ligand to the europium ion.^{162, 163} In addition to TTA, a number of other types of reagents, including macrocycles, can be used as antenna ligands.¹⁶⁴ This method also allows determination of samarium, terbium, gadolinium, dysprosium, and curium.¹⁶⁵ The advantage of these multicomponent systems is that they provide a possibility of determination of not only metal, but also an organic ligand from quenching¹⁶⁶ as well as from enhancement of the sensitised fluorescence.¹⁶⁷

Yet another implementation of organic reagents in the excited state is the determination of polycyclic aromatic hydrocarbons with the use of acridine dyes by means of sensibilised phosphorescence at room temperature in micelles.^{168, 169} The method is selective, because the excitation of a dye takes place in the visible range. The dye molecule excites from the singlet to the triplet excited state under the influence of a heavy atom, and then a triplet-to-triplet energy transfer to the hydrocarbon molecule occurs (the triplet excitation energy for polycyclic aromatic hydrocarbon is lower than that for dye), and the hydrocarbon phosphorescence is detected. With the use of micelles, one can avoid liquid-nitrogen techniques and study the phosphorescence in solution at room temperature. Reagents based on self-organ-

ised supramolecular ensembles are also promising (for a review, see Ref. 170).

VI. Conclusion

The analysis of more than hundred years history of applications of the organic reagents in the analytical chemistry shows that they have played a significant role in both the development of the theoretical concepts in this area of science and the practical chemical analysis of many organic and inorganic subjects. Virtually each element of the Periodic Table in various concentrations, amounts and forms can be determined with the help of different classes of organic reagents. According to a rough estimate, more than 6000 organic compounds were proposed as analytical reagents. About 100 of them can be considered 'basic', *i.e.*, original as regards their chemical structures and analytical properties (sensitivity, selectivity, *etc.*), while others are in fact their derivatives exceeding them in the major analytical parameters. Usually, this excess is not higher than 2–3 times, so the replacement of the 'basic' reagents by their analogues (which often are much more expensive) is not always reasonable, taking into account the necessity of modifying the established protocols.

An intense development of physical methods of analysis, especially since the mid-20th century together with their obvious advantages (sensitivity, possibility of express analysis and automation, in many cases multielement analysis, *etc.*) was seemingly condemning the chemical methods (in particular, those with the use of organic reagents) to the gradual deprecation. However, new approaches and potentials emerged in the 1970–1980's and are actively implemented since then.

1. Automation of almost all stages of chemical analysis (from sampling, decomposition, component separation, concentration, *etc.* to the determination of compounds and elements) became possible. This allows quick analysis of a large number of samples, which is especially important in environmental monitoring, sanitary analysis and in many other cases.

2. Low cost of chemical methods of analysis as compared to physical ones plays an important role since the necessary equipment and reagents in the former are by orders of magnitude cheaper. A set of test methods have been developed (much of them with the use of organic reagents), which use quite a compact equipment and are low energy-consuming, and hence can be used in field analysis and are indispensable for environmental control, in extraordinary situations, *etc.*

3. In the last 20–30 years, the approach to the synthesis of new organic reagents has changed dramatically. Chemists engaged in analysis (as well as in synthesis) came to a conclusion that the infinite broadening of the assortment of related organic reagents containing the same analytical functional group and giving only a slight enhancement of the analytical properties as compared to the parent reagent is unreasonable. The use of modified and immobilised organic analytical reagents (or systems) appeared to be more promising. It is important that the reagents in use are basically the same, but their analytical characteristics are enhanced multiply due to their modification with auxiliary reagents. The efficiency of their analytical use grows in the same proportion. The same statement holds to even greater extent for the organised media and the receptor molecules that operate on the principle of molecular recognition.

4. Modern electronic techniques and small-sized measurement devices (pocket-type of third and fourth generations) open up broad perspectives of the use of chemical methods of analysis (including those using organic reagents) for extensive quick analyses in the environmental monitoring, medicine and other fields of science and technology. Further progress in this direction can provide us with the new measurable parameters for such systems and ways of their measurement, as well as with the new instrumental and computing methods, taking into account the intense development of the computing techniques and high technologies.

The review was prepared with the financial support of the Russian Foundation for Basic Research (Project Nos 04-03-32526 and 04-03-32946). Authors are grateful to L S Shtykova for the cooperation in the preparation of this review.

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^c — *Radiochemistry (Engl. Transl.)*

^d — *Opt. Spectrosc. (Engl. Transl.)*

^e — *Dokl. Chem. (Engl. Transl.)*

^f — *Russ. Chem. Bull., Int. Ed. (Engl. Transl.)*

^g — *Colloid. J. (Engl. Transl.)*

Principal trends in the chemistry of amidinate complexes of main-group and transition elements

D A Kissounko, M V Zabalov, G P Brusova, D A Lemenovskii

Contents

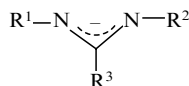
I. Introduction	351
II. Structures of amidinate complexes	351
III. Synthesis and chemical properties of amidinate complexes	354
IV. Conclusion	372

Abstract. Principal trends in modern organometallic chemistry of transition and main group elements containing amidinate ligands are analysed. The nature of element–amidinate ligand bonding inferred from the X-ray structural data and computational studies is discussed. Synthesis and reactivity of Group 1–15 metal amidinate complexes are reviewed. Particular emphasis is drawn to the use of amidinate complexes as catalysts for olefin polymerisation and organic synthesis. Prospects in the development in this area of chemistry are suggested. The bibliography includes 151 references.

I. Introduction

Over the past decade there has been a growing interest in non-metallocene main group and transition metals complexes as catalysts for olefin polymerisation and organic synthesis.¹ The rational for a closer attention to such systems is often explained as the lack of new groundbreaking chemical transformations for analogous metallocene complexes, which have been extensively studied since the mid-1950s. Hence, there is an essential need for other ancillary ligands, which would provide new types of organometallic complexes exhibiting unusual electronic and structural properties.

Complexes with allylic ligands and their heteroanalogues, *viz.*, NNN- (triazene) and PNP- (phosphazene) ligands are typically referred as non-metallocene derivatives. These compounds are widely used in such important area as asymmetric catalysis.^{2–4} Over the past decade the considerable attention has also been paid to NCN-analogues of allylic group, *viz.*, to amidinate ligands:



D A Kissounko Department of Chemistry and Biochemistry, University of Maryland, 20742 College Park, MD, USA. Fax (1-301) 314 91 21, tel. (1-301) 405 59 11, e-mail: denis@chem.wisc.edu
M V Zabalov, G P Brusova, D A Lemenovskii Department of Chemistry, M V Lomonosov Moscow State University, Leninskie Gory, 119922 Moscow, Russian Federation. Fax (7-495) 939 88 46, tel. (7-495) 939 38 87, e-mail: zabalov@org.chem.msu.ru (M V Zabalov), tel. (7-495) 939 12 34, e-mail: dali@org.chem.msu.ru (G P Brusova, D A Lemenovskii)

Received 27 June 2005

Uspekhi Khimii 75 (5) 395–421 (2006); translated by D A Yufit

The particular interest to amidinate is caused primarily by the commercial availability of a wide range of synthetic precursors — carbodiimides. Also of significant importance is the simplicity of preparation of amidinate complexes. Moreover, amidinate ancillary ligand is known to enhance the thermodynamic stability of a corresponding complex; thus, many cationic intermediates, which are unstable for related metallocene analogues, were isolated for amidinate derivatives. The ability to study such intermediates has greatly improved the knowledge of reaction mechanisms in such vital area as cationic olefin polymerisation.⁵

Synthesis and properties of amidinate complexes published prior to 1994 were comprehensively discussed in earlier reviews.^{6–9} However, despite the growing number of publications in this field over the past decade, there has been only a single review article dealing with ruthenium amidinate complexes.¹⁰ Hence, this justifies the need for an updated review on organometallic amidinate complexes. The present review is divided into two parts. The first part is devoted to a discussion of metal–amidinate ligand bonding inferred from X-ray diffraction data and computational studies. The other one deals with the chemical behaviour of amidinate complexes. The latter also contains detailed discussion of applications of amidinate derivatives in organic synthesis and catalysis. Future developments in the research of amidinate complexes are analysed in Conclusion.

Due to the limited space available, the metal complexes with neutral analogues of amidinate systems, *i.e.*, amidine ligands, are out of scope of the present review. Information about these compounds can be found in earlier reviews.^{11–13}

II. Structures of amidinate complexes

To date, the structures of amidinate complexes of different elements are reasonably well studied. Amidinate ligands behave as two- or (more often) four-electron donors depending on the nature of the central atom.⁷ Therefore, this system might be referred to as a hetero-analogue of the well known allylic ligand. However, the presence of molecular orbitals n^+ and n^- (Fig. 1) where the electrons of the nitrogen lone pairs are mostly localised results in significant difference in coordination modes of the amidinate and allylic fragments to metals.

Analysis of bonding of amidinate ligands with Group 14 elements (Si, Ge, Sn, Pb) as well as of the structure of a non-coordinated amidinate anion has been performed by detailed quantum-chemical calculations (by the extended Hückel method and by MP2/ECP-31G*).¹⁴ It was found that the N–C bond in a coordinated ligand is significantly longer (by ~ 0.1 Å) and the NCN bond angle is smaller in comparison with those in the non-coordinated anion. The decrease in the NCN bond angle occurs in

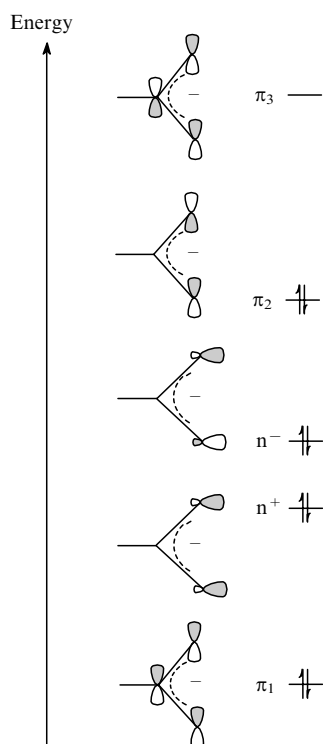


Figure 1. Molecular orbital diagram for the amidinate anion.

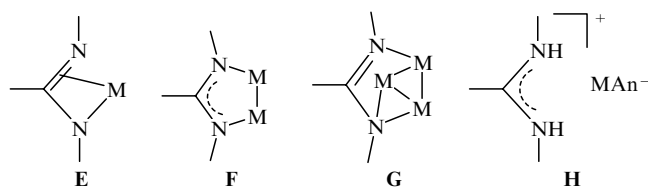
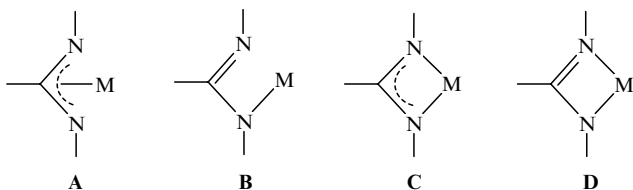
parallel to the decrease in the atomic radius of the corresponding element ($\text{Pb} < \text{Sn} < \text{Ge} < \text{Si}$). The calculated bond lengths and bond angles in amidinate complexes of Group 14 elements are listed below.

	E	The C≡N bond length/Å	The NCN angle/deg
—	—	1.252	125.7
Si	—	1.349	106.2
Ge	—	1.348	108.6
Sn	—	1.347	111.6
Pb	—	1.347	113.9

It should be noted that no calculations of this type have been documented for transition metal complexes. The only publication¹⁵ reports DFT calculations of ethylene molecule coordination parameters in titanium and zirconium bis(amidinate) complexes. However, no data on the geometrical parameters of the amidinate ligand itself are given and only bond angles NTiN and NZrN (128.3° and 127.8° , respectively) are presented.

Eight types of coordination of the amidinate ligand to metals can theoretically be predicted based on its electronic and spatial structures (structures **A–H**).

It should be noted that no η^3 -coordinated amidinate ligands (structure **A**, an analogue of the π -allylic system) and structures **E** have been reported so far. The other structural types have been discussed.^{8,9}

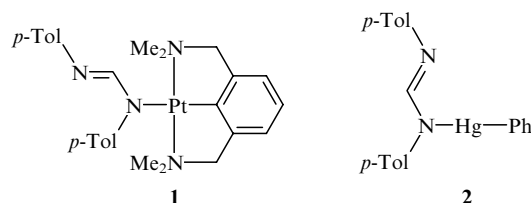


M is metal, An is anion.

The main sources of information about the structures of amidinate complexes are single crystal X-ray structural studies and the spectroscopic data (IR, NMR, *etc.*). Typically, the $\text{MN}(1)\text{CN}(2)$ metallacycle in amidinate complexes of transition and main-group elements is non-planar. In the **C**- and **D**-type structures, this ring usually adopts the 'folded envelope' conformation with dihedral angles between the $\text{MN}(1)\text{C}$ and $\text{MN}(2)\text{C}$ planes varying over a wide range (from 5° to 45°) (see Refs 8 and 9). The degree of pyramidalisation (ΣQ_N) of the nitrogen atoms in the amidinate ligand is yet another important criterion of non-planarity of the $\text{MN}(1)\text{CN}(2)$ metallacycle. This parameter is the sum of all bond angles of a nitrogen atom and is opposite to planarity. A decrease in ΣQ_N value, for example, due to a decrease in the bulk of substituents corresponds to higher degree of nitrogen pyramidalisation and, therefore, to greater deviation of the $\text{MN}(1)\text{CN}(2)$ metallacycle geometry from planarity. The mean values of the degree of pyramidalisation of nitrogen atoms in amidinate complexes are in the range of 335 – 360° (see Refs 8 and 9).

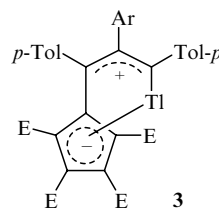
A short description of complexes of each known structural type is given below. The selection of examples of the structures **B–D** and **F–H** is entirely random. We just tried to emphasise the features of each coordination type as clearly as possible. Further in the text (see Section III), schematic depiction of complexes **B–G** implies a real structure determined objectively.

Very few examples of the structural type **B** with monodentate σ -amidinate ligands are known to date. Thus the $\text{Pt}–\text{N}$ distance in platinum complex **1** is equal to $2.132(6)$ Å and the NCN bond angle is $113.4(5)^\circ$ (see Ref. 16).



$p\text{-Tol} = 4\text{-MeC}_6\text{H}_4$.

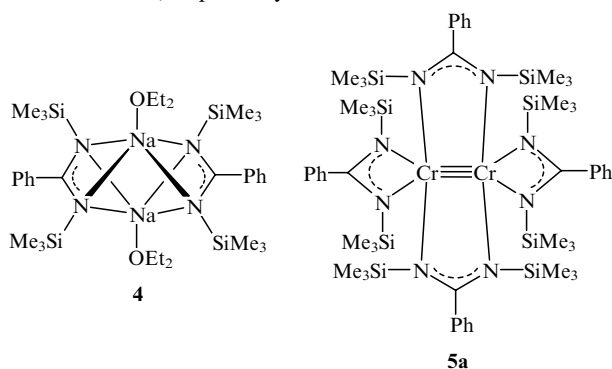
Yet another stable compound of this type is σ -organomercury complex **2** with unusual dynamic properties in solution.¹⁷ Also, type **B** compounds were postulated (based on the IR spectra) to serve as intermediates in the insertion of CO into the $\text{M}–\text{N}$ bond of rhodium amidinate complexes to yield the corresponding carbamide complexes.¹⁸ Unusual zwitter-ionic thallium amidinate complexes of the general formula **3** with formally positively charged amidinate groups have recently been obtained by Minkin and co-workers.¹⁹



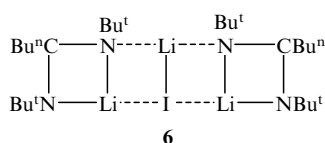
E = CO_2Me ; Ar = 1-naphthyl, 2- ClC_6H_4 , 2- $\text{Cl-6-MeC}_6\text{H}_3$.

According to X-ray diffraction data, the thallium atom in these complexes is σ -coordinated to the nitrogen atom and therefore these complexes may be regarded as type **B** compounds. The Tl–N distance is equal to 2.833(6) Å (for Ar = 2-Cl-6-MeC₆H₃). The distinctive features of complexes **3** include also η^5 -coordination of thallium with the π -system of the cyclopentadienyl ring and Z-configuration of the amidinate ligand. The C–N bond lengths are equal to 1.374(10) and 1.283(10) Å, the NCN bond angle is 119.8(7)°.

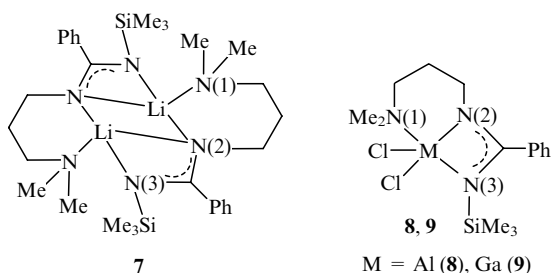
Most of known amidinate complexes belong to the structural type **C**. Dimers **4** (see Ref. 20) and **5** (see Ref. 21) are the most typical examples of such complexes of the main-group and transition elements, respectively.



The Na–N distances in compound **4** are equal to 2.617(5), 2.482(5), 2.426(5) and 2.725(5) Å; all NCN bond angles are 121.0(5)°. The Cr–N distances in complex **5a** amount to 2.100(4), 2.096(3), 2.092(4) and 2.095(3) Å; both NCN bond angles are equal to each other [116.4(4)°] as in the case of compound **4**. The derivatives of other alkali and alkaline-earth metals often form stable dimeric associates in crystals.^{8,9} The ‘ladder’-type aggregates are also known, in which dimerisation of amidinate salt is inhibited by co-crystallisation with inorganic salts MX (M is an alkali metal, X is an inorganic acid anion, for example Cl, I, Br) or with alkalis. Thus associate **6** was obtained by co-crystallisation of Li[BuⁿNC(Buⁿ)NBu^t] with LiI from a solution in THF.²²



Monomeric amidinate complexes with ‘constrained’ geometry can also be mentioned. In 2000, Lappert and co-workers²³ synthesised lithium complex **7**, which was transformed into aluminium (**8**) and gallium (**9**) amidinate derivatives.

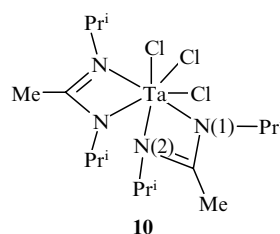


Complexes **8** and **9** are monomeric due to additional coordination of the nitrogen atom of the CH₂CH₂NMe₂ fragment by the central atom of the main-group metal. Usually, in the case of such additional coordination, the M–NMe₂ bond lengths became effectively equal to the M–N bond lengths in normal amidinate complexes. The structural parameters of compounds **7–9** are listed below.

Parameter	Compound		
	7 (M = Li)	8	9
Bond lengths / Å			
M–N(1)	2.050(3)	2.0929(16)	2.1407(18)
M–N(2)	2.015(3)	1.9053(15)	1.9592(15)
M–N(3)	1.989(3)	2.0182(16)	2.1130(17)
Bond angle N(2)CN(3) / deg	119.0(2)	111.20(15)	112.27(16)

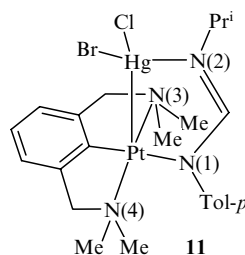
The NCN bond lengths in these complexes are within a standard range of the values for all amidinate ligands,^{8,9} which is common for all coordination types (**C**, **D**, **F** and **G**). A detailed structural analysis of a series of tris(amidinate) complexes of transition metals (Cr, Fe, Co, Ru) of type **C** is given by Cotton *et al.*²⁴

Non-symmetrically coordinated amidinate ligand represents the structural type **D**. In this case both nitrogen atoms are bonded to metal, but one forms formally a M–N σ -bond while another is coordinated by its lone electron pair. Quite a few complexes of this coordination type are known. Complex **10** can be taken as an example.²⁵



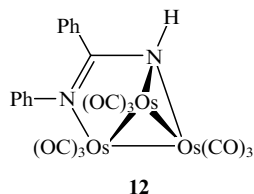
According to the X-ray data, the pairs of Ta–N distances are equal to 2.098(14), 2.196(16) and 2.058(15), 2.180(20) Å. The NCN bond angles are within expected values and are equal to 109.4(16)° and 105.4(20)°. Dihedral angles between TaN(1)C and TaN(2)C, where C is the central carbon atom in the NCN fragment of the amidinate ligand, are equal to 10.7° and 15.5°. The mean value of $\Sigma Q_N = 346.9^\circ$ indicates significant pyramidalisation of nitrogen atoms.

Structures **F** are relatively common for amidinate complexes possessing metal–metal bond. For instance, the platinum atom in bimetallic complex **11** (see Ref. 26) has a square-planar coordination with distances Pt–N equal to 2.155(9), 2.097(9) and 2.080(1) Å for nitrogen atoms N(1), N(3) and N(4) respectively.



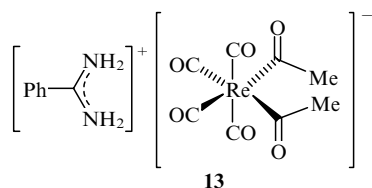
HgBrCl occupies an apical position relative to the plane of the platinum atom and two nitrogen atoms of the bis(dimethylamino)methylphenyl substituent with the Pt–Hg distance equal to 2.8331(7) Å. The amidinate ligand itself is bonded to mercury atom through the nitrogen atom of the NPrⁱ fragment, the Hg–N(2) bond length is 2.16(1) Å. The five-membered NCNHgPt ring is non-planar and the HgClBrN fragment is rotated such as to avoid staggered conformation of M–N bonds. In this case, the dihedral angle N(2)–Hg–Pt–N(1) is equal to 16.5(4)° and the NCN bond angle [125.0(1)°], in contrast to those found in most amidinate complexes, is larger than the theoretical value (120°). The ΣQ_N parameter for both nitrogen atoms is 360° indicating virtually planar trigonal configuration of nitrogen atoms in the amidinate ligand.

The structural type **G** is rather rare and has only been found in cluster complexes. For example, the amidinate ligand in the osmium cluster $[\text{Os}_3(\mu\text{-H})(\text{CO})_9]\{\text{NPhC(Ph)NH}\}$ **12** (see Ref. 27) is formally a five-electron donor. According to data from ^1H NMR spectroscopy, a bridging hydrogen atom is present in complex **12**; however, its position could not be located from X-ray diffraction analysis.

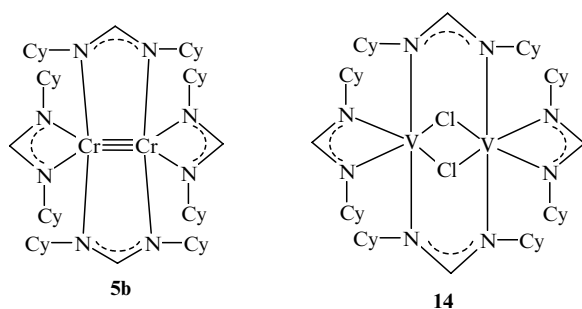


The Os–N bond lengths in metal complex **12** are equal to 2.198(23), 2.193(23) Å for osmium atoms linked to the nitrogen atom by a coordinated bond and to 2.141(22) Å for the σ -bond Os–N. Remarkably, the NCN bond angle [121.7(25)°] is slightly larger than the theoretical value, as it was also observed in complex **11**. Over the last decade, no new complexes of type **G** have been synthesised and therefore they are not discussed in the present review.

Structures **H** are of the most uncommon type of metal amidinate derivatives. In this case the protonated amidinate cation is a counter-ion of an organometallic anion, *i.e.*, there is no bonding between the amidinate moiety and the metal atom. Ionic complex **13** (see Ref. 28) is an example of such compound. Nitrogen atoms in salt **13** are virtually planar, the ΣQ_N parameter is 358°.

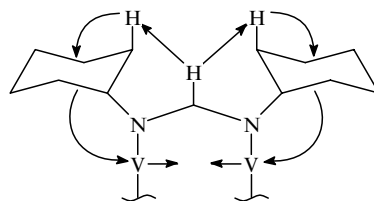


In closing this Section, it can be noted that the use of sterically hindered amidinate ligands often imparts unusual structural features to the molecules. For instance, the metal–metal distances in complexes **5b** (see Ref. 29) and **14** (see Ref. 30) are very short [$r_{\text{Cr-Cr}} = 1.913(3)$, $r_{\text{V-V}} = 1.698(2)$ Å] due to the presence of bulky cyclohexyl substituents at the nitrogen atoms.



Cy = cyclo- C_6H_{11} .

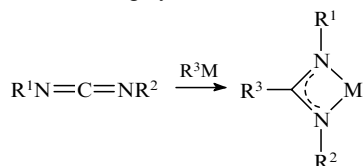
Presumably,³⁰ strong repulsion between the axial hydrogen atoms of the cyclohexane rings forces the two metal atoms to approach each other (a fragment of complex **14** is shown below). As a result, the equilibrium van der Waals radii of hydrogen atoms are equal to ~ 1.89 Å.



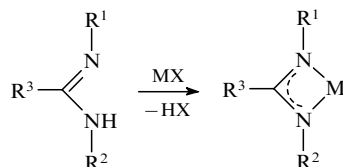
III. Synthesis and chemical properties of amidinate complexes

A large number of amidinate complexes of transition and main-group metals are currently known. In this Section synthesis and chemical properties of these compounds as well as their industrial applications are discussed. For the sake of convenience, the data are divided in two parts dealing separately with main-group and transition metals. The derivatives of the elements of Groups 1 to 15 of the Periodic Table are discussed.[†]

Four main approaches to the synthesis of amidinate complexes are known. The first one is the insertion of a σ -alkyl group (usually, the methyl group) of an organometallic fragment of the $\text{M}-\text{R}$ type into the $\text{C}=\text{N}$ double bond of carbodiimides. This method is fairly popular, since these reactions usually proceed under mild conditions and produce the corresponding amidinate derivatives in high yields.

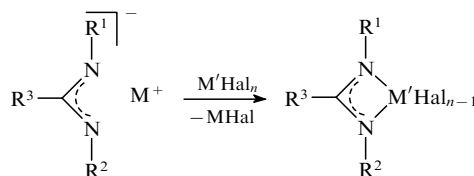


The second approach involves deprotonation of amidine ligands by organometallic compounds containing σ -alkyl ($\text{M}-\text{R}$) or σ -amide ($\text{M}-\text{NR}_2$) groups. This method is mainly used for the synthesis of alkali and alkaline-earth metal amidinates and derivatives of transition metals of Groups 3–5.



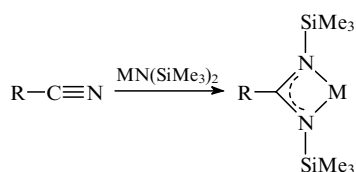
X = Alk, NMe_2 .

The most widespread method of synthesis of amidinate complexes of transition and main-group elements is the reaction of anionic amidinate salts of alkali and alkaline-earth metals with halides of Group 3–15 elements.



Finally, the reaction of metal bis(trimethylsilyl)amides with alkyl or aryl cyanides has to be mentioned as a general method of synthesis of 1,3-bis(trimethylsilyl)amidinate complexes.

[†] The 'long-period' version of the Mendeleev Periodic Table, in which the Groups of elements are indicated by Arabic numerals from 1 to 18, is used.



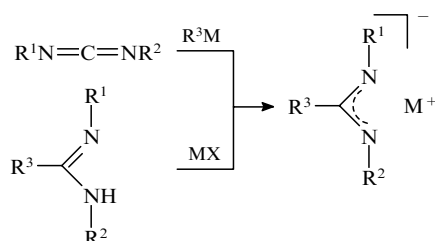
R = Alk, Ar.

Below we discuss the general methods of synthesis of amidinate complexes as well as specific reactions for each group of elements. The structures of all compounds mentioned in this Section are established by physicochemical analytical methods (IR- and UV-spectroscopy, NMR spectroscopy, mass spectrometry and in some cases by X-ray crystallography).

1. Amidinate complexes of main-group elements

a. Group 1 elements (Li, Na and K)

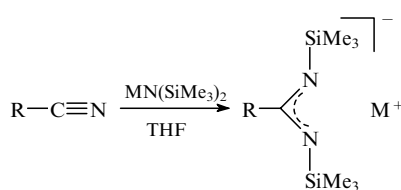
Alkali metal (mainly, lithium and sodium) amidinate derivatives attract attention as starting compounds in the synthesis of other amidinate complexes. Two major methods of synthesis of such compounds are known. The first one is the addition of an organometallic compound R–M (M = Li, Na) to the N=C double bond of carbodiimides.^{31–33}



R¹, R², R³ = Alk, Ar; M = Li, Na, K; X = Buⁿ, N(SiMe₃)₂.

An alternative way is the deprotonation of amidines by an organometallic base, for example, by BuⁿLi, NaN(SiMe₃)₂ or KN(SiMe₃)₂.^{34–36} Usually such reactions proceed in quantitative yields.

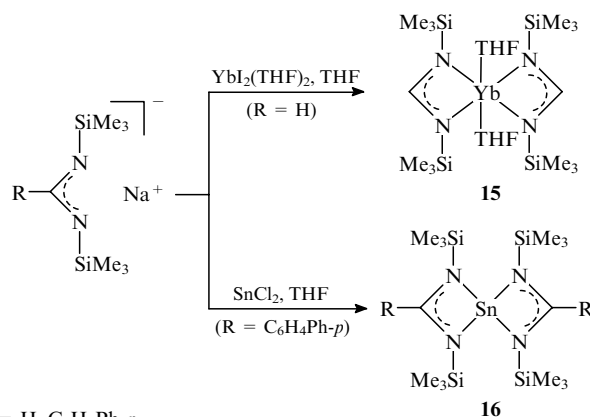
The reaction of carbonitriles with alkali metal bis(trimethylsilyl)amides is a convenient method of synthesis of 1,3-bis(trimethylsilyl)amidinate complexes.^{9, 37–40}



R = Alk, Ar; M = Li, Na, K.

Particular synthetic aspects for these compounds and their applications for the preparation of a series of 1,3-bis(trimethylsilyl)amidinate complexes of transition and main-group elements are described in detail in a review.⁹

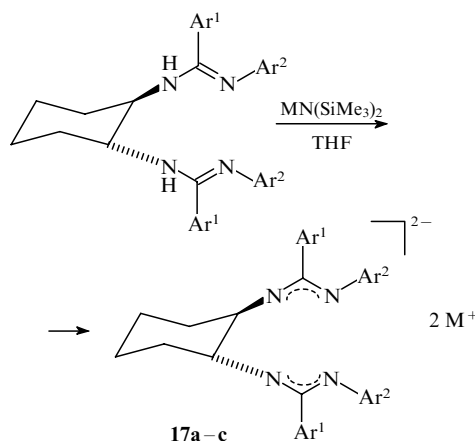
Amidinate complexes of Group 1 metals react with organic electrophiles yielding substituted amidines, and their reactions with metal halides afford the corresponding amidinate complexes. Preparation of complexes **15** and **16** is an example of the use of alkali metal amidinate complexes in the synthesis of the corresponding derivatives of transition and main-group elements.^{41, 42}



R = H, C₆H₄Ph-*p*.

These reactions will be discussed in detail in appropriate Sections. Studies on the synthesis of different amidinate complexes of Group 1 metal derivatives are summarised in reviews.^{6–9} This method is still widely used. A new development of this method is the synthesis of sterically hindered and/or chiral amidinate derivatives of alkali metals. These compounds can further be transformed into the corresponding transition metal complexes with a potential practical application in asymmetric catalysis.⁴³

In 2002 chiral bis(amidinate) complexes **17a–c** were obtained by direct metallation of amidines by lithium, sodium and potassium bis(trimethylsilyl)amides.⁴⁴

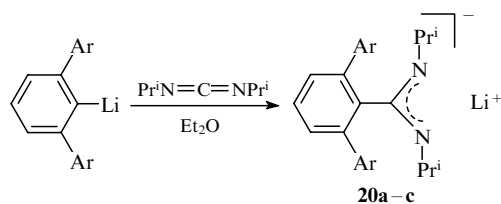


Ar¹ = Ar² = C₆H₄Me-*p*; M = Li (**a**), K (**c**);

Ar¹ = C₆H₄Bu^t-*p*, Ar² = C₆H₄OMe-*p*, M = Na (**b**).

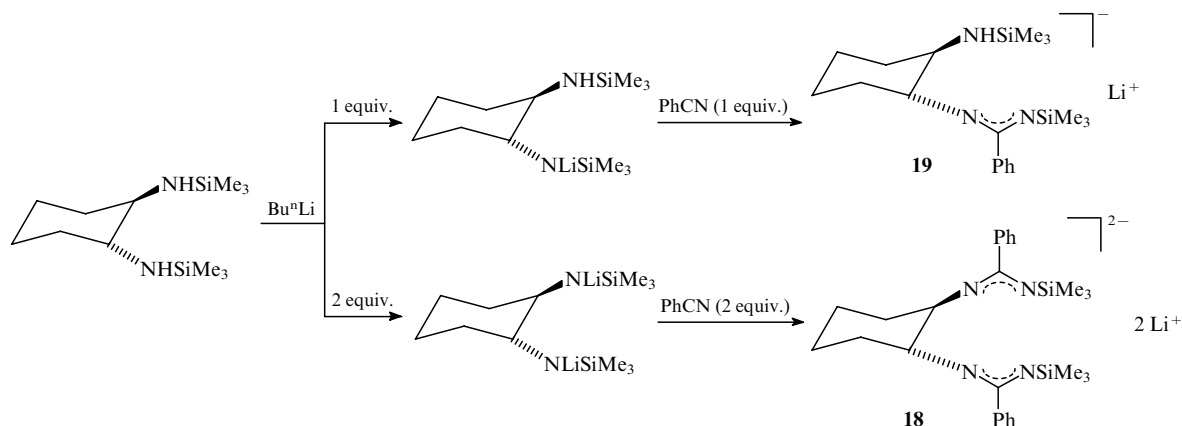
Similar trimethylsilyl derivatives **18** were obtained³⁵ by the addition of N-anions formed on treatment of bis(trimethylsilyl)amines) with 2 equiv. of butyllithium to the benzonitrile C≡N bond. Lithium monoamidinate complex **19** is formed in this reaction if equimolar amounts of the base and nitrile are used (Scheme 1).

Sterically hindered amidinate complexes **20a–c** were synthesised recently by the reaction of the corresponding aryllithium derivatives with diisopropylcarbodiimide.³⁴



Ar = Ph (**a**), C₆H₄Bu^t-*p* (**b**), 2,4,6-Me₃C₆H₂ (**c**).

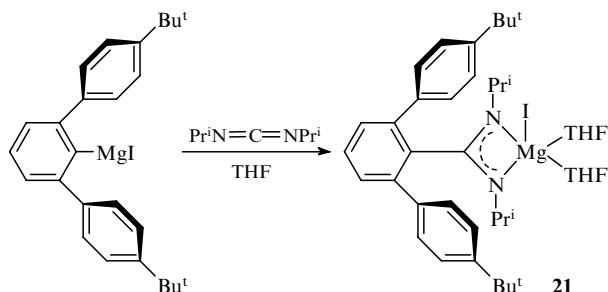
Scheme 1



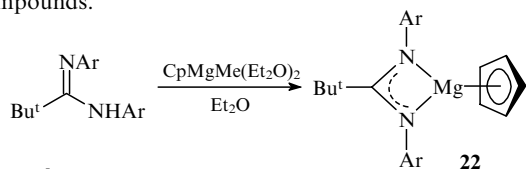
b. Group 2 elements (Mg, Ca, Sr and Ba)

Amidinate complexes of Group 2 elements are less studied than their alkali metal analogues. Data on the synthesis of these complexes published before 1994 were summarised in a review.⁹ No papers on the preparation of calcium, strontium and barium amidinate complexes have been published since 1994 and very few articles on the synthesis of the corresponding magnesium derivatives appeared. It has to be noted that no beryllium amidinate complexes are known so far.

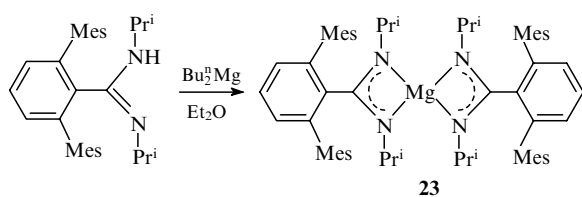
As for amidinate complexes of Group 1 metals, three general methods are used for the synthesis of organomagnesium derivatives. The first two methods afford the products in high yields (>80%). Thus complex **21** was synthesised³⁴ by addition of sterically hindered arylmagnesium iodide to the N=C double bond of diisopropylcarbodiimide. This complex was isolated and characterised as a THF solvate.



Mono- (**22**)⁴⁵ and bis(amidinate) (**23**)³⁴ complexes were obtained by deprotonation of amidines with organomagnesium compounds.

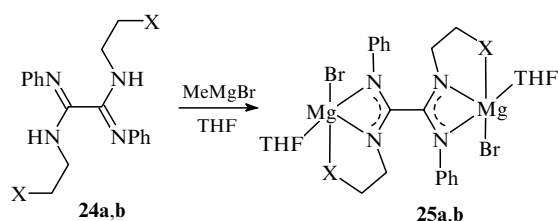


Cp = $\eta^5\text{-C}_5\text{H}_5$.



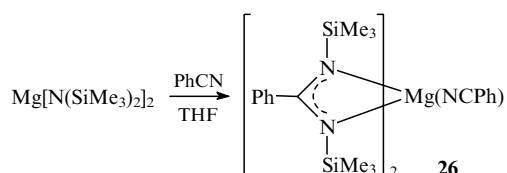
Mes = 2,4,6-Me₃C₆H₂.

Similar method was used in the synthesis⁴⁶ of dinuclear magnesium complexes **25a,b** from bisamidines **24a,b**.

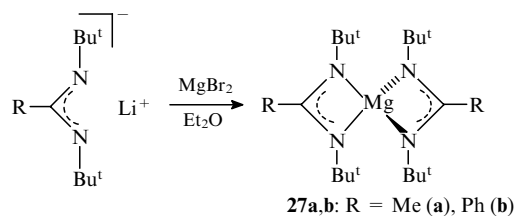


X = OMe (a), NMe₂ (b).

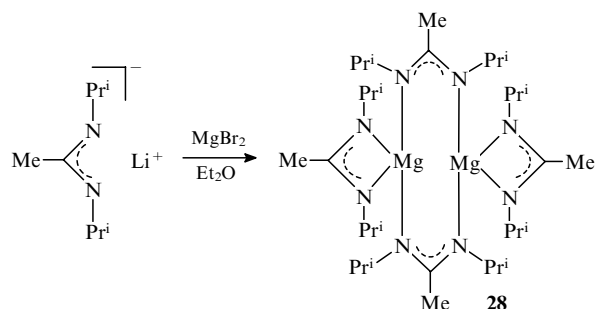
The addition of magnesium hexamethyldisylazide to the multiple C≡N bond of benzonitrile results in the formation of magnesium 1,3-bis(trimethylsilyl)amidinate complex **26**.⁴⁷

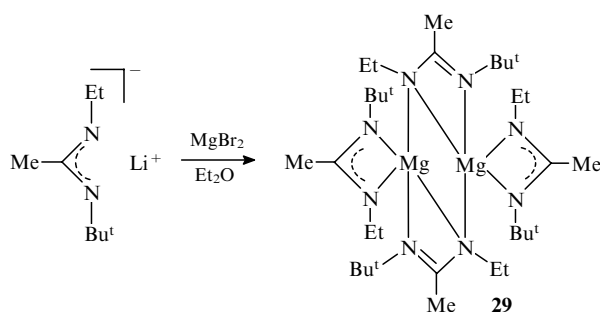


Magnesium amidinate complexes can also be obtained by amidinate ligand exchange between lithium amidinate and magnesium halide.⁴⁸ These reactions are usually carried out in ether and the driving force of the process is the formation of insoluble salt LiX (X = Cl, Br). Depending on the character of the substituents at the nitrogen atoms of the amidinate ligand, either mononuclear (**27a,b**) or dinuclear (**28, 29**) magnesium complexes are formed.



27a,b: R = Me (a), Ph (b)





Currently synthesis of sterically hindered ligands (for example, as in type **21** and **23** complexes) is the most intensively developing area in the chemistry of amidinate complexes of Group 2 metals. These derivatives were successfully used for the preparation of transition metal-based asymmetric catalysts.⁴³ For the same reason, the complexes with 'constrained' geometry (**25a,b**) are also of interest. In addition, magnesium amidinate derivatives **22** and **25a,b** are used as volatile organomagnesium compounds in CVD (Chemical Vapour Deposition) technology.^{45, 46}

c. Group 12 elements (Zn, Cd and Hg)

Unusual structural properties are the main reasons for the interest in zinc, cadmium and mercury amidinate derivatives. For example, the most unusual coordination types **B**,¹⁷ **F**²⁶ and **G**⁸ of the amidinate ligand are common for these compounds. A detailed discussion of the data on the synthesis, structure and properties of amidinate complexes of Group 12 elements is reviewed.⁸

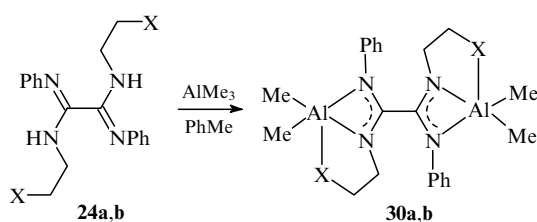
Due to the high toxicity of such elements as cadmium and mercury, no chemical studies on the amidinate complexes of Group 12 elements have been carried out since 1994. Therefore, this group of compounds is not discussed in the present review.

d. Group 13 elements (B, Al, Ga, In and Tl)

Among the amidinate complexes of Group 13 metals, aluminium derivatives, which are used as olefin polymerisation catalysts, are of prime importance.^{49–52} At present, gallium, indium and thallium amidinate complexes are of limited theoretical and practical interest; very few papers^{23, 53–57} have been published on this subject since 1994. Only one paper⁶⁰ dealing with the synthesis of new boron amidinate derivatives has been published since the discovery of organoboron amidinate complexes by Lappert and co-workers^{58, 59} in the early seventies. Difficulties encountered with the isolation of these boron compounds due to large amounts of by-products have been noted in all the three papers.

There are four major methods of synthesis of amidinate complexes of Group 13 elements.

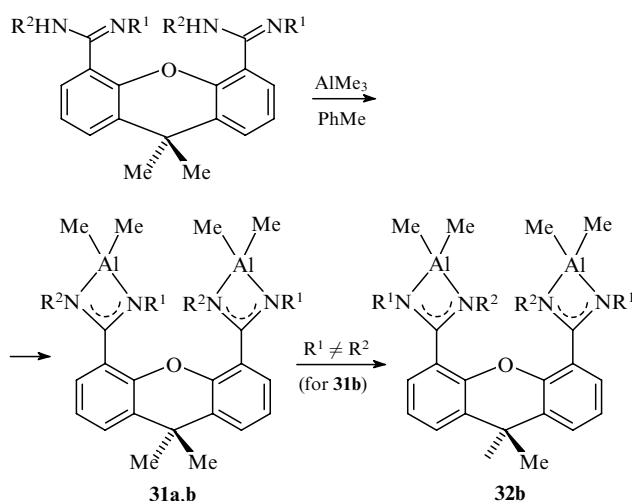
The first one is the deprotonation of amidines by organoaluminium compounds, in most cases by trimethylaluminium. Complexes **30a,b** with 'constrained' geometry were obtained from bis(amidines) **24a,b** by this method.⁴⁵



X = OMe (**a**), NMe₂ (**b**).

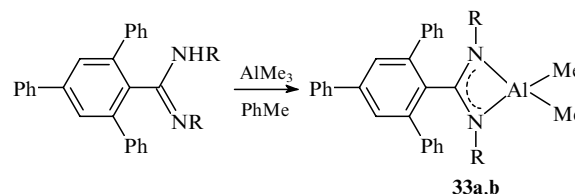
Bis(amidinate) complexes **31a,b** were synthesised similarly in moderate yields (35%–60%).⁶¹ If the amidine nitrogen atoms of compound **31** carry different substituents, this complex exists in solution as two structural isomers **31b** and **32b**. Depending on the mutual orientation of the amidinate ligands, these isomers are of either C_s- (**31b**) or C₂-symmetry (**32b**). According to data from

NMR spectroscopy (EXCHSY-experiment),⁶¹ the rotational barrier is very low and equal to 0.00(4) kcal mol^{−1}.



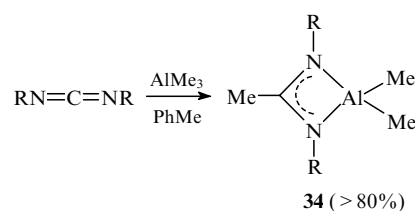
R¹ = R² = Prⁱ (**a**); R¹ = Et, R² = Bu^t (**b**).

This method was successfully used for the synthesis (in satisfactory yields) of dialkylgallium amidinate derivatives⁵⁶ and organoaluminium complexes **33a,b** with bulky amidinate ligands.⁶²



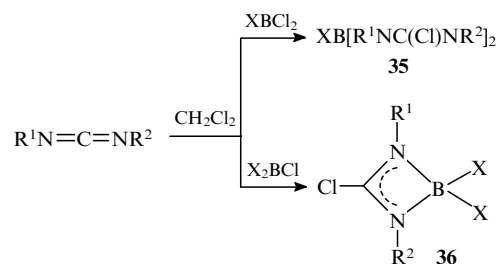
R = Prⁱ (**a**), Cy (**b**).

The second method is the addition of trialkylaluminium derivatives to the N=C double bond in carbodiimides.^{63, 64} These reactions proceed under mild conditions (ambient temperature) and in high yields.



R = Prⁱ, Cy, 2,6-Pr₂C₆H₃, 1-adamantyl.

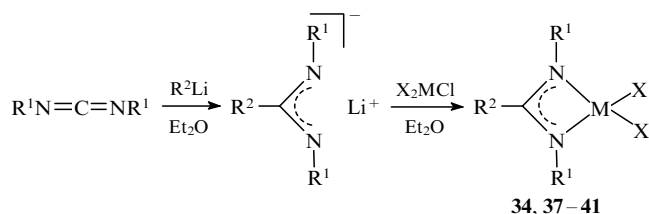
The addition of a B–Cl fragment to the carbodiimide double bond is a modification of this method. This reaction has been used by Lappert and co-workers^{58, 59} for the synthesis of boron amidinate complexes **35** and **36**.



R¹, R² = Ar; X = Cl, OAlk.

Unfortunately, the absence of X-ray diffraction data precludes unambiguous determination of the coordination mode of amidinate ligands in complexes **35** and **36**.

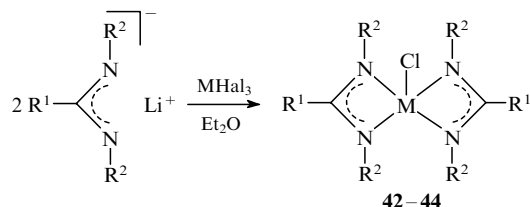
The third most widely used method of synthesis of amidinate complexes of Group 13 elements is the reaction of lithium amidinates with the corresponding metal halides. Dialkyl derivatives ($X = \text{Alk}$) of aluminium (**34**),^{63–65} gallium (**37**), indium (**38**) and thallium (**39**) were obtained by this method from the corresponding dialkylmetal chlorides used as halides.⁶⁵ Aluminium and gallium trichlorides were used as the starting compounds in the synthesis of the corresponding dichloroamidinate complexes **40**,^{63, 64} and **41**.⁵⁴



M = Al (**34**, **40**), Ga (**37**, **41**), In (**38**), Tl (**39**);

X = Alk (**34**, **37–39**), Cl (**40**, **41**); $\text{R}^1 = \text{Alk}$, SiMe_3 ; $\text{R}^2 = \text{Alk}$.

Aluminium, gallium and indium bis(amidinate) complexes, viz., compounds **42–44**, respectively, are formed in the reaction with a double excess of the starting amidinate salt.^{53, 54, 63}

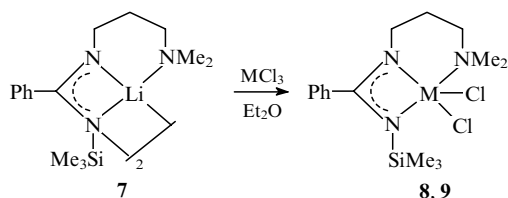


42: M = Al; $\text{R}^1 = \text{Me}$, Bu^t ; $\text{R}^2 = \text{Pr}^i$, Cy;

43: M = Ga; $\text{R}^1 = \text{H}$, Me; $\text{R}^2 = \text{Me}$, Bu^t , Ph;

44: M = In, $\text{R}^1 = \text{Bu}^t$, $\text{R}^2 = \text{Cy}$.

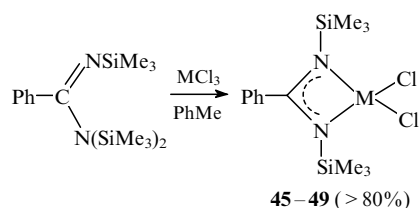
Aluminium and gallium amidinate complexes with 'constrained' geometry (**8** and **9**) were synthesised similarly.²³



M = Al (**8**, 85%), Ga (**9**, 78%).

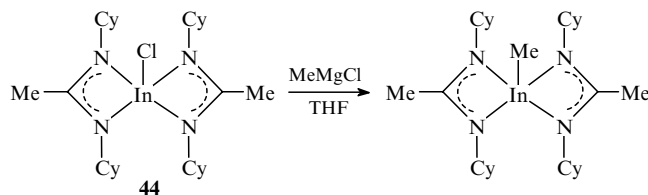
The yields of the complexes obtained by three above-mentioned methods vary from moderate to high (40%–90%).

Finally, the fourth method is metathesis of N–Si bonds in trimethylsilyl-substituted amidines and M–X bonds in Group 13 metal halides. This method was successfully used for the synthesis of corresponding dichloroamidinate derivatives of boron (compound **45**), aluminium (**46**), gallium (**47**), indium (**48**) and thallium (**49**).⁶⁰ All reactions proceeded under mild conditions and resulted in high yields of the target products.

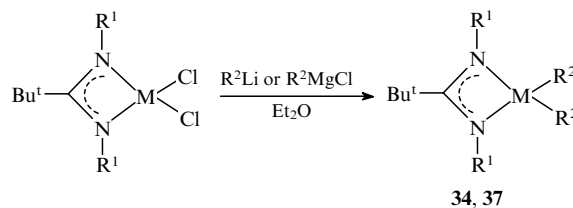


M = B (**45**), Al (**46**), Ga (**47**), In (**48**), Tl (**49**).

Complexes of monoalkyl and dialkyl derivatives of the elements of this Group can also be obtained by the reaction of the corresponding mono- and dichlorides with alkylmagnesium compounds. For instance, treatment of indium chloride amidinate complex **44** with methylmagnesium chloride results in the substitution of the methyl group for the chlorine.⁵³



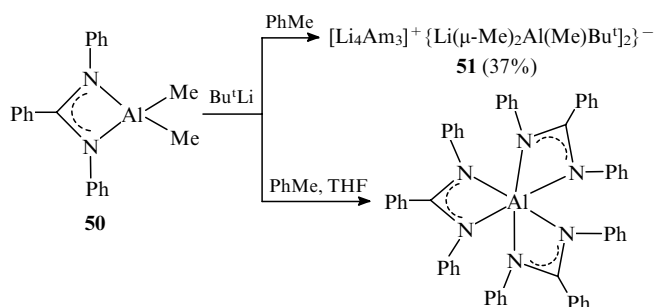
A series of dialkylaluminium⁶³ and -gallium⁵⁴ amidinate complexes were synthesised by this method.



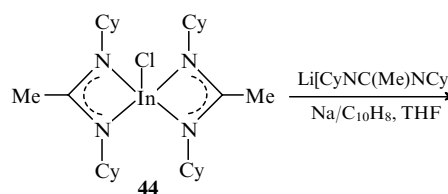
34: M = Al; $\text{R}^1 = \text{Pr}^i$, Cy; $\text{R}^2 = \text{Bn}$, CH_2Bu^t ;

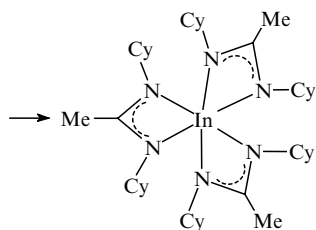
37: M = Ga; $\text{R}^1 = \text{Pr}^i$, Bu^t , Cy; $\text{R}^2 = \text{Me}$, Et, Bn.

It should be noted that amidinate complexes of Group 13 elements are not Lewis acids. Thus treatment of aluminium derivative **50** with *tert*-butyllithium in toluene resulted in displacement of the amidinate ligand out of the coordination sphere of aluminium and the formation of compound **51**,⁶⁶ i.e., a complete destruction of the original complex occurred. The cationic fragment $(\text{Li}_4\text{Am}_3)^+$ of the product **51** is a lithium–nitrogen cluster. Another unusual product was obtained in the reaction of *tert*-butyllithium with compound **50** in a mixture of toluene–THF.¹⁰ Alongside with unidentified compounds, an aluminium tris(amidinate) complex was formed.

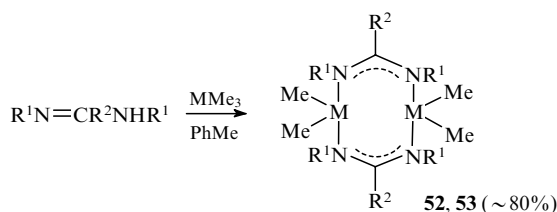


The reaction of bis(amidinate) derivatives with the corresponding lithium amidinate is yet another method of synthesis of tris(amidinate) complexes. Indium tris(amidinate) complex was obtained by this way from chloride **44**.⁵³





Dinuclear gallium and indium complexes with bridging amidinate ligand are known. Thus compounds **52** and **53** were obtained in the reaction of amidines with trimethylgallium⁵⁶ and -indium.⁵⁷

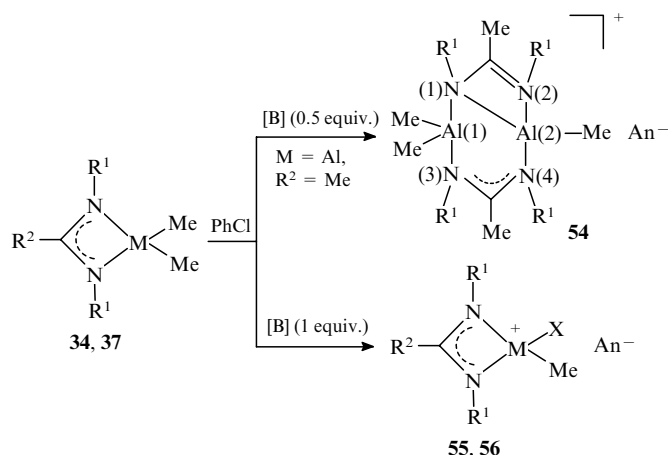


52: M = Ga; R¹ = R² = Me; R¹ = H, R² = Ph;

53: M = In, R¹ = Cy, R² = H.

Catalysis of olefin polymerisation is the main application of amidinate complexes of Group 13 elements. Cationic monoalkyl complexes with central aluminium atom are the most active in these processes.^{49, 50, 55} Their gallium analogues were also studied.⁵⁵ Such cationic complexes were obtained in quantitative yields by dealkylation of aluminium (**34**) and gallium (**37**) derivatives with arylboron reagents — [Ph₃C][B(C₆F₅)₄], [PhNHMe₂], [B(C₆F₅)₄] or B(C₆F₅)₃.

Either bi- (**54**) or mononuclear (**55**, **56**) aluminium and gallium complexes are formed in these reactions depending on the amount of the reagent used (0.5 or 1 equiv.). If the equimolar amount of [PhNHMe₂][B(C₆F₅)₄] is used as a cationic activator, the products contain the group X = NMe₂Ph in the organometallic cation.



M = Al (**34**, **54**, **55**), Ga (**37**, **56**); R¹ = Prⁱ, Cy, R² = Me, Bu^t;

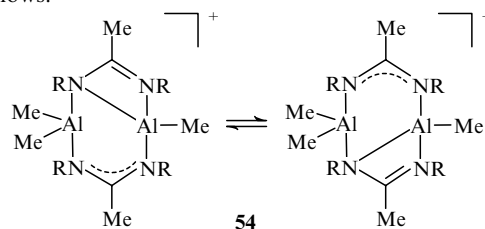
[B] = [Ph₃C][B(C₆F₅)₄], X is absent, An = [B(C₆F₅)₄];

[B] = B(C₆F₅)₃, X is absent, An = [MeB(C₆F₅)₃];

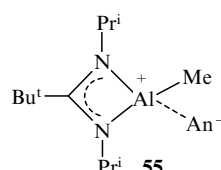
[B] = [PhNHMe₂][B(C₆F₅)₄], X = NMe₂Ph, An = [B(C₆F₅)₄].

Two amidinate ligands in dinuclear complexes **54** coordinate aluminium atoms differently.⁴⁹ One of them is bound to two aluminium atoms in the $\mu\text{-}\eta^1, \eta^1$ -mode (structure **F**, Section II). Another ligand coordinates one aluminium atom in the mixed $\mu\text{-}\eta^2, \eta^1$ -mode (structure **D**) and forms a donor-acceptor bond with the second one, *i.e.*, coordinates metal atom in the η^1 -mode. The Al–N distances in amidinate complex **54** (R¹ = Prⁱ, An = [B(C₆F₅)₄]) are 1.979 [Al(2)–N(1)], 1.927 [Al(2)–N(2)] and 2.027 Å [Al(1)–N(1)].⁵⁵ Complexes **54** are dynamically

active in solution, which was confirmed by ¹H NMR spectroscopy.⁵⁵ The dynamic equilibrium observed can be expressed as follows:



Cationic complexes **55** (R¹ = Prⁱ, R² = Bu^t) were used as catalysts of ethylene polymerisation.⁴⁹ Their efficiency appeared to be dependent on the character of the anion An[−] and temperature.



Thus the catalytic activity of compound **55** {An = [MeB(C₆F₅)₃]} at 23 °C in CD₂Cl₂ is low. Raising the temperature to 60 °C (polymerisation in toluene) results in a significant enhancement of the activity (up to 700 g mol^{−1} h^{−1} atm^{−1});[‡] the polyethylene (PE) produced had the following properties: the number average molecular mass (*M*_n) was equal to 176 100, the ratio *M*_w/*M*_n = 2.84 (*M*_w is the weight-average molecular mass). A more active catalyst was formed from amidinate complex **34** (R¹ = Prⁱ, R² = Bu^t) using [Ph₃C][B(C₆F₅)₄] as the demethylation reagent. Complex **55** {An = [B(C₆F₅)₄]} is more active in the reaction of ethylene polymerisation: its activity in toluene at 60 °C is 2480 (*M*_n = 272 200, *M*_w/*M*_n = 3.30) and at 85 °C, 3050 g mol^{−1} h^{−1} atm^{−1} (*M*_n = 184 700, *M*_w/*M*_n = 2.23).

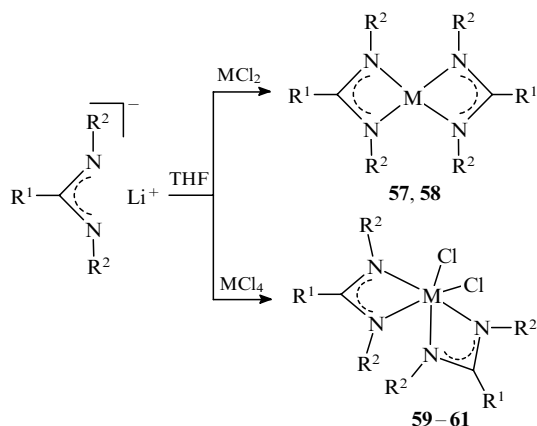
Polymerisation of ethylene in the presence of aluminium amidinate complexes **54** and **55** became the subject of detailed theoretical studies.^{67–70} This process was simulated by different quantum-chemical methods: *ab initio*,^{67, 70} semi-empirical (AM1)⁶⁹ and DFT.^{67, 68, 70} According to these calculations, the transfer of the polymeric chain occurs by a β -hydride shift mechanism. Low catalytic activity of dinuclear complexes of type **54** is due to a high activation barrier for the rate-determining stage of ethylene insertion. Mononuclear complexes **55** are more active polymerisation catalysts. The activity depends on their concentration in the solution. It was shown that the presence of bulky substituents (for example, Bu^t and Prⁱ) in the amidinate ligand favours the formation of mononuclear complexes and decreases the energy barrier to ethylene insertion during polymerisation. An increase in temperature has a similar effect.

Gallium amidinate complexes **56** are also used as catalysts of olefin polymerisation. Besides, they are used for the preparation of gallium nitride-based materials.^{71–73}

e. Group 14 elements (Si, Ge, Sn and Pb)

The recently increased interest in amidinate complexes of Group 14 elements is due to their potential application as starting materials in the manufacture of semiconductors based on germanium and tin nitrides.⁷⁴ The major method of the synthesis of amidinate derivatives of divalent (**57**, **58**) and tetravalent (**59–61**) elements is the reaction of element chlorides with 2 equiv. of lithium amidinate.^{75–80}

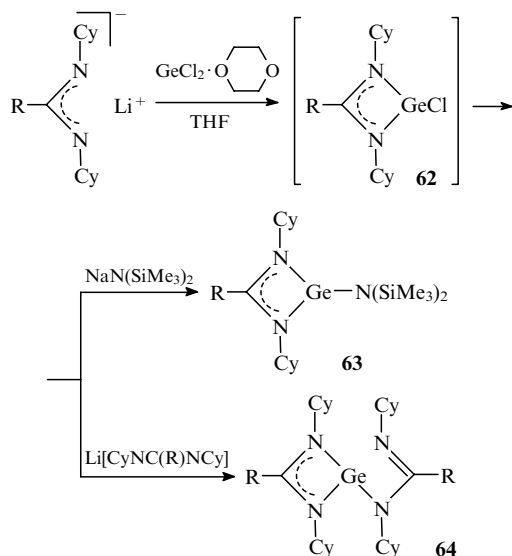
[‡] The activity of a catalyst is defined as the mass of a polymer per mol of the catalyst per hour at 1 atm.



57, 60: $M = Ge$, $R^1 = Me$, $R^2 = Pr^i$;
58: $M = Sn$; $R^1 = Me, Bu^t, Ph$; $R^2 = Cy, SiMe_3, SiMe_2Ph$;
59: $M = Si$, $R^1 = Me$, $R^2 = Pr^i$;
61: $M = Sn$; $R^1 = H, Me, Bu^t$; $R^2 = Cy, SiMe_3$.

These reactions proceed under mild conditions and for the tetravalent elements result in the corresponding bis(amidinate) complexes **57–61** in satisfactory yields (> 50%).

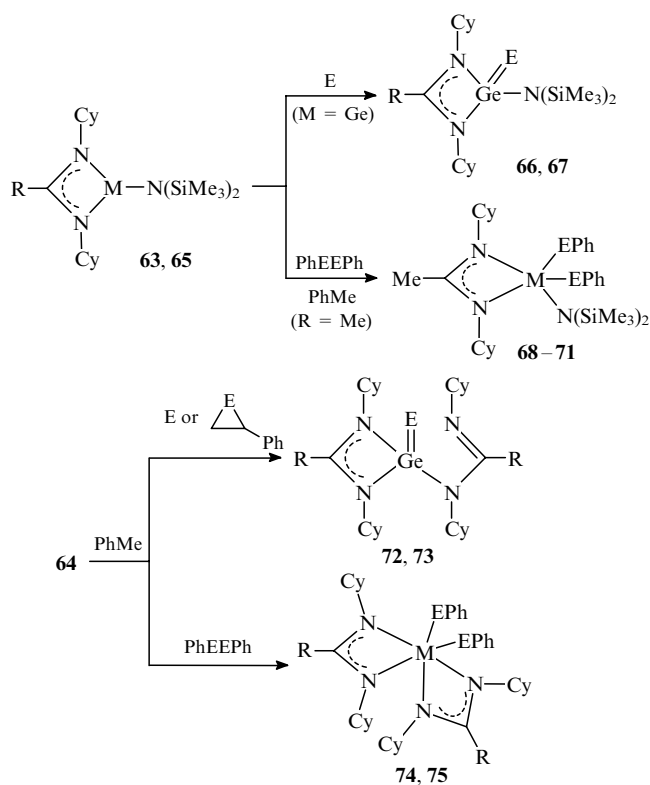
The process can be selectively stopped at the stage of mono-derivative **62** if one equivalent of the lithium salt is used in the reaction.⁷⁸ Further addition of $NaN(SiMe_3)_2$ results in the corresponding silylamidoamidinate derivative **63**. If the divalent germanium derivative **62** contains bulky substituents (*e.g.*, cyclohexyl), the second amidinate ligand coordinates the central atom in a σ -mode to form complex **64**.



$R = Me, Bu^t$.

Divalent germanium (**63, 64**) and tin (**65**) amidinate derivatives undergo oxidative addition of chalcogens (sulfur and selenium).^{78, 79, 81} Elementary sulfur and selenium,⁷⁸ 2-phenylthiirane(selenerane) as well as organic disulfides(diselenides) were used as reagents in these processes.^{79, 81}

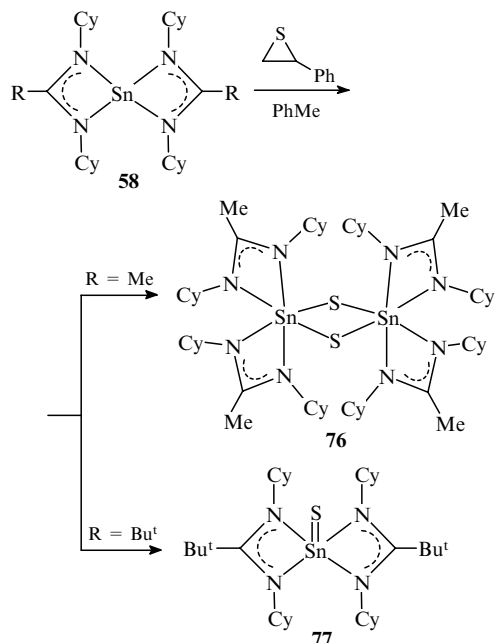
The reaction products are formed in high yields (> 80%). The structures of complexes **66–75** were determined by X-ray diffraction analysis. The $Ge-N$ bond lengths in η^1 -coordinated amidinate ligands are in the range of 1.8–2.0 Å, *i.e.*, they are shorter than the corresponding $Ge-N$ bonds in chelated amidinate ligands (2.0–2.05 Å). Interestingly, the coordination of the second amidinate ligand is changed upon formation of germanium bisulfide (or biselenide) amidinate complexes **74** and **75**. Such transformations are not observed in Sn-analogues due to the smaller atomic radius of germanium in comparison with that of tin.



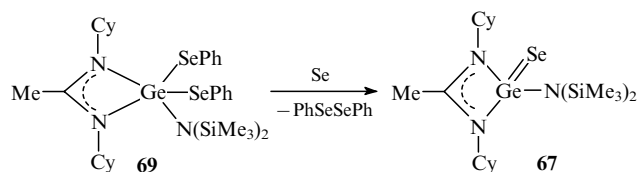
$R = Me, Bu^t$; $M = Ge$ (**63, 68, 69**), Sn (**65, 70, 71**);
 $E = S$ (**66, 68, 70, 72, 74**), Se (**67, 69, 71, 73, 75**).

One of the amidinate ligands in complexes **72** and **73** (as well as in the starting compound **64**) is linked to the metal atom through only one nitrogen atom.

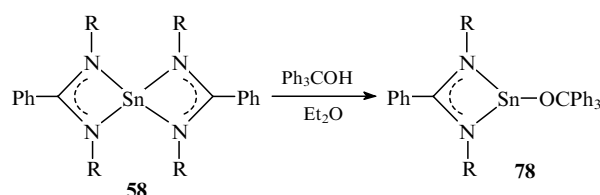
The steric strain in amidinate ligands also affects the structures of the complexes obtained in the oxidative addition reactions. Thus the structure of the reaction product of compound **58** with phenylthiirane depends on the bulk of the substituent at the amidinate carbon atom.⁷⁹ If this substituent is a methyl group, then bridged bisulfide dimer **76** is formed. In the case of a bulky *tert*-butyl substituent in the amidinate ligand, the tin atom is sterically overcrowded and only monomeric complex **77** containing a double bond $Sn=S$ is formed in this reaction.



The reaction of germanium biselenide complex **69** with elementary selenium yields compound **67** and diphenyl diselenide is eliminated.⁸¹



Tin(II) mixed amidinate-alkoxide complexes **78** were obtained in the reaction of the corresponding silylamide derivatives **58** with triphenylmethanol.⁸⁰ The coordination number 3 relatively rare for tin compounds is found for the tin atoms of both complexes by X-ray diffraction analysis.



R = SiMe₃, SiMe₂Ph.

Compounds **78** turned out to be active catalysts of lactide polymerisation in toluene at 80 °C. The activity of complex **78** with a trimethylsilyl substituent is 63.5 kg mol⁻¹ (polydispersity of the polymer obtained was 1.48), which is more than twice that of the compound with dimethylphenylsilyl group (28.9 kg mol⁻¹). However, the polydispersity of the polymer obtained using the latter catalyst was 1.18.

It can be noted at the end of this Section that not a single paper was published on lead amidinate derivatives during the last decade. Earlier papers dealing with lead amidinate complexes are cited in the review.⁹

f. Group 15 elements (Sb and Bi)

So far no practical application has been found for antimony and bismuth amidinate complexes due to their lability and difficulties of preparation. Data on the chemistry of these derivatives published before 1994 has been summarised in reviews.^{6,9} Phosphorus and arsenic amidinate derivatives, being purely organic compounds, are beyond the scope of the present review on organometallic complexes.

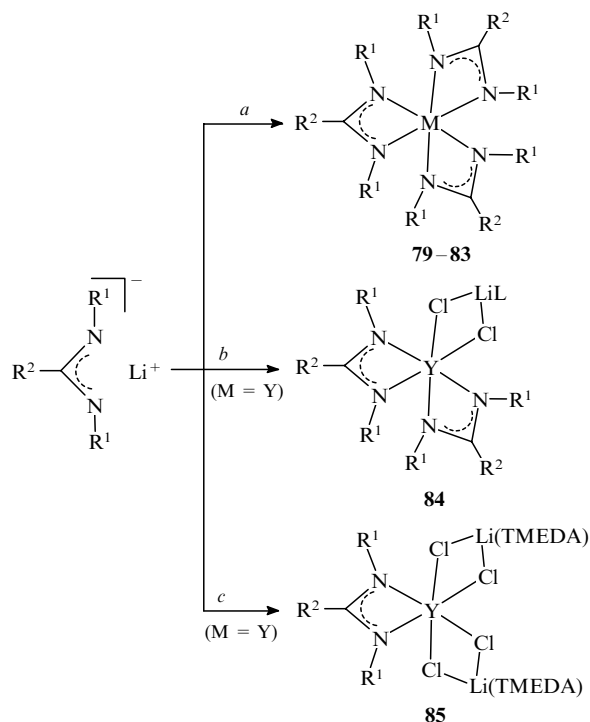
2. Amidinate complexes of transition metals

a. Group 3 elements (Sc, Y, lanthanides and actinides)

The chemistry of lanthanide amidinate complexes has been significantly developed over the last decade. Most of the data are documented in the review⁸² published in 2002. Here we discuss only those papers that have not been surveyed previously.

The reaction of the corresponding alkali metal (usually, lithium) amidinates with commercially available lanthanide chlorides is the major method of synthesis of tris(amidinate) derivatives of lanthanum group metals **79–83** as well as of the most similar complexes of transition metals.^{23, 82–85} These reactions proceed under mild conditions and result in high yields of the target products.

In some cases (like for yttrium), stable adducts **84** and **85** containing one or two lithium atoms coordinated to chloride ligands are obtained.



(a) MCl₃ (1/3 equiv.), Et₂O; (b) YCl₃ (1/2 equiv.), *N,N,N',N'*-tetramethylethylenediamine (TMEDA) or THF; (c) YCl₃ (1 equiv.), TMEDA, THF;

79: M = La; R¹ = Prⁱ; R² = Me, Bu^t;

80: M = Nd; R¹ = Cy; R² = Me, Ph;

81: M = Gd, R¹ = Cy, R² = Me;

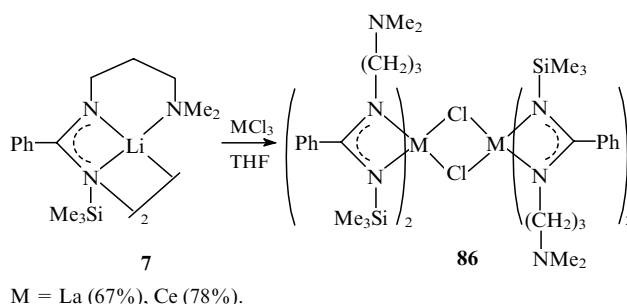
82: M = Yb; R¹ = Cy; R² = Me, Ph;

83: M = Y, R¹ = Cy, R² = Ph;

84: R¹ = SiMe₃, 2,6-Et₂C₆H₃; R² = Ph, *p*-Tol; L = TMEDA, THF;

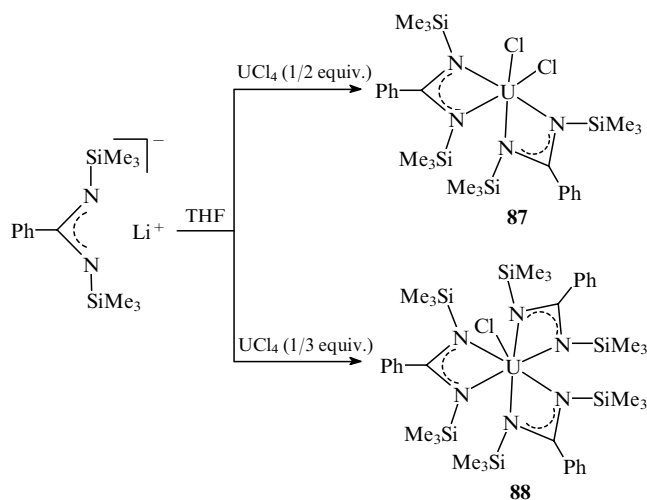
85: R¹ = Prⁱ, R² = 2,6-Me₂C₆H₃.

It should be noticed, that, due to their larger atomic radii, the lanthanum group metals are more prone to form bis- and tris(amidinate) complexes, than the Group 13 elements (B, Al, Ga, In). Thus the reaction of lithium derivative **7** with lanthanum and cerium trichlorides yields bis(amidinate) dinuclear complexes **86** containing pentacoordinated dimethylamino groups. At the same time, aluminium and gallium trichlorides form monoamidinate complexes **8** and **9** with 'constrained' geometry under similar conditions.²³ The yields of complexes **86** are ~70%.

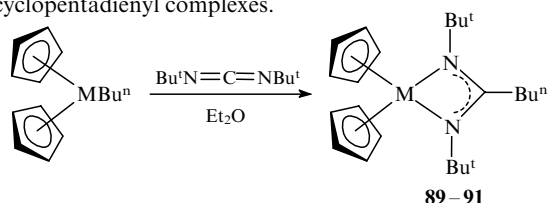


M = La (67%), Ce (78%).

Uranium bis- (**87**) and tris(benzamidinate) (**88**) complexes are formed in the reaction of uranium tetrachloride with two or three equivalents of lithium amidinate, respectively (yields are 60%–70%).⁸⁶ No corresponding mono- or tetrasubstituted amidinate derivatives were obtained.

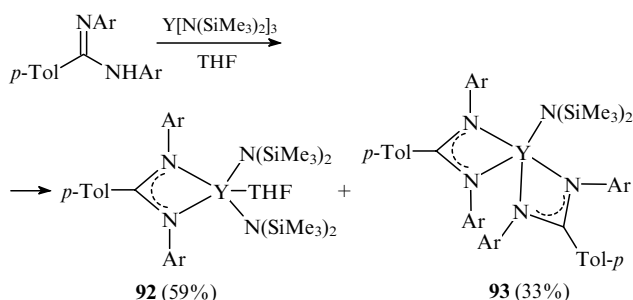


An alternative method of synthesis of lanthanide amidinate complexes is the addition of carbodiimide to the metal–carbon bond of alkylmetal derivatives. This method was applied for the synthesis of europium, ytterbium and gadolinium compounds.⁸⁷ For instance, amidinate complexes **89–91** were obtained by reaction of di(*tert*-butyl)carbodiimide with *n*-butyllanthanide dicyclopentadienyl complexes.



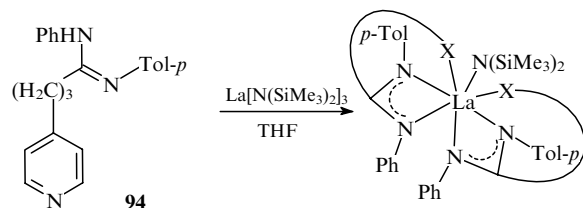
M = Er (**89**), Y (**90**), Gd (**91**).

Deprotonation of arylamidines by silylated lanthanide tris(amides) results in the corresponding amidinates. Thus a mixture of yttrium mono- (**92**) and bis(amidinate) (**93**) complexes was obtained by this method.⁸⁸



Ar = 2,6-Et₂C₆H₃.

A lanthanum bis(amidinate) complex with tridentate ligands was synthesised similarly from amidine **94**.⁸⁸



X = (CH₂)₃Py-4.

Little is known about the properties of amidinate complexes of lanthanides. Dynamic behaviour of some of them in solution and reactions with alkenes and terminal alkynes have been discussed.⁸² Practical interest in these compounds is caused by

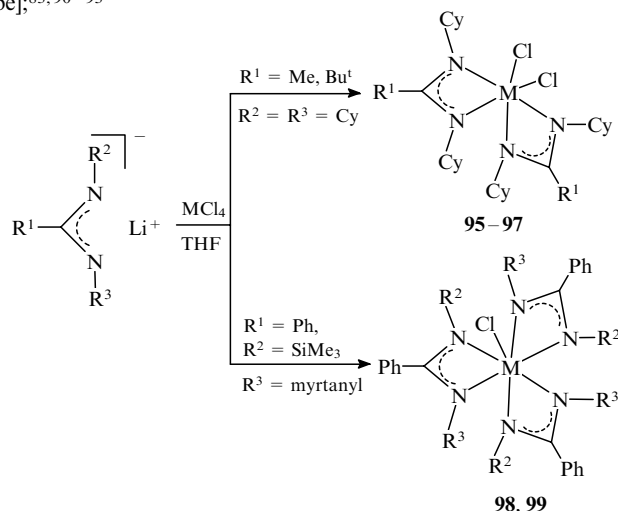
their high catalytic activities in polymerisation reactions of ethylene (compound **86**),⁸⁹ ε-caprolactone (complexes **79–83**),⁸⁴ D,L-lactide (compounds **84** and their phenoxide analogues obtained by substitution of the OC₆H₃R₂-2,6 group, where R = Me, Bu^t, for the chlorine)⁸⁵ as well as in the reaction of cyclotrimerisation of phenyl isocyanide (complex **90**).⁸⁷ The polymers formed have high molecular mass (> 10⁴) and low polydispersity (< 2). Moreover, volatile lanthanum amidinate derivatives were used in membrane manufacturing by CVD.⁸³

b. Group 4 elements (Ti, Zr and Hf)

Most of the papers on amidinate derivatives published over the last decade deal with the Group 4 metal complexes. This is due to several reasons: cheap and commercially available starting materials, simplicity of the synthesis of complexes, their thermal stabilities and, first of all, potential application in such an important area as catalytic polymerisation of olefins.

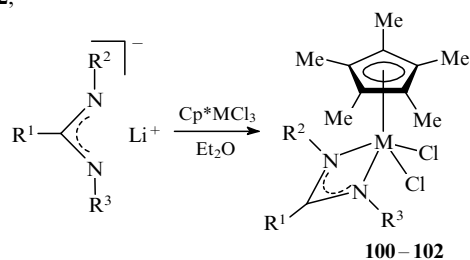
As for most known amidinate derivatives, the main method of synthesis of amidinate complexes of the Group 4 metals is the reaction of lithium amidinate with the corresponding metal halide (usually, chloride). Reactions with these commercially available reagents proceed under mild conditions and result in acceptable yields of the target products (> 60%). Lithium salts of different amidinate ligands are usually synthesised *in situ* from carbodiimides and alkyl lithium derivatives. Below, there are examples of three types of reaction of lithium amidinate with the Group 4 metal derivatives:

— reactions with chlorides [either bis- (**95–97**) or tris(amidinate) (**98, 99**) derivatives are formed depending on the ligand type];^{83, 90–93}



M = Ti (**95, 98**), Zr (**96, 99**), Hf (**97**); myrtanyl is 6,6-dimethylbicyclo[3.1.1]hept-2-ylmethyl.

— reactions with monocyclopentadienyl derivatives to give monoamidinate monocyclopentadienyl compounds **100–102**;^{94–97}



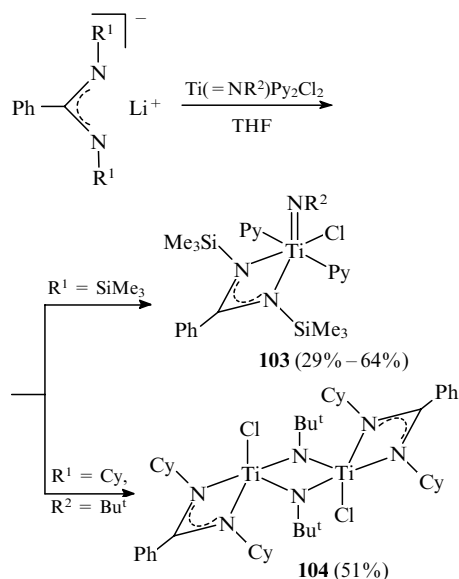
Cp* = η⁵-C₅Me₅;

100: M = Ti, R¹ = Me, R² = R³ = SiMe₃;

101: M = Zr; R¹ = H, Me, Bu^t, Ph; R² = R³ = Prⁱ, SiMe₃;
R² = Et, R³ = Bu^t;

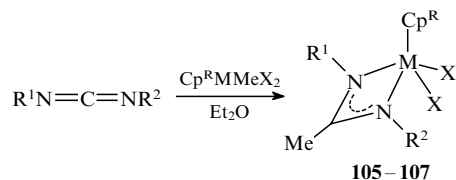
102: M = Hf; R¹ = Me; R² = R³ = SiMe₃; R² = Et, R³ = Bu^t.

— reactions with monoimide complexes to give monoamidinate monoimide complexes **103** or their dimers **104**.^{98, 99}



$\text{R}^2 = \text{Bu}^t, \text{Ar}$.

Another relatively common method of synthesis of amidinate complexes of the Group 4 metals is an insertion of free carbodiimide into a metal–carbon σ -bond. This approach was successfully used for the synthesis of titanium (**105**), zirconium (**106**) and hafnium (**107**) monocyclopentadienyl monoamidinate complexes.^{100–105} An alkyl (mostly, methyl) group is the most common substituent. The insertion reactions proceed under mild conditions and afford target products in good yields.

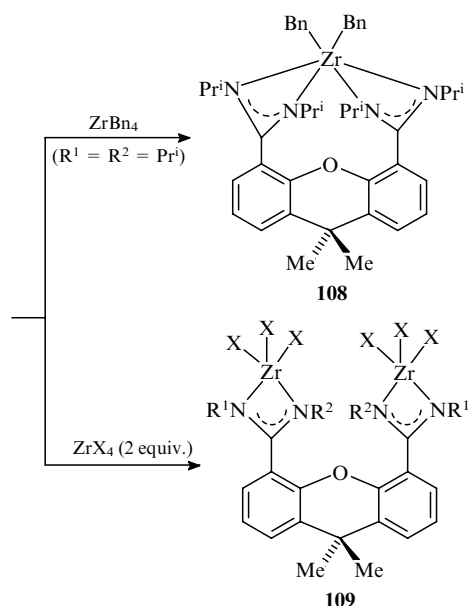
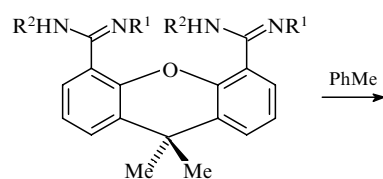


105: $\text{M} = \text{Ti}$; $\text{R}^1 = \text{Bu}^t, \text{Cy}$; $\text{R}^2 = \text{Et}, \text{Pr}^i, 2,6\text{-Me}_2\text{C}_6\text{H}_3$; $\text{Cp}^R = \text{Cp}, \text{Cp}^*$; $\text{X} = \text{Me}$;

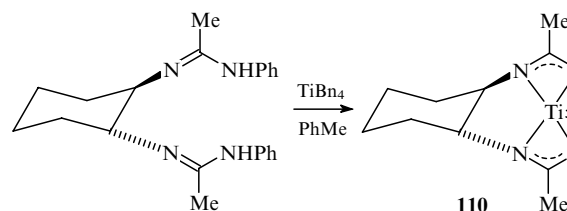
106: $\text{M} = \text{Zr}$; $\text{R}^1 = \text{Et}, \text{Pr}^i, \text{Bu}^t, \text{Cy}, o\text{-Tol}$; $\text{R}^2 = \text{Et}, \text{Pr}^i, \text{Bu}^t, \text{Bu}^t, \text{neo-C}_5\text{H}_{11}, \text{Bn}, 3\text{-ClC}_6\text{H}_4, \text{Mes}$; $\text{Cp}^R = \text{Cp}, \text{Cp}^*$; $\text{X} = \text{Me}, \text{Cl}$;

107: $\text{M} = \text{Hf}$; $\text{R}^1 = \text{Et}, \text{R}^2 = \text{Bu}^t, \text{Cp}^R = \text{Cp}^*, \text{X} = \text{Me}$.

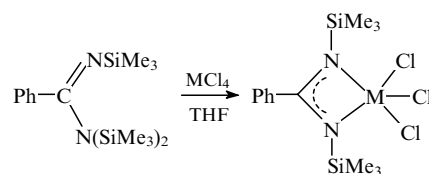
The third method of synthesis of titanium and zirconium complexes is the deprotonation of amidines, which has already been discussed earlier. Tetrabenzyl and tetrakis(dimethylamide) metal derivatives can be used as the deprotonating agents. Zirconium complexes **108** and **109** containing sterically hindered amidinate ligands were synthesised by this method.^{95, 106} Titanium bis(amidinate) complex **110** was also obtained by similar way.¹⁰⁷ However, this method is used less often than the two mentioned above mainly due to longer reaction times. In some cases, it also requires higher temperature, which usually results in lower yields of the target products.



$\text{R}^1 = \text{R}^2 = \text{Pr}^i, \text{X} = \text{Bn}$; $\text{R}^1 = \text{Et}, \text{R}^2 = \text{Bu}^t, \text{X} = \text{NMe}_2$.



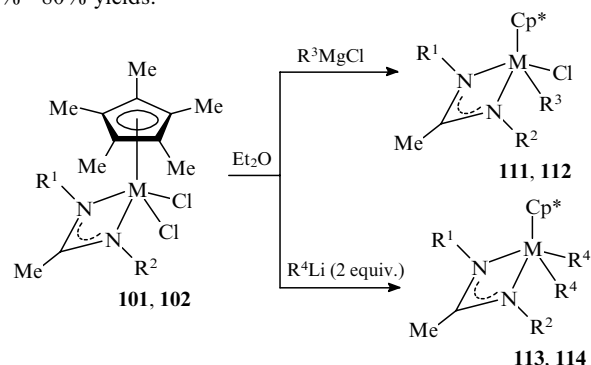
Yet another method of synthesis of amidinate complexes of the Group 4 metals is metathesis of metal tetrachlorides and silylated amidine derivatives.^{9, 108}



$\text{M} = \text{Ti}, \text{Zr}$.

At present, this method is almost out of use due to its synthetic limitations and the existence of other more convenient synthetic procedures.

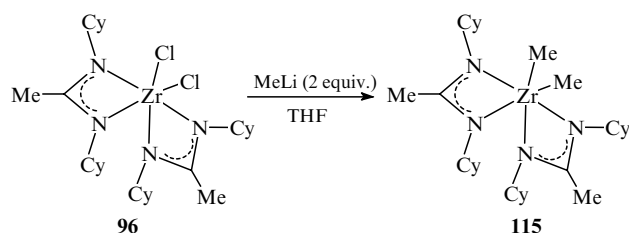
The properties of amidinate complexes of the Group 4 metals are fairly well studied. Thus the reaction of monocyclopentadienyl monoamidinate dichloride complexes **101**, **102** with the Grignard reagents and organolithium compounds (1 or 2 equiv.) has been investigated. In these reactions, mono- (**111**, **112**) and dialkylamidinate (**113**, **114**) derivatives are formed, respectively, in 40%–80% yields.^{109–113}



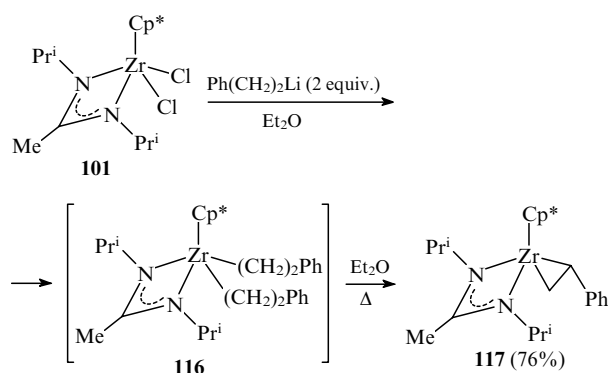
$\text{M} = \text{Zr}$ (**101**, **111**, **113**); Hf (**102**, **112**, **114**);

$\text{R}^1 = \text{Et}, \text{R}^2 = \text{Bu}^t$; $\text{R}^1 = \text{R}^2 = \text{Pr}^i$; $\text{R}^3 = \text{Me}, \text{Bu}^t$; $\text{R}^4 = \text{Bu}^n, \text{Bu}^i$.

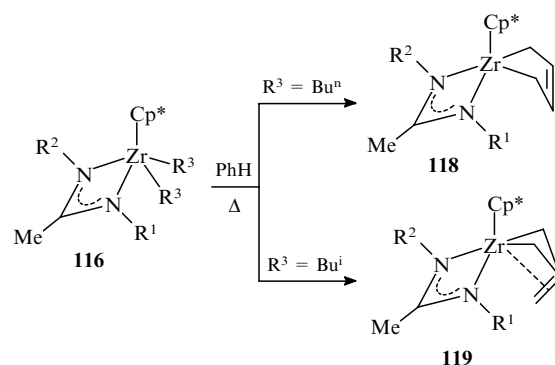
The reaction of zirconium bis(amidinate) dichloride complex **96** with 2 equiv. of methyllithium proceeds similarly furnishing compound **115**.⁹²



Unlike metallocene dialkyl complexes, their amidinate analogues are less prone to β -hydride elimination reactions. Some amidinate derivatives undergo thermal conversions resulting in metallacycles. Thus the intermediate dialkyl complex **116**, obtained from dichloride **101** ($\text{R}^1 = \text{R}^2 = \text{Pr}^i$) and dialkyl lithium, converts into phenylzirconacyclop propane derivative **117** on heating in ether.¹¹⁰

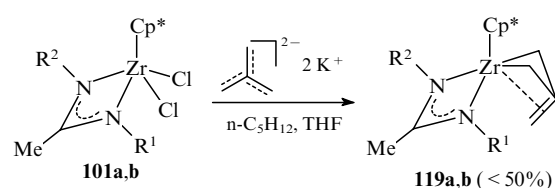


Thermolysis of *n*-butyl and isobutyl derivatives **116** results in the formation of complexes **118** and **119** as the main products in moderate yields and in elimination of butane and isobutane, respectively (according to data from NMR spectroscopy) and hydrogen.^{109, 111} The mechanisms of these thermal conversions are not established yet.



$\text{R}^1 = \text{R}^2 = \text{Pr}^i$; $\text{R}^1 = \text{Et}$, $\text{R}^2 = \text{Bu}^t$; $\text{R}^3 = \text{Bu}^n, \text{Bu}^i$.

Trimethylenemetane (TMM) derivatives **119a,b** were obtained by another method, *viz.*, by the reaction of corresponding dichlorides **101a,b** with dipotassium isobutylenediide.¹¹⁴

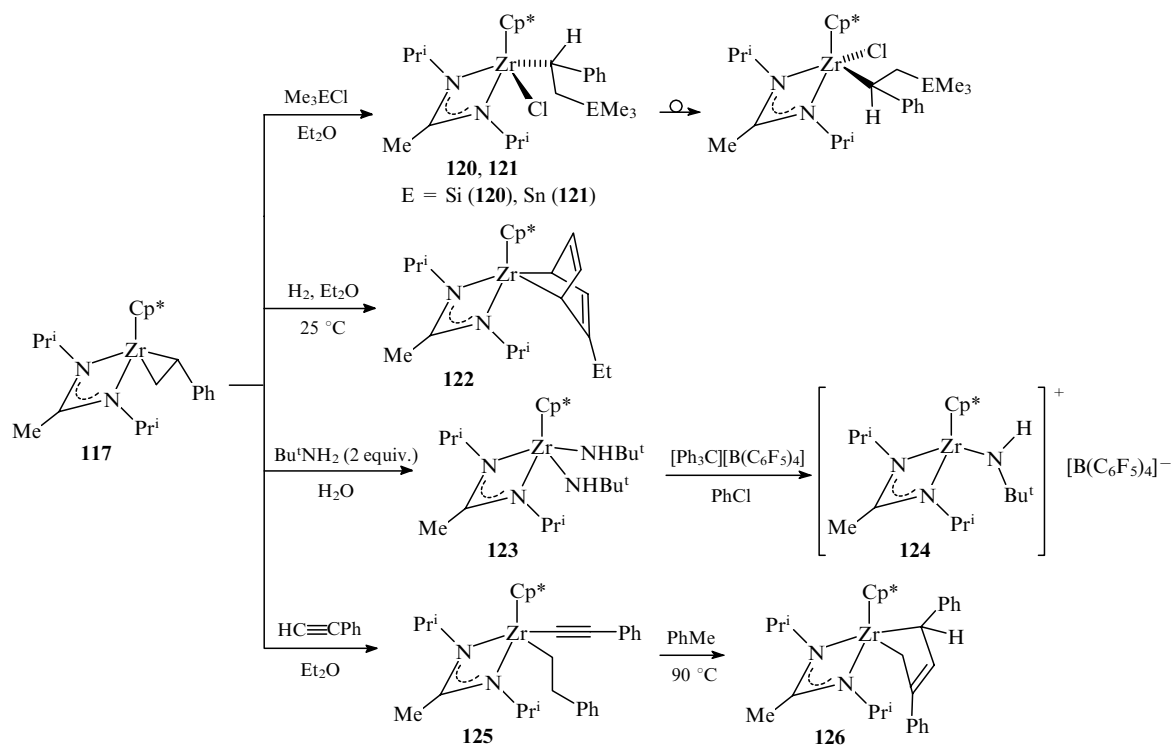


$\text{R}^1 = \text{R}^2 = \text{Pr}^i$ (**a**); $\text{R}^1 = \text{Et}$, $\text{R}^2 = \text{Bu}^t$ (**b**).

The chemical properties of zirconacyclop propane complex **117** and TMM derivatives **119** were studied in detail.^{111, 114, 115} A remarkable feature of these compounds is their high reactivities with respect to weak electrophilic reagents, such as Me_3SiCl , Me_3SnCl , *etc.*,^{111, 115} which does not occur for simple σ -alkyl zirconium complexes. Most of the reactions for compounds **117** and **119** proceed with quantitative yields. DFT quantum-chemical calculations of the complex **119a** reveal high polarisation of the molecule in the ground state,¹¹³ which was confirmed by relatively high experimental value of the dipole moment of this compound (3.5 D). Hence, the organic ligand (TMM) in such complexes carries significant negative charge and can react even with weak organic electrophiles.

Reactions of the phenylzirconacyclop propane derivative **117** with chlorotrimethylsilane and -stannane accompanied by three-

Scheme 2



membered ring opening have been described.¹¹¹ Chiral organo-metallic complexes **120** and **121** thus formed epimerise in benzene at room temperature (Scheme 2).

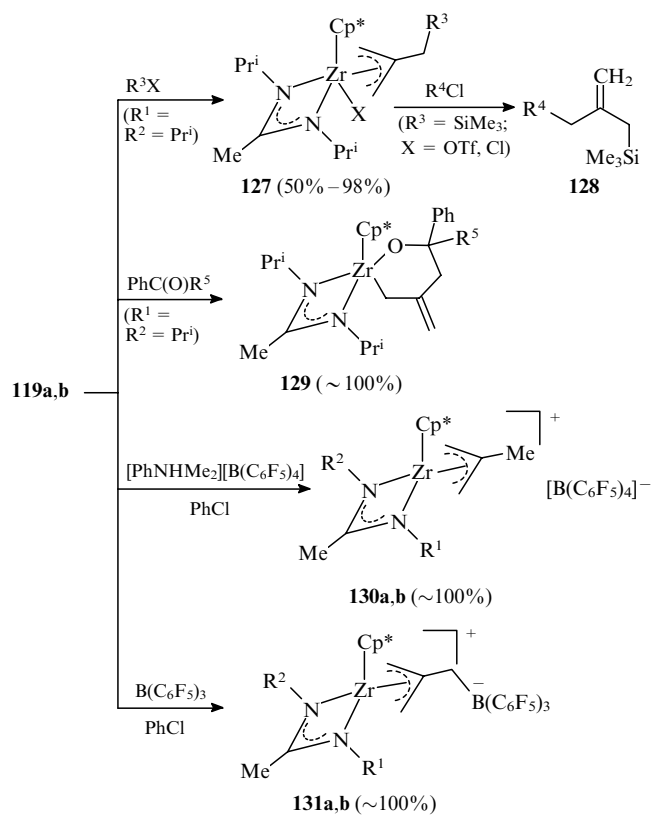
Compound **117** reacts with hydrogen at room temperature yielding an unusual zirconanorbornadiene complex **122** (see Ref. 111). The latter is of particular interest as a thermodynamically stable homoaromatic structure. In complex **122**, the lengths of two Zr–C σ -bonds are 2.313(2) and 2.3501(19) Å. Relatively short contacts between the metal atom and carbon atoms of the alkene (~ 2.51 Å) suggest the presence of non-valent interactions between the electron-deficient zirconium atom and C=C double bonds of the norbornadiene moiety. These interactions provide additional stability to the structure.

Metathesis of σ -alkyl bond in compound **117** in the presence of an excess of *tert*-butylamine results in the formation of corresponding bis(amidinate) derivative **123**. It should be noted that dimethyl derivative **105** ($R^1 = \text{Et}$, $R^2 = \text{Bu}^t$, $\text{Cp}^R = \text{Cp}^*$) is completely inactive in similar reaction even at elevated temperatures.¹¹¹ Bis(amidinate) complex **123** undergoes unique deamination in the presence of $[\text{Ph}_3\text{C}][\text{B}(\text{C}_6\text{F}_5)_4]$ yielding a cationic complex **124**.

Protolysis of compound **117** with phenylacetylene results in σ -alkynyl derivative **125**. Thermolysis of the latter furnishes zirconacyclopentenyl complex **126**.

Trimethylmethane complex **119a** also reacts with weak organic electrophiles. On treatment of trimethylsilyl derivatives **127** ($R^3 = \text{SiMe}_3$; $X = \text{Cl}$, OTf) with strong electrophiles (*e.g.*, B-catecholchloroborane or chlorotrimethylstannane) non-symmetrically substituted isobutylenes **128** are formed.¹¹⁵

The reaction of TMM complex **119** with carbonyl compounds yields C=O insertion derivatives **129**.

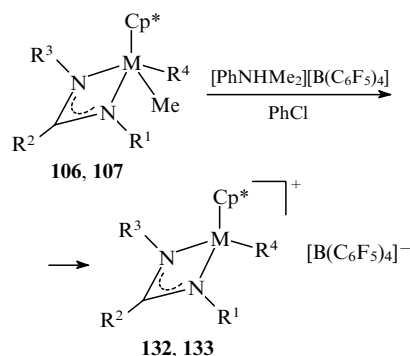


$R^1 = R^2 = \text{Pr}^i$ (a); $R^1 = \text{Et}$, $R^2 = \text{Bu}^t$ (b); $R^3 = \text{Me}$, Et, Bn, SiMe_3 ;

$R^4 = \text{phenylene-O-B}$; SnMe_3 ; $R^5 = \text{H}$, Ph; $X = \text{OTf}$, Cl, Br.

Complexes **119a,b** also react with Brønsted (*e.g.*, $[\text{PhNHMe}_2]$, $[\text{B}(\text{C}_6\text{F}_5)_4]$) and Lewis [*e.g.*, $\text{B}(\text{C}_6\text{F}_5)_3$] acids to give the corresponding allylic cationic (**130a,b**) and zwitter-ionic (**131a,b**) derivatives as the reaction products.¹¹⁵ The transition from neutral covalent complex **119b** to the metallyl derivative **130b** is accompanied by a significant shortening of the Zr–N bonds from 2.2306(12) to 2.149(3) Å. Such shortening of the metal–nitrogen bonds compared with those in neutral complexes is also typical of the majority of cationic amidinate derivatives of other elements, for example, aluminium,⁵⁶ and ruthenium.¹⁰

In spite of diverse reactivity of Group 4 metal amidinate complexes, the primary attention is paid to their application as olefin polymerisation catalysts.¹¹⁰ Monoalkyl cationic complexes of zirconium **132** (see Refs 102–104 and 116–120) and hafnium **133** (see Ref. 121) were obtained from dialkyl complexes **106**, **107** in the reaction with $[\text{Me}_2\text{NHPh}][\text{B}(\text{C}_6\text{F}_5)_4]$ as a protonating reagent in quantitative yields.

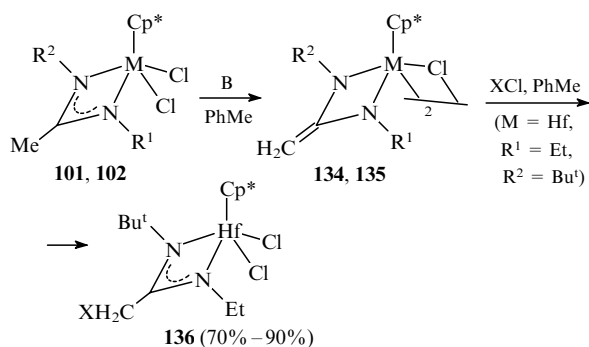


106, **132**: $M = \text{Zr}$; $R^1 = \text{Et}$, Pr^i , Bu^t , Bu^i , *neo*- C_5H_{11} , Cy, Bn, *o*-Tol, 3- ClC_6H_4 , Mes; $R^2 = \text{H}$, Me, Bu^t , Ph; $R^3 = \text{Et}$, Pr^i , Bu^t , Cy; $R^4 = \text{Me}$, Et, Bu^i ;
107, **133**: $M = \text{Hf}$; $R^1 = \text{Et}$; $R^2 = \text{Me}$; $R^3 = \text{Bu}^t$; $R^4 = \text{Me}$, Bu^i .

Really unique was the discovery of a high catalytic activity of such monoalkyl complexes in stereoregular living polymerisation of a number of α -alkenes (ethylene, propylene, but-1-ene, hex-1-ene, oct-1-ene, dec-1-ene, dodec-1-ene) as well as hexa-1,5-diene. Polymerisation of these olefins in chlorobenzene at -10°C results in isotactic polymers in almost quantitative yields and low (< 1.1) polydispersity, which is characteristic of living polymerisation. β -Hydride abstraction under these conditions is negligible. Cationic complex **132** ($R^1 = \text{Et}$, $R^2 = R^4 = \text{Me}$, $R^3 = \text{Bu}^t$)¹⁰² is the most efficient catalyst, but other complexes, for example, compounds **132** with $R^1 = \text{Bn}$, *neo*- C_5H_{11} , also show similar activity.¹⁰⁴ Such catalysts can be used for the preparation of different block co-polymers¹⁰³ and isotactic–atactic block co-polymers by degenerated alkyl group transfer mechanism (for details, see Ref. 120). The structure of catalytically active species has been studied.¹²⁰

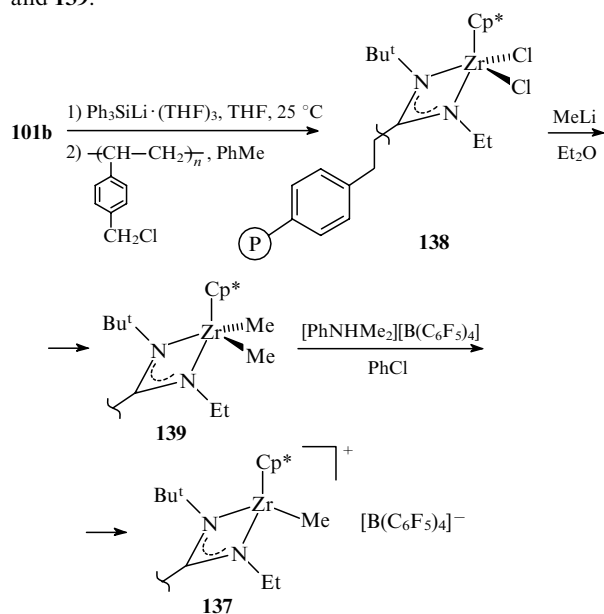
A series of titanium and zirconium monoamidinate complexes (**105** and **106**) were tested as catalysts for ethylene polymerisation in the presence of methylalumoxane (MAO).^{92, 101, 121–123} Quantum-chemical calculations were performed for this reaction.¹⁵ A detailed analysis of the polymerisation results is published in a recent review.⁵

A study of the reactions of zirconium and hafnium dichloride derivatives (**101** and **102**)¹²⁴ has to be noted among the latest papers on the properties of Group 4 metal amidinate complexes. Thus these compounds react with strong non-nucleophilic bases producing dimeric derivatives **134** and **135**, respectively.



The deprotonated carbon atom of the amidinate ligand in dimers **134** and **135** is nucleophilic. For instance, hafnium complex **135** ($R^1 = \text{Et}$, $R^2 = \text{Bu}^t$) reacts with such organic electrophiles as CH_2Cl_2 , BnCl and SiMe_2Cl_2 to give CH_2 -substituted amidinate derivatives **136**.¹²⁴

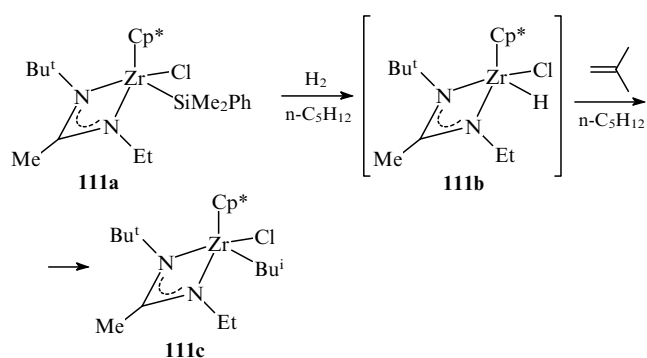
Similar reaction has been used for the synthesis of a polymer-bound amidinate catalyst **137**. The commercially available polystyrene polymer Bio-Beadstm S-X1 has been used as a support; the transformations involved immobilised zirconium complexes **138** and **139**.¹²⁵



(P) is a polymer.

Cationic complex **137** is quite resistant toward oxidation and at the same time is highly active as a polymerisation catalyst.

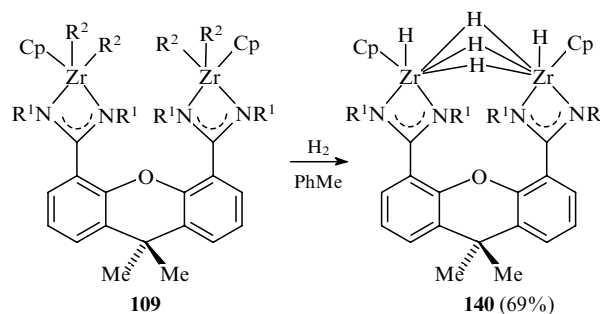
A possibility of synthesis of a hydride chloride monoamidinate analogue of Schwarz catalyst, Cp_2ZrHCl , starting from zirconium monocyclopentadienyl amidinate complexes was



studied. Hydride chloride intermediate **111b** was obtained by hydrogenation of the corresponding silyl chloride complex **111a**.¹²⁶

Intermediate **111b** is unstable and rapidly decomposes. However, it may be quenched as α -alkene hydrozirconation products, for example, as complex **111c** upon hydrozirconation of isobutylene.

Recently a stable zirconium hydride amidinate complex **140** has been obtained.

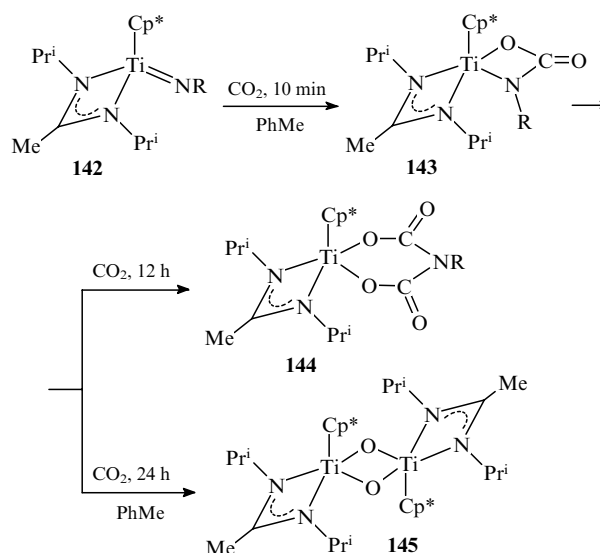


$R^1 = \text{Pr}^i$, $R^2 = \text{CH}_2\text{SiMe}_3$.

It was formed upon hydrogenation of the corresponding zirconium tetrakis(trimethylsilylmethyl) dinuclear derivative **109**.⁹⁵ Complex **140** exhibit dynamic behaviour, which results in exchange between bridged and terminal hydrogen atoms.

At the end of this Section, two recent publications^{127, 128} have to be noted. They describe the reactivities of titanium amidinate complexes **141** and **142**. The chloride ligand in monochloro derivatives **141** may be nucleophilically substituted by such groups as Cp , OAr , $\text{N}(\text{SiMe}_3)_2$, CHRSiMe_3 or by second amidinate ligand (Scheme 3).¹²⁷

Titanium pentamethylcyclopentadienyl amidinate complex **142** rapidly reacts with CO_2 giving rise to the insertion product **143**.¹²⁸ Depending on the duration of the reaction with carbon dioxide, different products, *viz.*, complexes **144** or **145**, are formed.

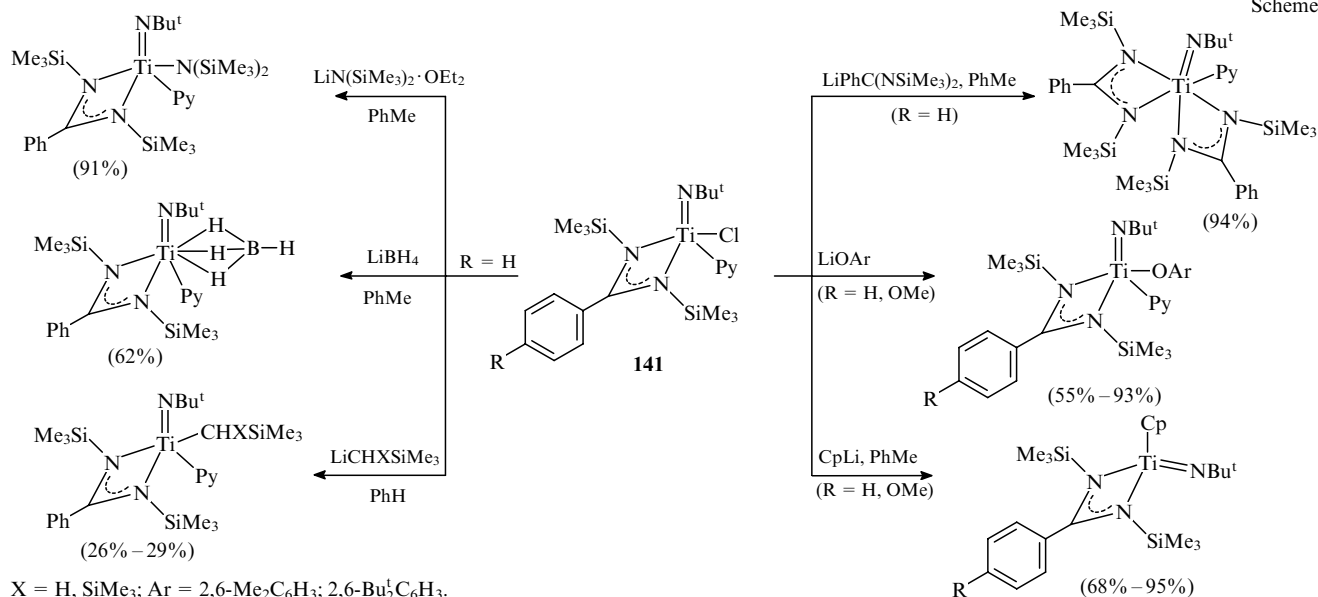


$R = \text{Bu}^t$, 2,6- $\text{Me}_2\text{C}_6\text{H}_3$.

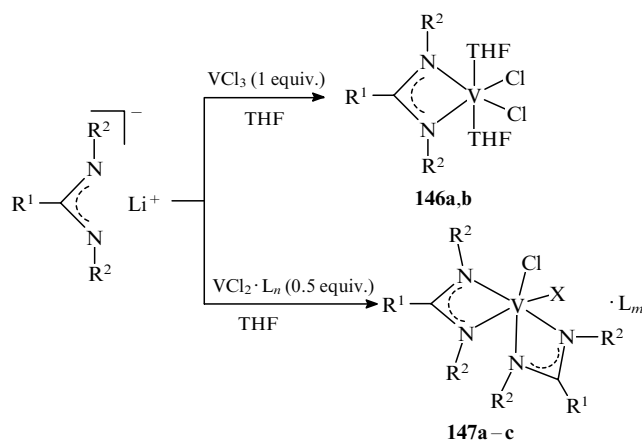
c. Group 5 elements (V, Nb and Ta)

Very few papers were published on Group 5 metal amidinate complexes over the last decade. The primary attention was given to vanadium and tantalum derivatives, while no niobium amidinate complexes have been synthesised during this period. Earlier work in this area has been summarised in reviews.^{8, 9}

Scheme 3

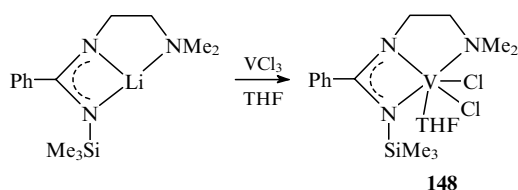


At present, the only method of synthesis of such derivatives is the reaction of lithium amidinates with Group 5 metal chlorides or organometallic chlorine-containing complexes.^{129–132} These reactions proceed under mild conditions in yields not less than 50%. For example, vanadium mono- (**146a,b**) and bis(amidinate) (**147a–c**) derivatives were synthesised by this method.

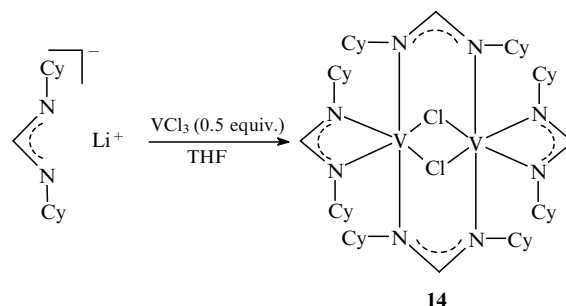


146: $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{SiMe}_3$ (**a**); $\text{R}^1 = \text{Bu}^t$, $\text{R}^2 = \text{Pr}^i$ (**b**);
147: $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{SiMe}_3$ (**a**); $\text{R}^2 = \text{Cy}$; $\text{R}^1 = \text{H}$ (**b**), Me (**c**);
 $\text{L}_n = \text{Cl}$, $\text{X} = \text{THF}$, L_m is absent;
 $\text{L}_n = \text{TMEDA}$, THF : $\text{X} = \text{Cl}$, $\text{L}_m = \text{L}_n$.

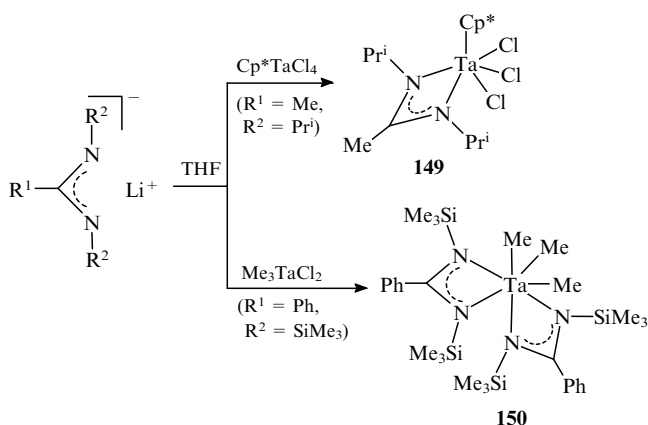
Vanadium complex **148** with a tridentate amidinate ligand was obtained similarly.¹²⁹



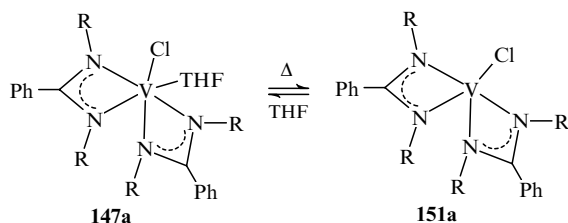
When bulky substituents, such as cyclohexyl ring, were present at the nitrogen atoms of the amidinate fragment, the bridged dinuclear complexes **14** were obtained in the reaction of vanadium chloride with 2 equiv. of lithium amidinate.¹³⁰



Tantalum mono- (**149**)¹³³ and bis(amidinate) (**150**)¹³² complexes were synthesised from lithium amidinates using the organo-tantalum chlorides as the reagents.

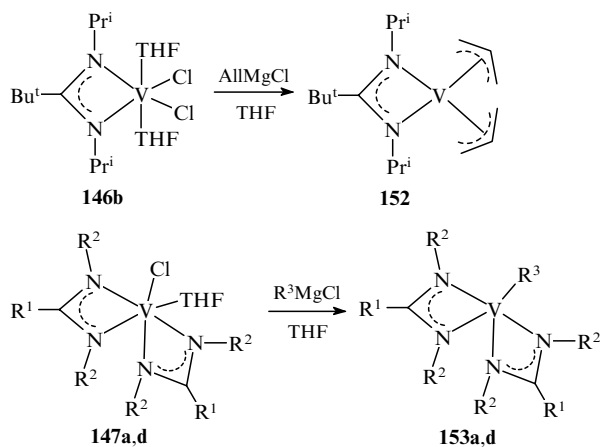


A characteristic feature of vanadium amidinate complexes is the formation of adducts with donor molecules, for example, with THF, which is a common solvent.¹³¹ Thus, either a solvent molecule or a ligand from the reagent (organometallic complex) can be inserted into the coordination sphere of the metal. It becomes possible, because the coordination of vanadium atom in such complexes is incomplete. Sometimes, especially in the cases of sterically hindered complexes like **147a**, such insertion is reversible: heating of the product results in formation of penta-coordinated vanadium compound **151a**.



R = SiMe₃.

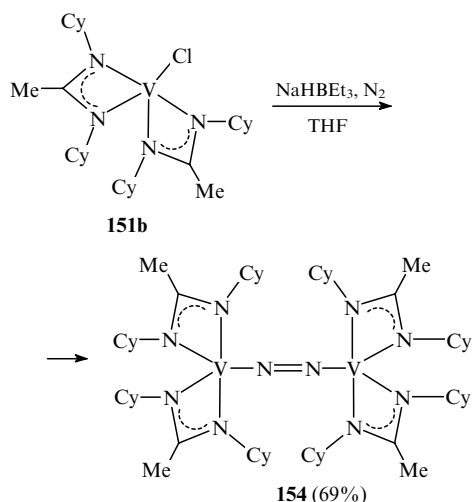
The mechanism of formation of amidinate derivatives of Group 5 metals discussed above may be regarded as nucleophilic substitution of the amidinate group for the chloride ligand. Chloride ligands in complexes **147b** and **147a,d** undergo further substitution in reactions with alkyl and allyl (All) Grignard reagents resulting in acceptable yields of the corresponding derivatives **152** and **153a,d** (see Refs 131 and 134).



R¹ = Ph, R² = SiMe₃ (**a**); R¹ = Bu^t, R² = Prⁱ (**d**); R³ = Et, All.

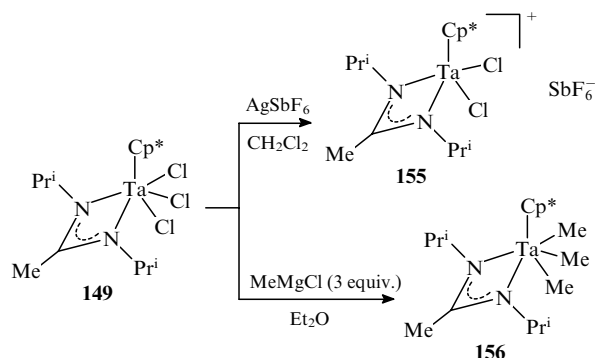
Different types of coordination of allylic ligands in vanadium mono- (**153**) and bis(allyl)- (**152**) complexes are worth mentioning. In the former, the allyl group is η¹-bound to the metal, while in the latter, both allyl ligands are η³-coordinated.

An unusual reaction has been found in the reduction of compound **151b** with sodium triethylborohydride in THF.¹³⁰ The reaction product is a dimeric complex **154** containing a diazo-bridge, which is formed upon insertion of a molecule of the atmospheric nitrogen.

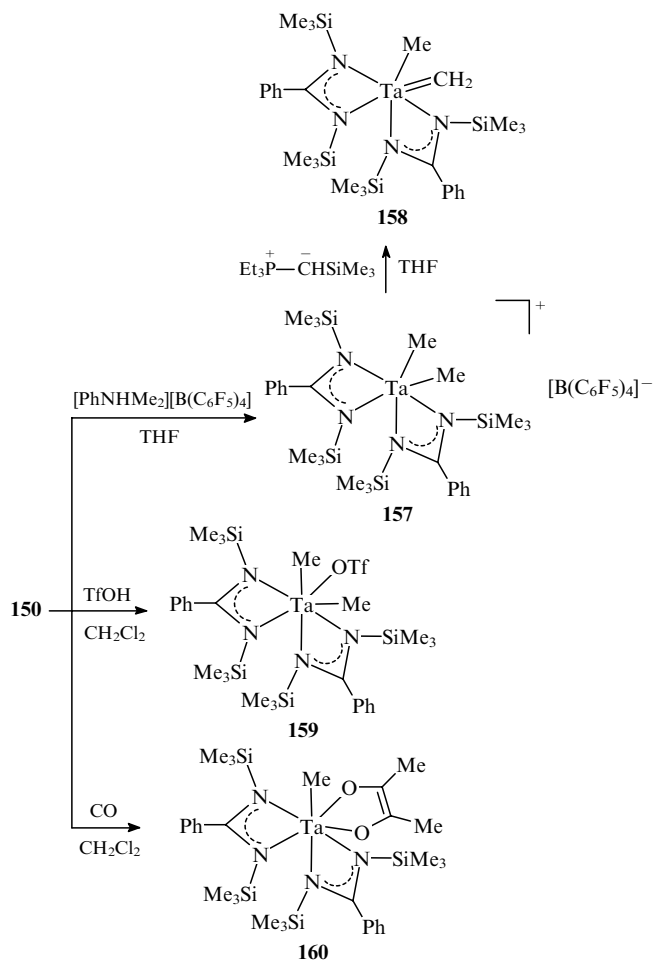


Cationic compound **155** is formed in reaction of silver hexafluoroantimonate with tantalum monocyclopentadienyl amidinate complex **149**.¹³³ The reaction of the latter with 3 equiv.

methylmagnesium chloride yields compound **156** in which all three chloride ligands are substituted by alkyl groups.



Chemical properties of tantalum trialkyl bis(amidinate) derivatives **150** are described in detail.¹³² The structure of the protonation product of complex **150** depends on the protonating reagent. Ionic derivative **157** is formed when [PhNHMe₂][B(C₆F₅)₄] is used. The reaction of compound **157** with phosphorus ylide yields the carbene complex **158**. If the trifluoromethanesulfonic acid (TfOH) is used as a protonating reagent, the dialkyl monotrifluoromethanesulfonate derivative **159** is obtained. In the presence of an excess of CO, the starting complex **150** undergoes double insertion of carbon dioxide into the Ta–C bond furnishing compound **160**.



And finally, it has to be noted that vanadium and tantalum amidinate complexes were studied as catalysts of olefin polymerisation. Thus compounds **147** (X = THF), **148** and **149** are highly reactive as catalysts of ethylene polymerisation in the presence of MAO.^{133, 134} The activity of tantalum complex **149** containing three chloride ligands is equal to 470 g mol^{−1} h^{−1} (see Ref. 133),

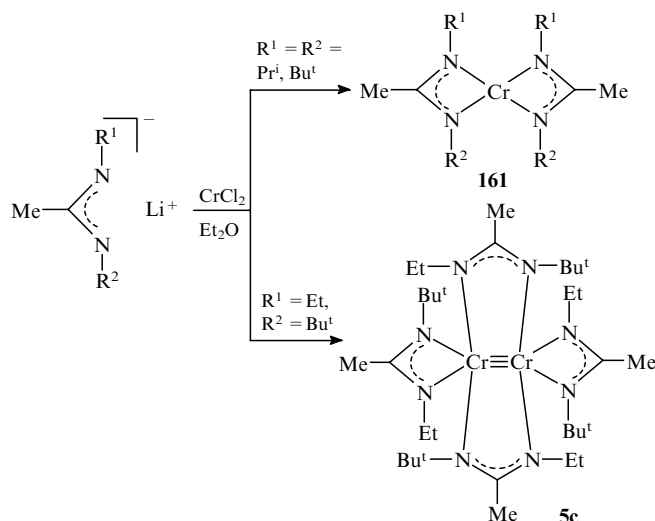
while its trimethyl analogue is inactive under similar conditions. Vanadium complexes **147** ($X = \text{THF}$) are significantly less reactive, $\sim 10 \text{ g mol}^{-1} \text{ h}^{-1}$ (see Ref. 134), the molecular mass of the obtained polyethylene is 80 kDa. At the same time, the activity of vanadium complex **148** with tridentate amidinate ligand is nearly the same ($447 \text{ g mol}^{-1} \text{ h}^{-1}$) as the activity of tantalum derivative **149**.

d. Group 6 elements (Cr, Mo and W)

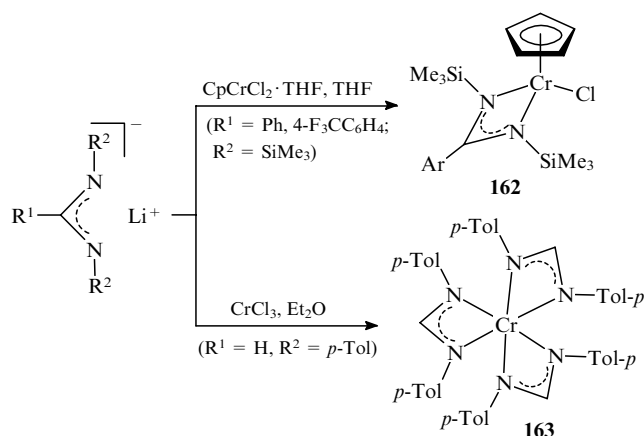
Seven papers on the amidinate complexes of Group 6 metals have been published since 1994. The unusual structures of chromium derivatives with very short Cr–Cr distances ($1.84\text{--}1.96 \text{ \AA}$)^{135, 136} are of special interest.

Most of the described chromium and molybdenum amidinate complexes were obtained by standard method, *viz.*, by the reaction of lithium amidinate salts with the corresponding metal halides or with organometallic halogen-containing complexes.^{24, 135, 137–139}

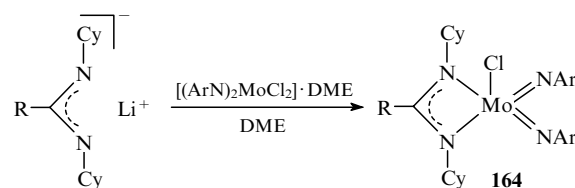
Mononuclear bis(amidinate) derivatives **161** are obtained by the reaction of chromium(II) compounds with amidinates containing bulky substituents (Pr^i , Bu^t) at the both nitrogen atoms. In the case of less sterically hindered amidinate salts, dinuclear complexes **5c** with multiple $\text{Cr}\equiv\text{Cr}$ bonds are obtained.¹³⁵ The yields of compounds **161** and **5c** are 50%–60%.



The same method was used for the synthesis of chromium mono- (**162**) and tris(amidinate) (**163**) complexes¹³⁷

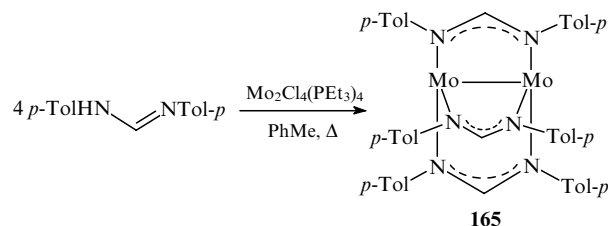


as well as molybdenum derivatives **164**.¹³⁸



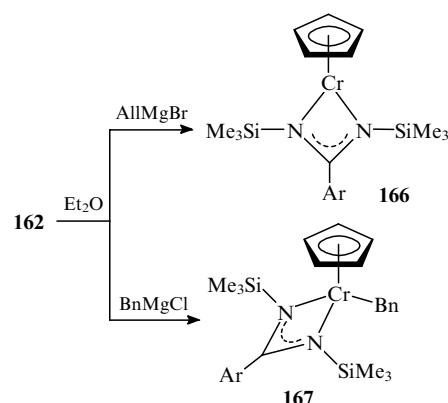
$R = \text{Me, Ph}$; $\text{Ar} = 2,6\text{-Pr}_2^i\text{C}_6\text{H}_3$; DME is dimethoxyethane.

Refluxing of molybdenum tetrakis(phosphine chloride) derivative in toluene with 4 equiv. of amidine yields molybdenum dinuclear tris(amidinate) complexes **165**.¹³⁹ According to the X-ray diffraction data, the Mo–Mo bond in the complex **165** is single.

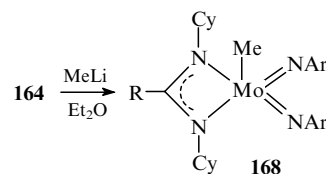


The chemical properties of the amidinate complexes of Group 6 metals are scarcely studied. Only the reactions of chromium complexes **162** and molybdenum complexes **164** with the Grignard reagents or alkyllithium resulting in substitution of the chloride ligands have been described.^{137, 138}

Allylmagnesium bromide reduces compound **162** into Cr(II) derivative **166**, while benzylmagnesium chloride replaces the chloride ligand yielding complex **167** (see Ref. 137).



Methyl-substituted amidinate complex **168** was obtained in the reaction of molybdenum complexes **164** with methyllithium.



$R = \text{Me, Ph}$; $\text{Ar} = 2,6\text{-Pr}_2^i\text{C}_6\text{H}_3$.

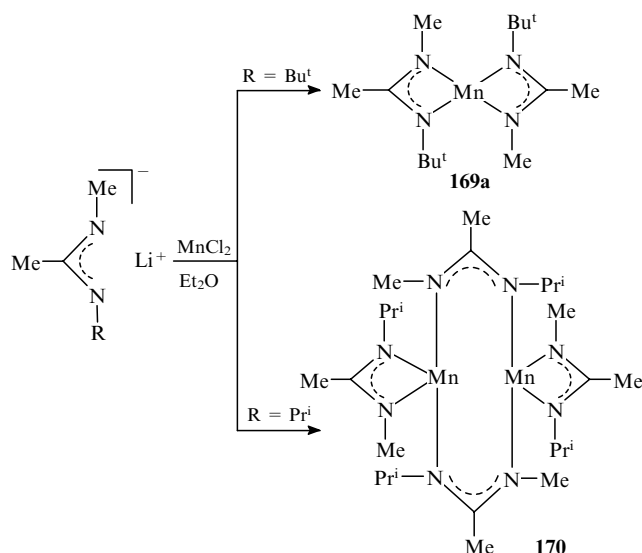
No new tungsten amidinate derivatives have been synthesised during the last decade. Earlier results are summarised in the reviews.^{8,9}

e. Group 7 elements (Mn, Re and Tc)

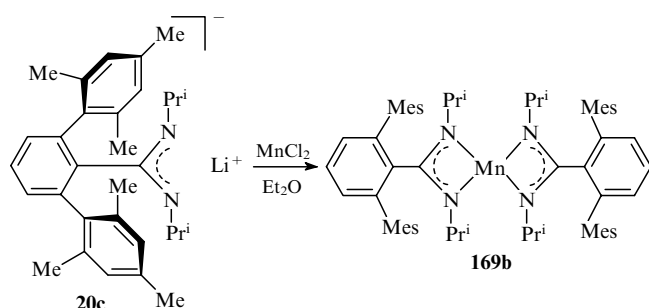
There are very few studies of amidinate complexes of Group 7 metals. Earlier papers mainly discussed the results of X-ray structural studies (see, for example, a review⁸). However, the

application of manganese bis(amidinate) complexes as starting compounds for CVD has been mentioned recently.⁸³

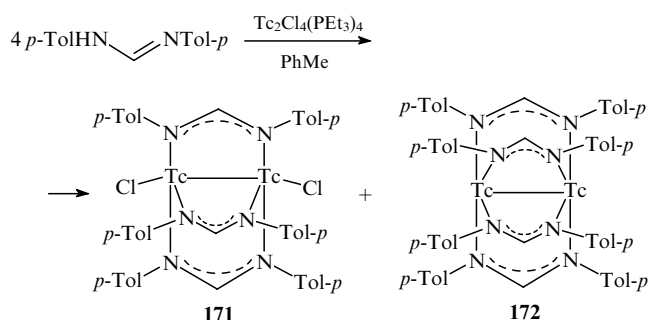
All known Mn(II) bis(amidinate) complexes were synthesised by reaction of lithium amidinates with MnCl_2 .^{83, 140} Mononuclear bis(amidinate) derivative **169a** was obtained in the reaction where the amidinate ligand carried bulky *tert*-butyl substituent at the nitrogen atom. In the case of less bulky isopropyl group, the dinuclear compound **170** was formed.



However, if the starting salt contains sterically hindered substituent at the carbon atom of the amidinate fragment (for example, 2,6-dimesitylphenyl in complex **20c**), the bis-derivative **169b** is also formed. The yields of compounds **169a,b** and **170** vary from low to moderate.



Techetium dinuclear tris- (**171**) and tetrakis(amidinate) (**172**) derivatives were obtained by heating ditechetium tetrakis(phosphine chloride) with 4 equiv. of amidine.¹³⁹

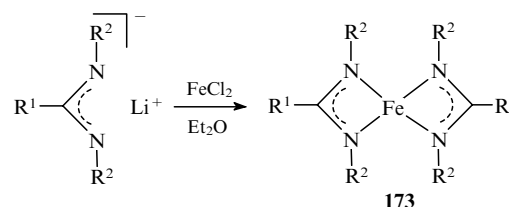


f. Group 8 elements (Fe, Ru and Os)

The chemistry of the amidinate complexes of Group 8 metals was successfully developed during the last decade. First of all, it concerns ruthenium amidinate derivatives, which are widely used as the catalysts of the Harash and Tsuji–Trost reactions.¹⁰ The

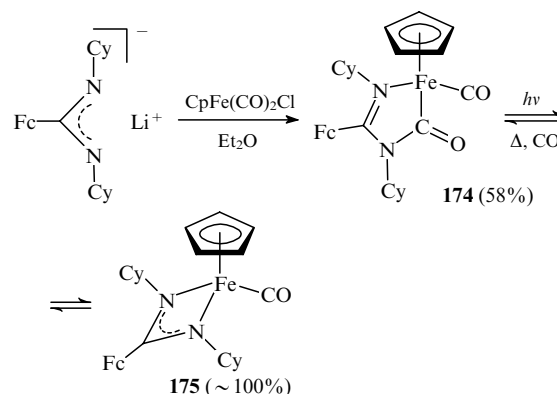
methods of synthesis and chemical properties of these compounds are summarised in a recent review¹⁰ and therefore will not be discussed here.

The studies of iron amidinate complexes were focused mainly on the synthesis of Fe(II) bis(amidinate) derivatives containing bulky chiral amidinate ligands and ferrocenyl substituents.^{43, 83, 140–142} Complexes **173** were obtained in satisfactory yields from lithium amidinates and iron dichloride as the starting compounds.

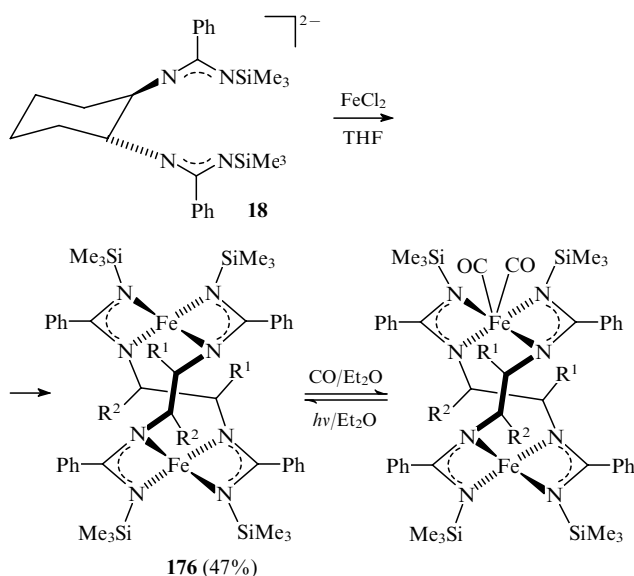


$\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{Bu}^t$; $\text{R}^1 = (\eta^5\text{-C}_5\text{H}_5)\text{Fe}(\eta^5\text{-C}_5\text{H}_5)$ (Fc), $\text{R}^2 = \text{Cy}$;
 $\text{R}^1 = 2,6\text{-Mes}_2\text{C}_6\text{H}_3$, $\text{R}^2 = \text{Pr}^i$.

However, in the reaction with $\text{CpFe}(\text{CO})_2\text{Cl}$, ferrocenyl-substituted lithium amidinate forms compound **174**, which is an insertion product of one of the carbonyl groups into the Fe–N bond.¹⁴² UV irradiation of derivative **174** yields the amidinate complex **175**, which is converted to the starting complex **174** on heating in a CO atmosphere.



The synthesis of iron chiral dinuclear complex **176** is described.⁴³ It appeared that this complex can also add the CO ligands reversibly.



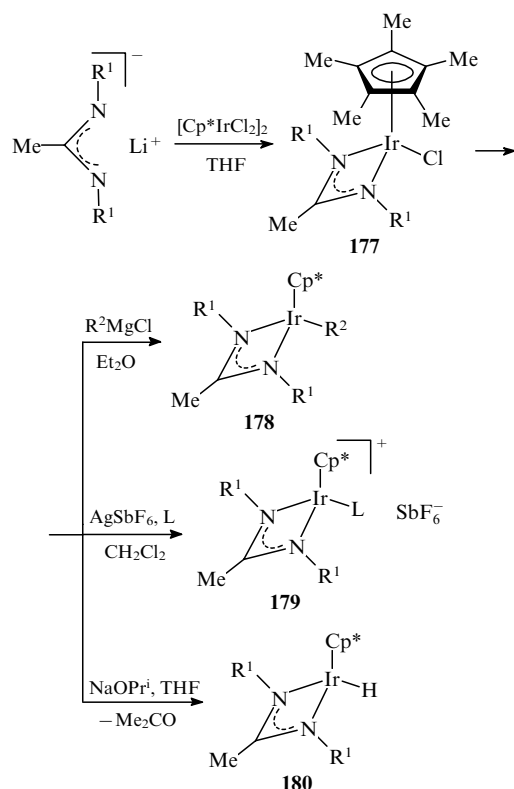
$\text{R}^1 - \text{R}^2 = (\text{CH}_2)_4$.

However, in this case the carbonyl group coordinates the iron atom rather than inserts into the Fe–N bond.

No new osmium amidinate derivatives have been synthesised during the last decade. Data on the chemistry of iron and osmium amidinate complexes can be found in reviews.^{8,9}

g. Group 9 elements (Co, Rh and Ir)

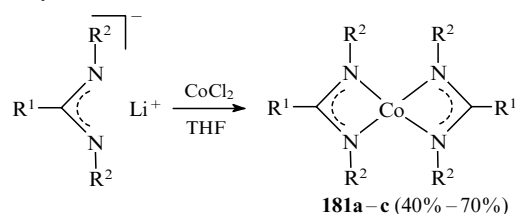
Only one systematic study¹⁴⁴ on the chemistry of amidinate complexes of Group 9 metals has emerged since the publication of a series of papers^{8,9,18,143} on the synthesis and reactivity of rhodium amidinate complexes. The authors synthesised iridium derivatives **177** starting from lithium acetamidinates and a chlorine-containing iridium complex and studied their properties.



$\text{R}^1 = \text{Pr}^i, \text{Cy}$; $\text{R}^2 = \text{Me, Et, Bn}$; $\text{L} = \text{Py, CO}$.

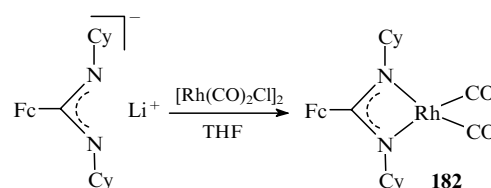
The corresponding monoalkyl derivatives **178** were obtained from compounds **177** in good yields ($>70\%$) by reaction with equimolar amounts of the Grignard reagents. In the presence of compounds that easily coordinate to metals, such as pyridine or CO, compound **177** reacts with AgSbF_6 yielding cationic complexes **179**. In the absence of such ligands, the iridium intermediate decomposes. The reaction of compound **177** with sodium isopropoxide proceeds in an unusual way: hydride complexes **180** are formed instead of the expected isopropoxide derivatives. Apparently, the β -hydride shift accompanied by elimination of acetone occurs in the isopropoxide intermediate.

Both conventional cobalt bis(amidinate) derivatives **181a,b** and their analogue **181c** with sterically hindered 2,6-dimesitylphenyl substituent in the amidinate ligand have been synthesised recently.^{83,140,142}



$\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{Pr}^i$ (**a**); Bu^t (**b**); $\text{R}^1 = 2,6\text{-Mes}_2\text{C}_6\text{H}_3$, $\text{R}^2 = \text{Pr}^i$ (**c**).

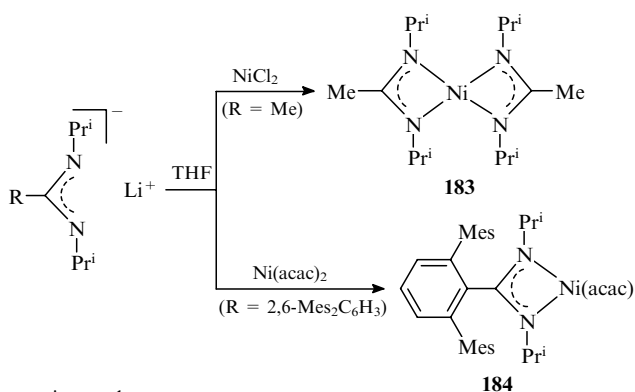
Compound **182**¹⁴² is the only ruthenium amidinate complex described so far.



Complexes **181a,b** and **182** are used as starting compounds in the manufacture of metal oxide thin films.⁸³

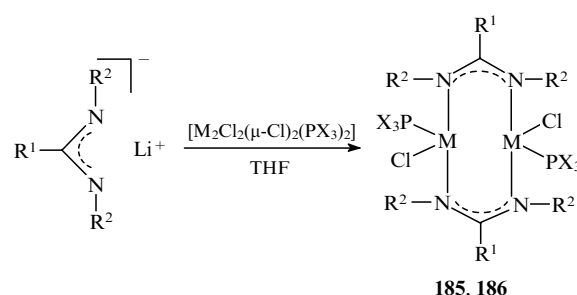
h. Group 10 elements (Ni, Pd and Pt)

There was no new significant breakthrough in the chemistry of amidinate complexes of Group 10 metals during the last decade. A small number of new complexes have been synthesised from the corresponding lithium amidinates.^{83,140,145} Thus nickel bis(amidinate) derivative **183** was obtained by the reaction of lithium salt with nickel chloride. Similar reaction with nickel bis(acetylacetonate) furnishes monoamidinate complex **184**. The yields of the products in these cases are moderate (40%–60%).



acac is acetylacetonate.

A series of dinuclear palladium (**185**) and platinum (**186**) complexes containing two bridging amidinate ligands were synthesised by similar method.¹⁴⁵ Chlorine-containing phosphine complexes of these metals were used as the reagents.



185: $\text{M} = \text{Pd}$; $\text{X}_3 = \text{Et}_3, \text{Bu}_3^i, \text{Me}_2\text{Ph}$; $\text{R}^1 = \text{H, Me}$; $\text{R}^2 = \text{Ph, } p\text{-Tol, } 4\text{-MeOC}_6\text{H}_4$;

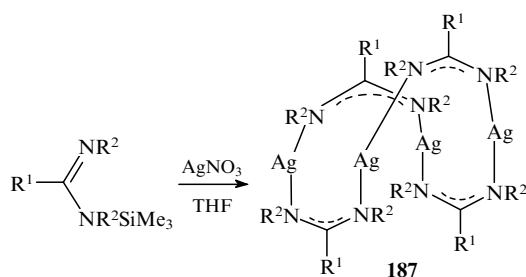
186: $\text{M} = \text{Pt}$; $\text{X}_3 = \text{Bu}_3^i, \text{Me}_2\text{Ph}$; $\text{R}^1 = \text{H}$; $\text{R}^2 = \text{Ph}$.

Chemical properties of amidinate derivatives **183–186** are almost unknown. The use of compounds **183** and **184** as the starting components in the manufacture of oxide thin films is an example of practical application of amidinate complexes of Group 10 elements.⁸³

i. Group 11 elements (Cu, Ag and Au)

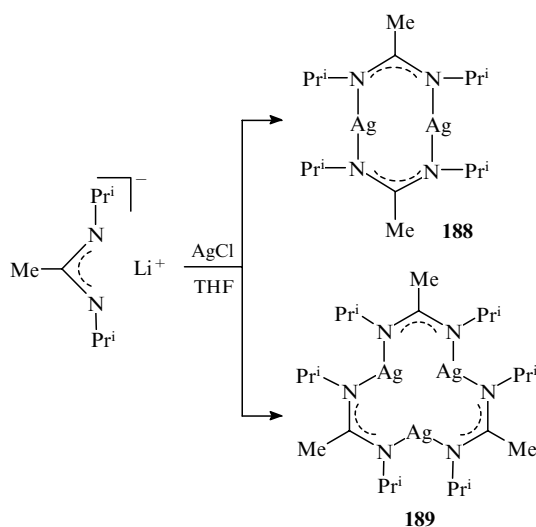
Homoleptic complexes with the composition $[\text{M}(\text{R}^2\text{NC}(\text{R}^1)\text{NR}^2)]_n$ ($n = 1\text{--}4$) are at present the best known amidinate derivatives of Group 11 metals. The metathesis reaction of trimethylsilyl derivatives of amidinates with inorganic metal salts is the main method of synthesis of such complexes.^{146,147}

Typically, silver complexes **187** obtained by this method have tetranuclear structures.^{8, 147}

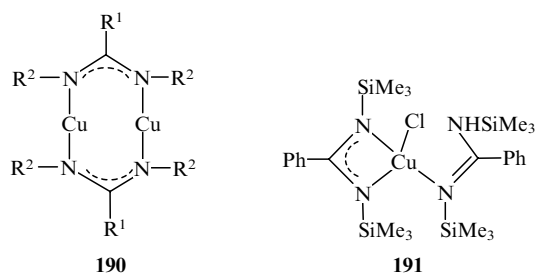


$R^1 = \text{Me, Pr}^n, \text{Bu}^n, n\text{-C}_5\text{H}_{11}, n\text{-C}_8\text{H}_{17}$;
 $R^2 = \text{Ph, 4-Bu}^n\text{C}_6\text{H}_4, 4\text{-MeOC}_6\text{H}_4$.

Silver dinuclear (**188**) and trinuclear (**189**) complexes are also known.⁸³ They were synthesised by the reaction of AgCl with lithium amidinate salts.



Dinuclear structure is also typical of copper amidinate complexes. The synthesis of bis(amidinate) derivatives **190** containing bridging ligands is described.¹⁴⁶ An exception from this structural type is the mononuclear complex **191** obtained by the reaction of lithium amidinate salt with copper dichloride.¹⁴⁶ Wet acetonitrile has to be used as a solvent in the synthesis of this compound.

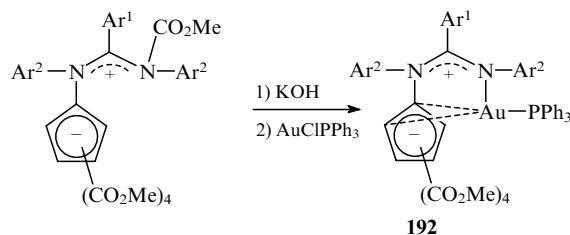


$R^1 = \text{H, } R^2 = 4\text{-Bu}^n\text{C}_6\text{H}_4$; $R^1 = \text{Me, } R^2 = \text{Pr}^i$; $R^1 = \text{Ph, } R^2 = \text{SiMe}_3$.

Copper amidinate complexes **190** and **191** were tested as catalysts in polymerisation of carbodiimides¹⁴⁶ and methyl methacrylate.¹⁴⁸ In the presence of these complexes, the polymerisation of carbodiimides proceeds without chain transfer, *i.e.*, living polymerisation occurs, and the activity of the catalysts in an inert atmosphere is almost the same as that in the presence of oxygen. The yields of polymers are 70%–90%.

Unusual gold amidinate complexes with chiral cyclopentadienyl ligands with *N*-donor side chain have recently been

obtained by Minkin and co-workers.^{149–151} Treatment of zwitter-ionic cyclopentadienyl ligands with alkaline solution followed by addition of Ph_3PAuCl results in the formation of complexes **192** in high yields.



$\text{Ar}^1 = \text{Ph, Ar}^2 = p\text{-Tol}$; $\text{Ar}^1 = 1\text{-naphthyl}$; $\text{Ar}^2 = m\text{-Tol, } o\text{-Tol}$.

According to X-ray diffraction analysis, the metal in these compounds is σ -coordinated by a nitrogen atom of the amidinate ligand and, therefore, complexes **192** belong to the structural type **B** (see Section II). Moreover, the η^2 -type coordination of metal by the π -system of cyclopentadienyl ligand is observed, which is highly unusual for gold cyclopentadienyl derivatives.

Copper and silver amidinate complexes are used as starting components in the production of oxide thin films.⁸³

The earlier references to the chemistry of amidinate complexes of Group 11 metals can be found in the review.⁸

IV. Conclusion

In conclusion to the review, the large number of publications into the chemistry of main Group and transition metal amidinate complexes unambiguously suggests that this field of research is still under rapid development and growth. It is evident that this trend will continue for at least a near future. Furthermore, despite the fact that there has been no single unique method for the synthesis of amidinate complexes developed since 1994, the existing synthetic methods allow for almost any amidinate derivatives. Most of the metal amidinate complexes known to date are mononuclear. However, di- and polynuclear structures are more common for the late transition metal amidinates (nickel and copper groups) as well as for cationic aluminium amidinate complexes. Metal amidinate complexes have found significant application as catalysis for olefin polymerisation (including stereocontrolled synthesis of block-copolymers) and for a number of organic transformations, as demonstrated for ruthenium amidinate derivatives.

Several potential areas of further studies may be outlined. Thus amidinate complexes of Group 4 and 5 metals may find use as catalysts for nitrogen fixation. Amongst all, Group 4, 8 and 13 metal amidinate complexes are most promising for further studies. Dinuclear amidinate complexes and organometallic clusters with amidinate ligands, which are barely studied yet, may demonstrate unusual reactivity as chemical reagents as well as catalysts of various chemical transformations. Moreover, amidinate ligands are promising precursors for synthesis of volatile organometallic compounds used for the production of metal coatings and membranes. Successful development in this area is related to several factors, namely, availability of starting materials, existence of convenient methods for the synthesis of amidinate complexes, and also thermal stability of amidinate derivatives even when similar metallocene compounds are labile.

Thus, this paper has demonstrated a significant potential of main Group and transition metal amidinate complexes for both fundamental and applied research studies.

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^a — *Russ. Chem. Bull., Int. Ed. (Engl. Transl.)*

^b — *J. Struct. Chem. (Engl. Transl.)*

^c — *Mendeleev Chem. J. (Engl. Transl.)*

The chemistry of peroxynitrite. Reaction mechanisms and kinetics

V L Lobachev, E S Rudakov

Contents

I. Introduction	375
II. Formation of peroxynitrite	375
III. Physical and chemical properties	376
IV. Decomposition and isomerisation	378
V. Reactions with hydrocarbons and other compounds	381
VI. Biochemical role of peroxynitrite	391
VII. Conclusion	392

Abstract. Methods for the preparation of peroxynitrite and its physical and chemical properties are considered. The pathways, mechanisms and kinetics of the decomposition and best-studied reactions with hydrocarbons, dimethyl sulfoxide and other substrates are analysed. The emphasis is placed on the nature of reactive species in peroxynitrite reactions and on the reasons for its high and polyfunctional reactivity. The biochemical role of this important inorganic oxidant formed *in vivo* is outlined. The bibliography includes 268 references.

I. Introduction

Peroxynitrous acid ONOOH and peroxynitrite anion ONOO[−] have the same conventional name ‘peroxynitrite’. [According to IUPAC recommendations,¹ they should be called hydrogen oxoperoxonitrate and oxoperoxonitrate(1 −), respectively.]

Peroxynitrite was first detected more than 100 years ago as unstable product of the interaction of nitrites with hydrogen peroxide in acid media, which possesses unusually high oxidative ability. Its formula, ONOOH, which is commonly accepted at present, was proposed in 1929.²

About 40 studies concerning peroxynitrite were reported before 1990. They were followed by rapidly increasing interest in this research avenue due to the discovery³ of *in vivo* formation of ONOO[−] and to establishment of its important role in physiological processes,^{4–11} in atmosphere chemistry¹² and in chemistry of natural water.¹³ The total number of reports on the subject vigorously increases, being more than 7300 at the moment.

The main avenues of research in chemistry of peroxynitrite include (1) pathways and mechanisms of ONOOH decay over a wide range of pH values, (2) reasons for high reactivity and the mechanisms of reactions with organic compounds and biomolecules and (3) pathways of synthesis and transport of peroxynitrite in biological systems.

V L Lobachev, E S Rudakov L M Litvinenko Institute of Physical Organic and Coal Chemistry, National Academy of Sciences of Ukraine, ul. R Luxemburg 70, 83114 Donetsk, Ukraine. Fax (38-0622) 55 85 24, tel. (38-0622) 55 84 35, e-mail: lobachev@skif.net (V L Lobachev), rudakov@skif.net (E S Rudakov)

Received 13 May 2005

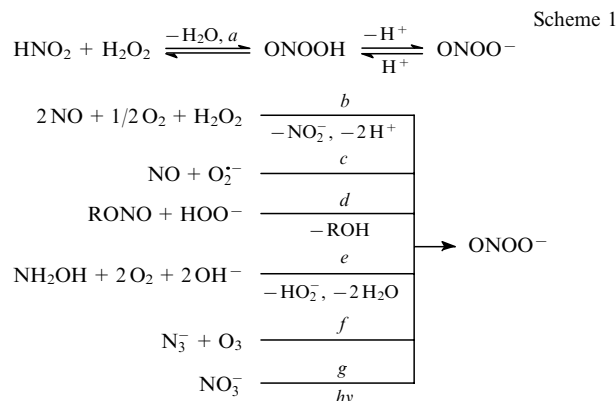
Uspekhi Khimii 75 (5) 422–444 (2006); translated by A M Raevskiy

High reactivity of peroxynitrite is usually explained by generation of ‘hydroxyl-like’ radicals in the homolysis of ONOOH. However, in spite of numerous studies in this field, the nature of the reactive species is still highly debatable. This is due to instability of peroxynitrite in neutral and acid media, large number of possible transformation paths and to the fact that many reactions involving the compound are catalysed by metal complexes, carbon dioxide and carbonyl compounds.

The first systematic review¹⁴ on the chemistry of peroxynitrite appeared in 1994; biochemical aspects were first considered in detail in a monograph.¹⁵ A number of more recent interesting reviews are also available.^{4, 7, 9, 11, 16–18} In this review we will dwell on the reactions of peroxynitrite formation (including *in vivo* formation), preparative synthesis, pathways and mechanisms of peroxynitrite decay and other reactions involving the compound. We will also briefly outline its role in biochemical processes. In addition to the results of studies on the interaction of peroxynitrite with sulfides, carbon dioxide, carbonyl compounds, phenols and ascorbic acid, we will present a detailed consideration of recent data on the kinetics and mechanisms of model reactions with hydrocarbons (alkanes, alkenes, alkylbenzenes) and DMSO obtained in the authors’ laboratory.

II. Formation of peroxynitrite

Chemical reactions resulting in peroxynitrite are shown in Scheme 1.



1. Reaction of H₂O₂ with HNO₂ (route *a*). It was established^{14, 19–23} that peroxynitrous acid is rapidly formed (as

intermediate) in acidic media, but the compound is unstable (half-life is a few seconds at 0 °C).^{14, 21, 24, 25} In practice, relatively stable ONOO[−] anions can be generated using instantaneous 'quenching'^{25, 26} of the reaction mixture with an excess of alkali. Solutions thus obtained contain nitrite, hydrogen peroxide and nitrate impurities. The yield of peroxynitrite can be significantly increased using simple flow reactors (Fig. 1).^{22, 23, 27} The nitrite and acidified hydrogen peroxide solutions are introduced, by means of compressed gas²⁷ or vacuum,²² into a mixing cell and then, through a short pipe, into the second mixing cell where the reaction is 'quenched' with a sodium hydroxide solution. Optimisation of the reagent feed rates and the tube length allows peroxynitrite to be synthesised in high yield (> 91%) and with low impurity content.

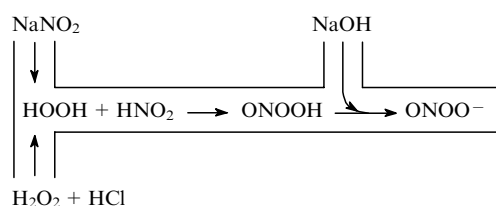
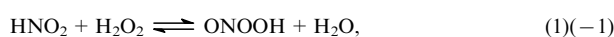


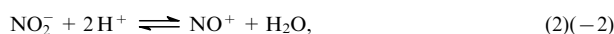
Figure 1. Scheme of peroxynitrite formation in a quenched flow reactor.²²

Reaction *a* is reversible:²⁸



K (25 °C) = $(1.33 \pm 0.05) \times 10^3$ litre mol^{−1}.

Formation of ONOOH in the H⁺–HNO₂–H₂O₂ system involves intermediate generation of nitrosyl cation²⁰

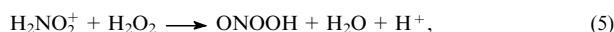
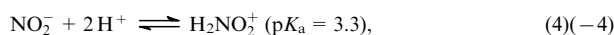


The corresponding kinetic equation has the form

$$\frac{d[\text{ONOOH}]}{dt} = \frac{k_2 k_3 [\text{H}^+]^2 [\text{NO}_2^-] [\text{H}_2\text{O}_2]}{k_{-2} [\text{H}_2\text{O}] + k_3 [\text{H}_2\text{O}_2]},$$

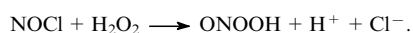
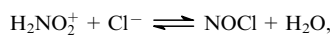
where $k_2 = 5.8 \times 10^6$ litre² mol^{−2} s^{−1} and $k_3/k_{-2}[\text{H}_2\text{O}] = 2.4$ litre mol^{−1} (pH 4–6, 25 °C).²⁰

It is believed^{23, 29} that protonated nitrous acid H₂NO₂⁺ is a more probable nitrosating agent in this system:



where $k_4 = 600$ litre mol^{−1} s^{−1} and $k_5/k_{-4} = 2.31$ litre mol^{−1}.

Nitrosyl chloride NOCl formed in the presence of chloride ions also reacts with hydrogen peroxide:²³



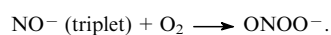
2. Reaction of H₂O₂ with NO in alkaline media (route *b*).^{19, 30, 31} This reaction cast some doubt until it was found³¹ that it proceeded only in the presence of oxygen involving formation of N₂O₃ as intermediate, which is then attacked by the hydroperoxide anion [$k = (1.0 \pm 0.6) \times 10^9$ litre mol^{−1} s^{−1}] (see Refs 19, 30, 31). The rate constant for the reaction of N₂O₃ with H₂O₂ is three orders of magnitude lower.

3. Reaction of NO with O₂^{•−} (route *c*). Both being of radical nature, the superoxide ion and nitrogen(II) oxide recombine at a diffusion rate [$k = (3.8–19) \times 10^9$ litre mol^{−1} s^{−1}, Refs 32–38]

to give −OONO.[†] The reaction plays a key role *in vivo*^{3, 9, 11, 16, 39} (see Section VI). It is reversible, but the equilibrium is almost completely shifted towards ONOO[−]. Indeed, $K = (3.1–3.6) \times 10^{-12}$ ($k = 0.017–0.0023$ s^{−1} for the reverse reaction) in aqueous solutions at 25 °C.^{40–42} Based on this reaction, new efficient methods of synthesis of peroxynitrite were developed, namely, the interaction of trimethylammonium superoxide with nitrogen(II) oxide in liquid ammonia⁴³ and a heterogeneous reaction of crystalline potassium superoxide with NO.⁴⁴ Both methods result in high yield of peroxynitrite and minimum content of nitrates and nitrites.

4. Reaction of alkyl nitrites with hydrogen peroxide (route *d*)^{45, 46} proceeds in alkaline media involving hydroperoxide anion HOO[−] as reagent. The reaction is of preparative value, but peroxynitrite thus obtained contains an equimolar amount of alcohol as impurity (alcohol can be oxidised with peroxynitrite). The advantage of this procedure consists in low content of nitrite, nitrate and hydrogen peroxide impurities.

5. Autooxidation of hydroxylamines and chloramines (route *e*). Alkaline oxidation of the compounds containing nitrogen in the oxidation states below +3 results in peroxynitrite in 20%–25% yield with respect to the starting substrate.^{47, 48} The reaction involves formation of a triplet NO[−] anion as intermediate.



The interaction of oxygen with triplet NO[−] produced in the photolysis of trioxodinitrates also leads to peroxynitrite.⁴⁹

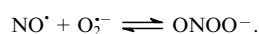
6. Ozonation of azides (route *f*) makes it possible to prepare peroxynitrite solutions that are of low ionic strength and free from H₂O₂ impurities.^{50, 51}

7. Radiolysis and photolysis of nitrates in solutions or in the crystalline state (route *g*).^{14, 52–55} These processes occur in atmosphere, natural water and on the Earth surface. Photolysis of nitrates is associated with the formation of peroxynitrite on Martian surface, which was detected by the 'Viking' Mars landers.¹⁴ Various photolysis techniques are used for fast generation of peroxynitrite in studies of its reactivity. For instance, pulse radiolysis was used for measuring the rate constants for formation, breakdown and other reactions of peroxynitrous acid; its UV spectrum was also recorded.⁵⁵ Solid solutions of ONOOK in KNO₃ were prepared by photolysis of crystalline KNO₃ ($\lambda = 250–450$ nm, 2 h).^{55, 56}

Preparative syntheses of peroxynitrite are mainly based on the reactions *a*, *e*, *f* and *c*. The last-named method makes it possible to obtain pure tetramethylammonium peroxynitrite that is free from nitrites, nitrates, hydrogen peroxide, hydroxylamine and azide.

III. Physical and chemical properties

The physicochemical properties of peroxynitrite are summarised in Tables 1–4. The experimental standard enthalpy of formation, $\Delta_f H^\circ$, of ONOO[−] anion in aqueous solutions is -42 ± 4 kJ mol^{−1}. Different values were reported for the absolute entropy ($\Delta_f S^\circ$) of ONOO[−] anion in solution, ranging from 63 (see Ref. 59) to 130 J K^{−1} mol^{−1} (see Refs 13 and 61). The standard free energy of formation ($\Delta_f G^\circ$) of ONOO[−] lies between ~ 70 and 42 kJ mol^{−1}. A recently reported⁴² $\Delta_f G^\circ$ value of 68.5 ± 1.4 kJ mol^{−1} was derived from the experimental rate constants for the direct and reverse reactions in equilibrium



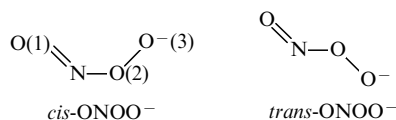
[†] The most reliable value of the rate constant, $(16 \pm 3) \times 10^9$ litre mol^{−1} s^{−1}, was obtained in the studies^{37, 38} carried out using three different flash photolysis techniques.

Table 1. Selected thermodynamic characteristics of peroxynitrite.

End product or reaction equation	$\Delta H^\circ / \text{kJ mol}^{-1}$	Ref.	$\Delta G^\circ / \text{kJ mol}^{-1}$	Ref.	$\Delta S^\circ / \text{J K}^{-1} \text{mol}^{-1}$	Ref.
Formation						
ONOO ⁻ (aq.)	-42 ± 4	57, 58	42 ± 8 59 ± 13 67.4 ± 1.3 68.5 ± 1.4	24 60 29 42	63 130 ± 29 188	59 16, 61 24
ONOOH (aq.)	-59 ± 8 -60 ± 4	16, 61 62	21 ± 13 29.7 ± 0.8 31 ± 2 32.2	61 29 42 41, 59	197 ± 21	16, 61
ONOOH (gas)	4 ± 13	16, 61	54 ± 13	16, 61	301 ± 8	16, 59, 61
Ionisation						
ONOOH (aq.) $\rightleftharpoons$ ONOO ⁻ (aq.) + H ⁺	~ 0 17 ± 8 29	24, 59 16, 61 21	-36.8 ± 0.8 (see ^a)	16, 61	-67 ± 21 -79	16, 61 21
Isomerisation						
ONOOH $\rightarrow$ HNO ₃	-163 ± 4	16, 61	-167 ± 13	16, 61	13 ± 33	16, 61

^a pK_a = 6.5.

The free energy of peroxynitrite is 150 kJ mol^{-1} higher than that of isomeric nitrate;^{24,57} nevertheless, ONOO⁻ anion is relatively stable, that is, it lives in alkali solutions for a few weeks. The reason is the conformation of this species. According to quantum chemical calculations,¹⁴ the order of the bond between the nitrogen atom and the peroxide oxygen atom, O(2), in peroxynitrite approaches a value of 1.5, thus providing an explanation for the existence of *cis*- and *trans*-isomers.



The *cis*-isomer is $8\text{--}17 \text{ kJ mol}^{-1}$ more stable than the *trans*-isomer^{70–73} due to (i) partial delocalisation of negative charge over the entire molecule and (ii) partial bonding between the O(1) and O(3) atoms (the bonding energy is comparable with the energy of a hydrogen bond). Delocalisation stabilises peroxynitrite in the *cis*-conformation and precludes either rotation of the O(3) atom about the N–O(2) bond axis or a change in the N–O–O bond angle in order to adopt the *trans*-configuration. In *cis*-ONOO⁻, the terminal atom O(3) cannot attack the nitrogen atom to give a nitrate, in spite of high driving force of the reaction

Table 2. Activation parameters of peroxynitrite isomerisation (ONOOH $\rightarrow$ HNO₃).

Parameter, units of measurement	Value	Ref.
$\Delta_{\text{iso}}H^\circ / \text{kJ mol}^{-1}$	75 ± 4	24
	82	21
	86 ± 4	16
	88.7	40, 62
$\Delta_{\text{iso}}S^\circ / \text{J K}^{-1} \text{mol}^{-1}$	13 ± 8	24
	31	21
	54	40, 62
$\Delta_{\text{iso}}V^\ddagger / \text{cm}^3 \text{mol}^{-1}$	1.7 ± 1.0	16, 36
	4.8 ± 0.2	63
	6.7 ± 0.9	63
	9.7 ± 1.4	64
	10.2 ± 1.1	65
	10.7 ± 1.9	66

($\Delta G = -150 \text{ kJ mol}^{-1}$). Such an attack becomes possible in the *trans*-configuration owing to a decrease in the N–O–O bond angle ($\sim 117^\circ$ for the *cis*- and $\sim 112^\circ$ for the *trans*-isomer) and to elongation of the O–O bond (from $\sim 1.37 \text{ \AA}$ for the *cis*- to $\sim 1.40 \text{ \AA}$ for the *trans*-isomer) (results of *ab initio* calculations).

According to calculations,^{70–73} the energy barrier to isomerisation of the *cis*-anion to the *trans*-isomer lies between 88 and 113 kJ mol^{-1} and the process is impossible at physiological temperatures. For peroxynitrous acid, this barrier reduces to $40\text{--}50 \text{ kJ mol}^{-1}$, *cis*-ONOOH being only $2\text{--}8 \text{ kJ mol}^{-1}$ more stable than *trans*-isomer.^{70,71,73–76}

Spectral studies confirmed that peroxynitrite in alkali solutions exists only as *cis*-isomer. In particular, the ¹⁵N NMR spectra of peroxynitrite in 0.3 M NaOH exhibit^{15,71} a single peak (would both *cis*- and *trans*-isomers be present in solution, two peaks should be recorded). Small frequency shifts in the Raman spectra of ¹⁵N-peroxynitrite are consistent with the presence of only *cis*-isomer.⁷⁰

Table 3. Gibbs free energies of peroxynitrite homolysis reactions.

Reaction equation	$\Delta G^\circ / \text{kJ mol}^{-1}$	Ref.
ONOOH (aq.) $\rightarrow$	46.4	67
NO ₂ [•] (aq.) + HO [•] (aq.)	57 ± 2	40, 42
	67	16, 61
ONOOH (gas) $\rightarrow$	30	16, 61
NO ₂ [•] (gas) + HO [•] (gas)	37.7	68
ONOO ⁻ (aq.) $\rightarrow$	54.4	67
NO [•] (aq.) + O ₂ ^{•-} (aq.)	65.3 ± 0.2	42
	75	16, 61

Table 4. Redox potentials of peroxynitrite.

Reaction equation	E° / V (pH 0)	Ref.	E° / V (pH 7)	Ref.
ONOOH + H ⁺ + e ⁻ $\rightarrow$	2.0 ± 0.1	16, 61	1.6 ± 0.1	16, 61, 69
NO ₂ [•] + H ₂ O	2.12	42	1.70	59
ONOOH + 2 H ⁺ + 2 e ⁻ $\rightarrow$	1.67	29	1.3 ± 0.1	16, 61, 69
HNO ₂ + H ₂ O	1.68	42, 59	1.37	59

Infrared spectra in Ar matrix obtained at -260 and -266 °C showed^{77,78} that under these conditions the *cis*- and *trans*-isomers of peroxyxynitrous acid are in equilibrium, with the higher content of *cis*-isomer. Exposure of ONOOH to UV irradiation leads to an increase in the content of the *trans*-isomer, whereas the action of IR radiation causes the equilibrium to completely shift towards the *cis*-isomer.⁷⁸

The UV spectrum of peroxyxynitrite anion in aqueous solutions exhibits²⁵ a broad absorption band with a maximum at 302 nm and an extinction coefficient, ϵ , of 1670 ± 50 litre mol⁻¹ cm⁻¹. The UV spectrum of unstable peroxyxynitrous acid was obtained⁵⁵ by pulse radiolysis: $\lambda_{\text{max}} = 240$ nm and $\epsilon = 770 \pm 50$ litre mol⁻¹ cm⁻¹. The IR and Raman spectra of these species and other relevant information are also available.^{70,79,80}

The values of the ionisation constant ($\text{p}K_a$) of this acid, ONOOH, measured by different methods range from 5.3 to 8.3 (Refs 3, 25, 26, 47, 54, 81–83) as a consequence of instability of the compound. More reliable values, namely, $\text{p}K_a = 6.8$ – 6.5 at 25 °C were obtained^{4,36} by the stopped-flow technique from the plot of the rate of ONOOH isomerisation to nitrates *vs.* pH values.



The reaction is described by the following kinetic equation

$$-\frac{d[\text{PN}]}{dt} = k_{\text{eff}}[\text{PN}] = \frac{k_6[\text{PN}][\text{H}^+]}{K_a + [\text{H}^+]}, \quad (7)$$

where $[\text{PN}] = [\text{ONOO}^-] + [\text{ONOOH}]$ and $k_6 = 1.2$ – 1.3 s⁻¹ at 25 °C.^{4,24,36,84} The ionisation constants determined from Eqn (7) depend on the compositions and concentrations of buffer solutions, which can be illustrated using the following data for 25 °C:³⁶

Buffer	Buffer concentration / mol litre ⁻¹	$\text{p}K_a (\pm 0.10)$
Phosphate	0.65	7.33
	0.25	7.12
	0.05	6.71
	0.001	6.55
Ammonium	0.05	7.11
Borate	0.1	8.59

This dependence of $\text{p}K_a$ was explained³⁶ by an increase in the apparent rate of isomerisation of peroxyxynitrous acid owing to either general acid catalysis (phosphate buffer) or the reaction of peroxyxynitrite with ammonium and borate components of the solutions.

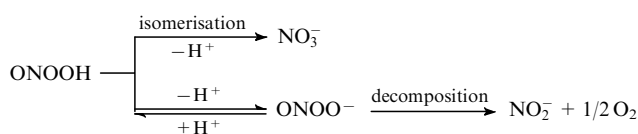
The ionisation constant of ONOOD in phosphate buffer (concentration 0.1 mol litre⁻¹) at 25 °C is 3.3 times lower ($\text{p}K_a^D = 7.3$) than that of ONOOH.⁸⁵ The thermodynamic parameters of the ionisation reaction are listed in Table 1.

Peroxyxynitrite is a strong one- and especially two-electron oxidant. The E° potential of the two-electron reaction of the acid, ONOOH (see Table 4) is similar to the E° values for alkyl peroxides and peroxy acids,^{59,86} whereas the potential of one-electron reaction of ONOOH is 0.95 and ~ 0.8 V higher compared to alkyl peroxides and peroxy acids, respectively.⁵⁹

IV. Decomposition and isomerisation

1. Decay pathways

Decay[‡] of peroxyxynitrite can occur as isomerisation to nitrate or as decomposition into nitrite and oxygen.



The former reaction is the major pathway at $\text{pH} < \text{p}K_a$, while the latter becomes significant at $\text{pH} > 7$ and peroxyxynitrite concentrations above 10^{-4} mol litre⁻¹ (see Refs 38, 88–91). Quantitative yield of nitrate in acid solutions ($\text{pH} \sim 4$) was reported.²⁰ At $\text{pH} < 7$, the yield of nitrate is at least 90%, being slightly dependent on the initial concentration of peroxyxynitrite, pH value and temperature.⁹¹ As the acidity of the medium decreases, the yield of nitrate also decreases, while the yield of nitrite increases and reaches a limiting value at $\text{pH} \sim 10$, being strongly dependent on the initial concentration of peroxyxynitrite.^{90,91} For instance, the yields of nitrite are 30% and 80% at pH 10 for the 5×10^{-5} and 2.5×10^{-3} M peroxyxynitrite solutions, respectively.⁹¹ The formation of nitrite is accompanied by production of oxygen ($[\text{NO}_2^-]:[\text{O}_2] \approx 2$, see Refs 88–91).

In phosphate buffer, the yields of NO_3^- and NO_2^- depend on acidity ($\text{pH} = 1$ – 14) in a complex manner; the curves exhibit inflection points at pH values of about 3.1, 5.8, 6.8, 8.0 and 11.9 (Fig. 2).⁹⁰ At $\text{pH} > 7$, the yield of nitrite appreciably increases while the yield of nitrate correspondingly decreases, namely, $65 \pm 5\%$ for NO_2^- and $35 \pm 5\%$ for NO_3^- at pH 9–10. Contrary to earlier data,^{40,62} it was found recently⁹⁰ that at $\text{pH} > 11$ the yield of nitrate again increases and the nitrate becomes the major product in strong alkaline media (80% at pH 14). At all pH values, the sum of the yields of nitrite and nitrate is a constant equal to the initial concentration of peroxyxynitrite. The dependences of the yields of NO_2^- , NO_3^- and O_2 on the initial concentration of peroxyxynitrite, measured at pH 5.8, 7.4 and 8.5, were linear only at pH 5.8 (see Ref. 90).

A study⁹² of the reactions of peroxyxynitrite with methaemoglobin and 9,10-diphenylanthracene (specific probes for the presence of singlet dioxygen, $^1\text{O}_2$) revealed the formation of nitrosylhaemoglobin and intracyclic 9,10-diphenylanthracene peroxide in high yields. Based on this, it was assumed that a possible pathway of decay of peroxyxynitrous acid involves its transformation to $^1\text{O}_2$ and $^1\text{NO}^-$ *via* a four-membered cyclic intermediate.

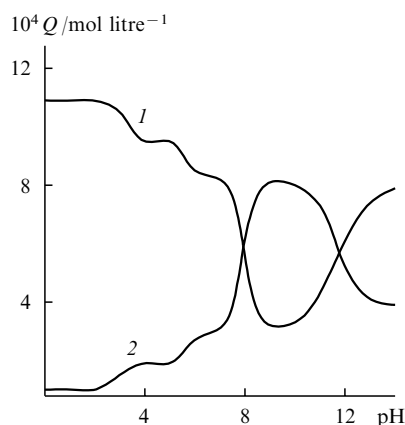
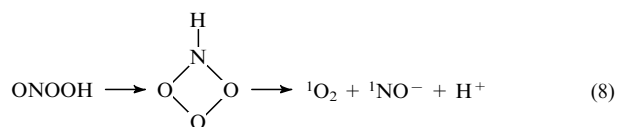
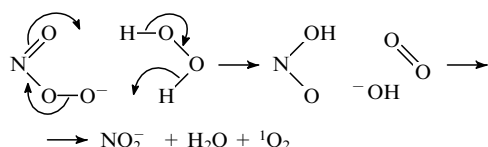


Figure 2. Yields (Q) of nitrate (1) and nitrite (2) plotted *vs.* pH value for the decay of peroxyxynitrite $[(1.02 \pm 0.03) \times 10^{-3}$ mol litre⁻¹] in phosphate buffer (0.05 mol litre⁻¹) at 30 °C.⁹⁰

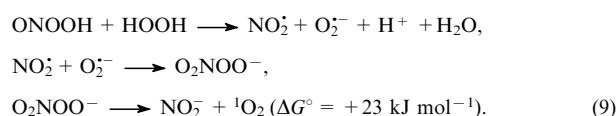
[‡] According to the IUPAC recommendations⁸⁷ for the names of various processes, the decay of peroxyxynitrite is any process accompanied by disappearance of the compound; isomerisation is a process resulting in nitrate; and decomposition is the breakdown into nitrite and oxygen.

However, no nitrosylhaemoglobin was revealed in a more thorough study of the interaction of methaemoglobin with peroxynitrite containing no H_2O_2 and NO_2^- impurities;^{93,94} nor was observed emission at 1270 nm characteristic of $^1\text{O}_2$.⁹⁴ Besides, according to quantum chemical calculations,⁹⁴ the energy barrier to formation of cyclic intermediate in reaction (8) is about five times higher than the experimental activation enthalpy of decay of peroxynitrite (415 vs. 86.5 kJ mol⁻¹, respectively).⁸⁵ Probably, the reason for difference between the results reported in Ref. 92 and in studies^{93,94} consists in that peroxynitrite contained⁹² hydrogen peroxide impurity.

The formation of $^1\text{O}_2$ in the oxidation of H_2O_2 by peroxynitrite was detected in another study.⁹⁵ Two mechanisms were proposed, namely, a concerted reaction of *cis*- ONOO^- with H_2O_2 (see Ref. 95)



and one-electron of oxidation hydrogen peroxide by peroxynitrous acid followed by heterolysis of peroxy nitrate that formed in the reaction^{96,97}



The formation of singlet oxygen in reaction (9) was reported to be thermodynamically unlikely.⁹⁴ Direct oxidation of superoxide by nitrogen dioxide



is thermodynamically favourable and seems to be more probable.

2. Decay kinetics

Earlier studies^{14,21,24–26,98} were carried out assuming that Eqn (7) is valid for the whole range of pH values at which ONOOH breaks down. However, recent data³⁶ showed that this holds only at low peroxynitrite concentrations and at $\text{pH} < \text{p}K_a$ (e.g., at a pH value of 7.9 and $[\text{PN}] = 4.8 \times 10^{-5} \text{ mol litre}^{-1}$; see Fig. 3, curve 1). If the initial concentration of peroxynitrite is ten times higher, the decomposition of this compound is described by a simple exponent only in the initial portion and then dramatically decreases (Fig. 3, curve 2). It was assumed³⁶ that at $\text{pH} > 6.8$ and high concentrations of peroxynitrite it decomposes involving the for-

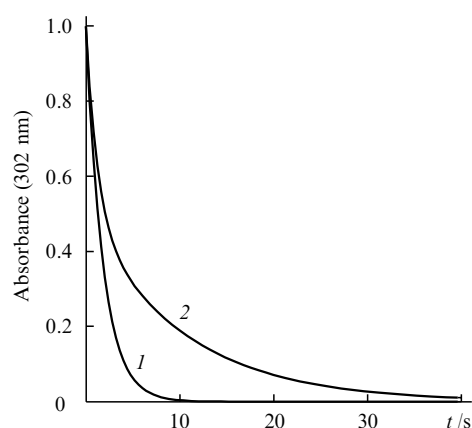
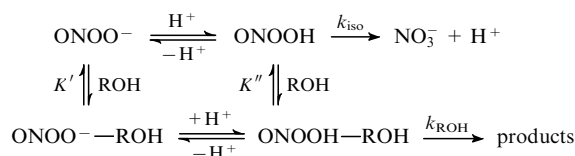


Figure 3. Kinetic curves for peroxynitrite decomposition in phosphate buffer ($\text{pH } 7.9$, 25°C).³⁶ $[\text{PN}] = 4.8 \times 10^{-5}$ (1) and $4.8 \times 10^{-4} \text{ mol litre}^{-1}$ (2).

mation of $[\text{ONOOH} \cdots \text{ONOO}^-]$ adduct as intermediate. The decomposition rate and the character of kinetics are strongly affected by the buffer composition,^{15,36} impurities (H_2O_2 ²⁹ and NO_2^- ^{29,36,38,99}) and trace amounts of transition metals.^{14,25,100} Recently,¹⁰¹ it was established that the decomposition rate of peroxynitrous acid in phosphate buffer at $\text{pH } 5.8\text{--}8.0$ decreases upon addition of ethanol or mannitol. This effect was explained by the mechanism involving stabilisation of peroxynitrite owing to fast equilibrium formation of a complex with the alcohol.



The stability constants K'' are $(9.6 \pm 1.5) \times 10^{-3}$ and $(6.7 \pm 0.9) \times 10^{-3}$ and the rate constants for decomposition of the complexes k_{ROH} are 0.95 ± 0.01 and $0.83 \pm 0.01 \text{ s}^{-1}$ for ethanol and mannitol, respectively.

The plots of the apparent rate constants for decomposition (k_{eff}) on the acidity of the medium exhibit three portions (Fig. 4).^{14,24} In the pH region from 10 to 7 the constant k_{eff} increases as the acidity increases and reaches a plateau at $\text{pH} \approx 6$. Here, Eqn (7) obeys at $k_6 = 1.2 \text{ s}^{-1}$ and $\text{p}K_a = 6.8$.^{24,26,36,83,85} The activation parameters for this portion are listed in Table 2. The secondary kinetic isotope effect for the decomposition of ONOOH (ONOOD), $k_6^{\text{H}}/k_6^{\text{D}}$, weakly depends on temperature in the range $5\text{--}55^\circ\text{C}$ and is equal to 1.6 ± 0.2 and the ionisation isotope effect, $K_a^{\text{H}}/K_a^{\text{D}}$, of peroxynitrous acid is 3.3.⁸⁵ At $\text{pH} < 2$, the decomposition rate increases with an increase in acidity. This was treated^{14,21} as indication of an acid catalysed route:

$$-\frac{d[\text{ONOOH}]}{dt} = k_{\text{H}^+} [\text{ONOOH}][\text{H}^+]. \quad (10)$$

The k_{H^+} values are listed in Table 5. The activation enthalpy and activation entropy corresponding to this route are $\Delta H^\ddagger = 61.2 \pm 0.8 \text{ kJ mol}^{-1}$ and $\Delta S^\ddagger = 22.2 \pm 2.9 \text{ J K}^{-1} \text{ mol}^{-1}$, respectively (see Refs 14 and 21).

At $\text{pH} > 10$, the decomposition kinetics are less understandable. Experimental k_{eff} values are much higher than those calculated from Eqn (7) for $[\text{H}^+] \ll K_a$, $k_6 = 1.2 \text{ s}^{-1}$ and $\text{p}K_a = 6.8$ and show a rather large scatter (see Fig. 4).¹⁴ These deviations

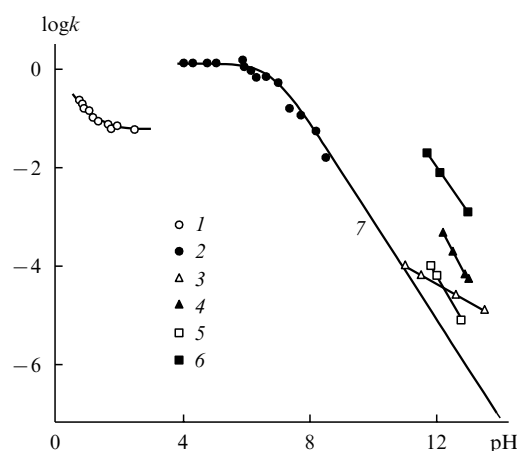


Figure 4. Rate constants for peroxynitrite decay plotted vs. pH values: at 1.5°C (1),²¹ at 25°C (2),²⁴ (3),¹² (4),²⁵ (5)¹⁰² and in the presence of Cu^{2+} (6).¹⁷ Line 7 corresponds to data calculated from Eqn (7) with $k_6 = 1.2 \text{ s}^{-1}$ and $\text{p}K_a = 6.8$.²⁴

Table 5. Rate constants for the acid catalysed route (10) of peroxyxynitrite isomerisation.

T/K	k_{H^+} /litre mol ⁻¹ s ⁻¹	Ref.
281.5	1.295 ± 0.196	14
286.0	2.450 ± 0.112	14
297.0	5.414 ± 0.312	14
308.5	15.790 ± 1.547	14
273.7	0.596 ± 0.008	14, 21
310.0	14.30 ± 0.49	14, 21

were associated¹⁴ with a catalytic route in this range of pH values owing to the presence of transition metal (M) ions, especially copper:

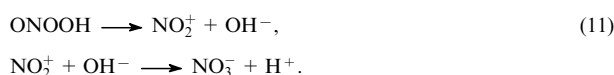
$$k_{\text{eff}} = \frac{k_6[H^+]}{K_a} + k_M[M][H^+].$$

Indications of metal complex catalysis of this reaction were also reported in other studies.^{25, 26, 100, 102}

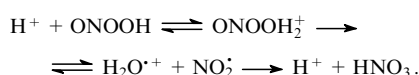
3. Isomerisation mechanisms

Four routes of isomerisation of peroxyxynitrous acid to nitrate are assumed.^{16, 24}

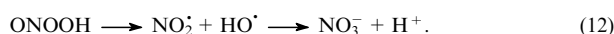
1. Heterolysis and interaction of nitroyl cation with water:^{16, 24}



Although the change in the Gibbs free energy of reaction (11) is nearly zero,^{16, 24} high activation energy (188 kJ mol⁻¹) (see Ref. 24) makes this route unlikely under normal conditions. However, it can occur in the case of acid catalysed decomposition of peroxyxynitrous acid at pH < 2.^{16, 24} Yet another possible mechanism of acid catalysed isomerisation involves equilibrium protonation of ONOOH followed by O–O bond homolysis with the formation of two radical species, H₂O^{•+} and NO₂[•], that recombine to give a nitrate:¹⁴



2. Homolysis followed by recombination of HO[•] and NO₂[•] radicals:^{19, 60, 62, 65, 88, 100, 103, 104}



The mechanism of homolysis belongs to the most debatable issues in chemistry of peroxyxynitrous acid. In 1952, Halfpenny and Robinson¹⁰⁵ observed the formation of biaryls in the oxidation of arenes by peroxyxynitrous acid and assumed that ONOOH undergoes homolysis. In 1990, Beckman *et al.*³ reported that decomposition of peroxyxynitrite generates a strong oxidant capable of initiating many reactions typical of OH radical. The maximum yields of [•]OH in the decomposition of peroxyxynitrite (pH 6.0), determined using deoxyribose and DMSO as scavengers of OH radicals, are $5.1 \pm 0.1\%$ and $24 \pm 1.0\%$, respectively.³ Different methods give for the yield of OH radicals a range of values from 0% to 40%.^{40, 62, 98, 100, 103, 104, 106}

Koppenol *et al.*^{16, 36, 38, 61} reported kinetic and thermodynamic arguments against the sequence of reactions (12) in aqueous solutions. Using the estimate of the free energy of homolysis of ONOOH, $(\Delta G_{\text{hom}}^{\circ})_{\text{aq}} = 67 \pm 10$ kJ mol⁻¹ and the experimental rate constant for the reverse reaction



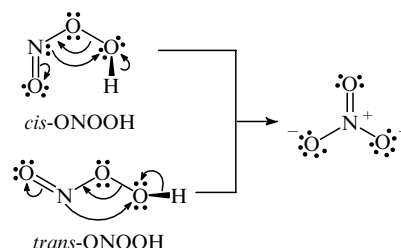
($k_{-13} = 4.5 \times 10^9$ litre mol⁻¹ s⁻¹), they found⁶¹ $k_{13} = 0.6 \times 10^{-4}$ s⁻¹ and, taking into account the rate constant for

isomerisation (k_6), concluded that homolysis of ONOOH in aqueous solutions is unlikely. In the gas phase, the free energy of homolysis of peroxyxynitrous acid is much lower [$(\Delta G_{\text{hom}}^{\circ})_{\text{gas}} = 30$ kJ mol⁻¹] and production of OH radicals is more probable.^{61, 104} Besides, it was shown^{16, 54} that in aqueous solutions (in contrast to the gas phase¹⁰⁷) the interaction of hydroxyl radicals with nitrogen dioxide results in quantitative formation of peroxyxynitrous acid following reaction (–13) rather than formation of nitrate following reactions (12).

Homolysis of the O–O bond is inconsistent with two other data sets. Namely, (i) the yield of ¹⁵N-nitrate in the oxidation of ¹⁵N-nitrite by peroxyxynitrous acid is much lower than it follows from the homolytic model^{38, 99} and (ii) no ascorbyl radicals were detected in the oxidation of hydroascorbate anion.^{38, 108}

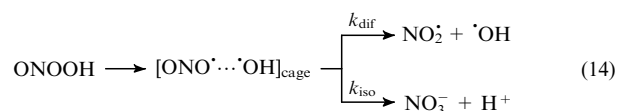
Sometimes, the activation volume for isomerisation ($\Delta_{\text{iso}}V^{\ddagger}$) (see Table 2) is used as argument *pro* (or *contra*) the homolytic mechanism. However, data obtained by different methods are significantly different (from 1.7 to 10 cm³ mol⁻¹; see Refs 36, 63–65) and can therefore not serve as indicators of a particular mechanism.^{38, 63}

3. Intramolecular rearrangement. An alternative to the homolytic mechanism of isomerisation of ONOOH involves a *cis*–*trans* conversion of peroxyxynitrite accompanied by migration of the terminal oxygen atom to the nitrogen atom and formation of nitrate.^{16, 24, 70, 74, 85}



Oxygen shift in the course of *cis*–*trans*-isomerisation is only possible if the O–O bond is directed normal to the O=N–O plane.^{16, 74} The reactive species in the oxidation reactions is thought^{16, 24, 70, 74} to be the excited peroxyxynitrous acid. Its molecule has a *trans*-configuration with elongated O–O bond and the terminal oxygen atom located near the nitrogen atom; this is structurally similar to the transition state of the isomerisation of ONOOH to HONO₂. The radical-like reactivity of ONOOH is associated with the presence of two unpaired electrons in the triplet excited state.^{16, 74} Quantum chemical calculations confirmed the existence of such a low-lying state.⁷⁴

4. Homolysis in the solvent cage. A mechanism was also proposed,^{4, 59, 62, 103, 104} which involves intermediate formation of a radical pair in a ‘cage’. Diffusion of the radical pair out of the cage produces what is called free radicals [•]OH and NO₂[•] while their recombination results in nitrate.



Quantum chemical calculations⁶⁸ showed that in the gas phase the radical pair [ONO[•]...OH] is 8 kJ mol⁻¹ more stable than free radicals NO₂[•] + [•]OH owing to the formation of the OH...O hydrogen bond but ~63 kJ mol⁻¹ less stable than *cis*-HOONO.

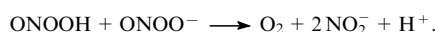
The sequence of reactions (14) is similar to the homolytic mechanism if we assume that hydroxyl radicals can escape the cage and react with substrate or to the ‘triplet’ mechanism of intramolecular rearrangement under assumption that the radicals remain within the cage. The ratio of the rate constants for these routes, $k_{\text{iso}}/k_{\text{dif}}$, is about 2 (Ref. 62) and 2.6,¹⁰³ which corresponds to 30%–40% yields of the OH radicals.

Earlier,²⁰ it was reported that nitrate formed in the reaction retains both peroxide oxygen atoms. However, a recent study¹⁰⁹

revealed that 17% of the oxygen atoms of peroxynitrite are involved in oxygen exchange with water in the course of isomerisation. These data were treated as substantiation of the intramolecular mechanism. The kinetic isotope effect of solvent (1.4–1.5) is also consistent with intramolecular rearrangement of ONOOH to nitrate.^{16,85} Besides, oxygen exchange between the $\cdot\text{OH}$ radical in the radical pair and H_2O should be fast,¹⁰⁹ which excludes this structure from being considered as intermediate. Calculations of the models including a molecule water showed that homolysis (12) is the most energetically favourable mechanism and, therefore, the radicals $\cdot\text{OH}$ and $\text{NO}_2\cdot$ should collapse to nitrate without oxygen exchange;¹¹⁰ however, this contradicts experimental data. At the same time, chemically induced nuclear polarisation (enhanced absorption of $^{15}\text{NO}_3^-$ signal) observed during the decomposition of peroxynitrous acid indicates that nitrate is formed as a result of recombination of the radical pair $[\cdot\text{OH}\cdots^{15}\text{NO}_2\cdot]$.¹¹¹

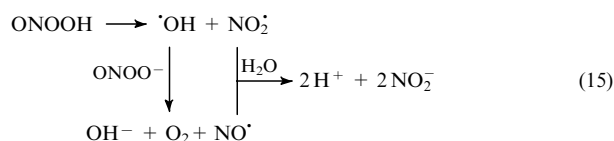
4. Peroxynitrite decomposition mechanisms

In weak alkaline media, isomerisation of peroxynitrite is accompanied by its decomposition following the stoichiometric equation^{88–91} given below

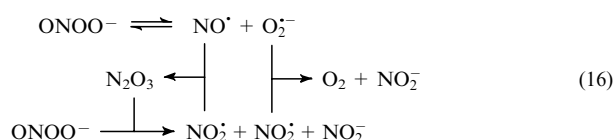


The mechanisms of decomposition and isomerisation have been highly debatable issues. A radical mechanism^{40,42,62,64,88,89} and a bimolecular one^{36,38,60,91} are possible.

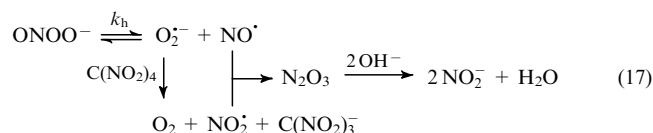
The radical mechanisms imply either homolysis of the $\text{ONO}-\text{OH}$ bond at the rate-limiting step,^{64,89} resulting in the $\cdot\text{OH}$ and $\text{NO}_2\cdot$ radicals,



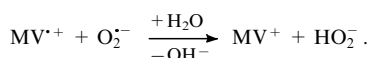
or homolysis of the $\text{ON}-\text{OO}^-$ bond, resulting in nitrogen oxide and superoxide.^{40,42,62,64,88}



The radical pathway is substantiated by the absence of the dependence of the relative yields of nitrite and oxygen on the initial concentration of peroxynitrite^{88,89} and by coincidence of experimental yields of NO_2^- as function of the pH value with the results of the calculations based on reactions (15).^{64,90} Production of superoxide in reactions (16) was proved using the $\text{O}_2^{\cdot-}$ scavengers, namely, tetranitromethane^{41,64,112,113}

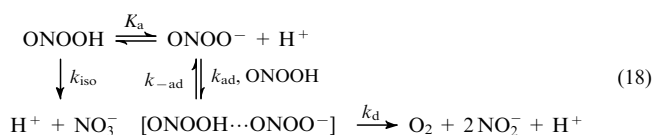


and methyl viologen ($\text{MV}^{\cdot+}$) radical⁴²

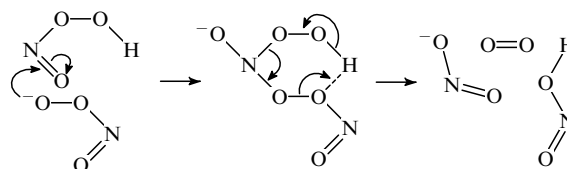


The rate constant for ONOO^- homolysis was found to be the same for both cases ($k_h = 0.017 \text{ s}^{-1}$). The homolytic mechanism (16) is also substantiated by a decrease in the yield of $\text{C(NO}_2)_3^-$ anion in the presence of excess nitrogen oxide,^{41,113} which shifts the equilibrium in reactions (17) towards peroxynitrite.

In contrast to the results^{41,64,113} presented above, Koppenol *et al.*⁶⁰ reported that NO^* radicals do not inhibit the formation of $\text{C(NO}_2)_3^-$ and that the decomposition of peroxynitrite ($>10^{-4} \text{ mol litre}^{-1}$) at $\text{pH} > 7$ does not obey the first-order kinetics in the general case.³⁶ They also found that the relative yields of nitrite and oxygen^{38,91} and the apparent rate constants for decomposition^{16,36} increase as the initial peroxynitrite concentration increases. Quantum chemical estimates¹¹⁴ showed that homolysis of the anion by the mechanism (16) is possible, but this is a thermodynamic 'dead end' because the $[\text{NO}^*\cdots\text{O}_2^{\cdot-}]$ radical pair formed mostly reverts to the starting peroxynitrite. All these results are inconsistent with the homolytic mechanisms. It is believed¹¹⁴ that strong solvation effects make the decomposition of ONOO^- anion a more complicated process (compared to isomerisation of the acid, ONOOH) which involves the formation of an acid–anion adduct.^{16,36,38,91}



The $[\text{ONOOH}\cdots\text{ONOO}^-]$ dimer undergoes a concerted rearrangement involving a cyclic transition state.



The sequence of reactions (18) is analogous to a commonly accepted mechanism of the decomposition of peroxy acids¹¹⁵ and correctly describes the dependences of the yields of nitrate and nitrite and the apparent rate constants for decomposition on the initial concentration of peroxynitrite and on the pH values at $k_{\text{iso}} = 1.15 \text{ s}^{-1}$, $\text{p}K_a = 6.8$, $k_{\text{ad}} = 1.7 \cdot 10^4 \text{ litre mol}^{-1} \text{ s}^{-1}$, $k_{\text{-ad}} = 0.025 \text{ s}^{-1}$ and $k_d = 0.05 \text{ s}^{-1}$ (see Ref. 38). The effective rate constant ($k_{\text{eff}} = 1.8 \times 10^4 \text{ litre mol}^{-1} \text{ s}^{-1}$) for peroxynitrite decomposition at pH 4.7 was obtained¹¹⁶ from the slope of the initial portion of the curve of O_2 accumulation. This is similar to $k_{\text{eff}} = k_{\text{ad}}k_d/(k_{\text{-ad}} + k_d) = 1.1 \times 10^4 \text{ litre mol}^{-1} \text{ s}^{-1}$ calculated from the results of study³⁸ and substantiates¹¹⁶ the mechanism (18).

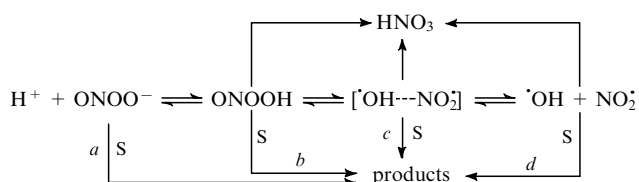
Thus, in spite of intensive research the mechanisms of isomerisation and decomposition of peroxynitrite are still to be clarified. This requires detailed studies on the kinetics of peroxynitrite decomposition and on the reactions of peroxynitrite with various model substrates.

V. Reactions with hydrocarbons and other compounds

1. Typical mechanisms

Peroxynitrite is a strong one- and two-electron oxidant (see Table 4). The interaction of peroxynitrite with the substrates (S) possessing the properties of strong reducing agents can follow four routes (Scheme 2).

Scheme 2

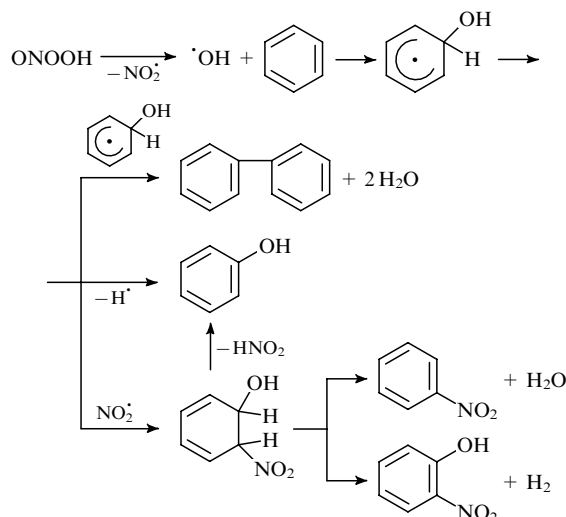


Routes *a* and *b* are first-order reactions with respect to substrate and peroxynitrite. They are characteristic of the reac-

tions involving sulfides,^{117,118} thiols,⁸³ Ni(II)-cyclam complex (cyclam is 1,4,8,11-tetraazacyclotetradecane),¹¹⁹ Br[−] and I[−] anions (see Refs 105 and 119, respectively) and of nucleophilic addition of ONOO[−] to CO₂.^{120–123} Reactions with [Fe(CN)₆]^{4−} (see Ref. 119) and typical scavengers of free radicals, namely, DMSO^{3,98,104} and 2,2'-azinobis(3-ethylbenzothiazole-6-sulfonate) (ABTS)⁹⁸ follow routes *c* and *d*, which are first-order reactions with respect to peroxynitrite and zero-order reactions with respect to substrate; they involve the formation of a hydroxyl-like reactive intermediate.^{3,68,106,119} In addition to free OH radical and [HO[•]...NO₂][•] pair,⁶⁸ a possible candidate is the excited *trans*-ONOOH, which is similar to the radical pair.^{16,24,70,74,98,124} The oxidation of methionine, 2-keto-4-thio-methylbutanoic acid and ascorbate anion follows route *b* (or routes *b* and *d*) at high (or low) substrate concentrations.^{125,126}

Production of OH radicals in the homolysis of ONOOH was first proposed by Halfpenny and Robinson¹⁰⁵ who observed not only nitration and hydroxylation products, but also conversion of arenes to biaryls (Scheme 3).

Scheme 3



The rate constants for the oxidation of hydrogen peroxide and nitrite by peroxynitrous acid and hydroxyl radicals are similar.¹⁰⁰

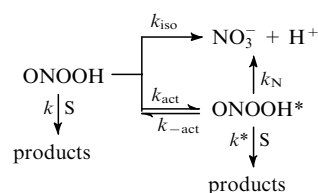
Using the stopped-flow technique, it was found^{98,119,127,128} that the oxidation of many compounds by peroxynitrous acid has no effect on the decomposition kinetics of ONOOH. It was assumed that the rate-limiting step of decomposition of peroxynitrous acid (but not peroxynitrite anion!) involves the formation of a reactive intermediate which then rapidly reacts with substrates in a fashion typical of OH radicals. For instance, peroxynitrous acid can initiate polymerisation of methyl acrylate,¹⁹ hydroxylation and nitration of alkanes, alkenes¹²⁹ and arenes,¹⁰⁵ oxidise DMSO and deoxyribose to formaldehyde and malonic dialdehyde, respectively,³ damage DNA and cause degradation of proteins.⁵⁶ Many of these reactions are inhibited by scavengers of OH radicals (alcohols, benzoic acid and their derivatives, uric acid) and are not catalysed by metal ions.

Hydroxylation at the aromatic ring of phenylalanine results in approximately equal yields of *ortho*-, *meta*- and *para*-derivatives. This feature is used as highly sensitive and specific method for detection of OH radicals.¹³⁰ Similar products and an identical distribution of isomers was reported for the reaction with ONOOH.¹²⁴ The yield of tyrosine and its *ortho*- and *meta*-isomers increases with the acidity of the medium (at pH 6–9) and the concentration of ONOOH, being independent of the substrate concentration. Not only hydroxylation products but also 3-nitro-tyrosine and 4-nitrophenylalanine (and fluorescing bityrosine, in the reaction with tyrosine) were detected among reaction products. These facts and a decrease in the yields of reaction products in the presence of mannitol (specific scavenger of OH radicals) are consistent with route *d* (see Scheme 2).

Production of reactive radical species is accompanied by isomerisation of peroxynitrite following reaction (14). The yield of free radicals was estimated at about 32% based on the O₂ evolution in the oxidation of hydrogen peroxide or nitrite by peroxynitrous acid,¹⁰⁰ at about 24% based on the yield of formaldehyde in the oxidation of DMSO³ and at 40% based on the yield of ABTS^{•+} radical cations in the oxidation of ABTS.^{98,106}

Both peroxynitrous acid and its anion can immediately react with various substrates (routes *a* and *b* in Scheme 2). Since many studies were carried out at neutral pH values, it is often difficult to conclude which of the two forms, ONOOH or ONOO[−], is more reactive. Table 6 lists the rate constants for some second-order reactions of organic and inorganic substrates with peroxynitrite. Under particular conditions, these reactions can proceed much faster than homolysis of ONOOH and be of physiological value.

A mechanism was proposed,^{84,143} which involves a direct oxidation of substrate by the acid, ONOOH, and an indirect oxidation by the activated form of the acid (ONOOH*).



In the direct oxidation (first-order reaction with respect to substrate and reagent) the yield of products with respect to peroxynitrite can be as high as 100%. In the indirect oxidation (first-order reaction with respect to peroxynitrous acid and zero-order reaction with respect to substrate) about 50%–60% of ONOOH isomerise into nitric acid (*k*_{iso}) and only 40%–50% is

Table 6. Rate constants for second-order reactions involving peroxynitrite in aqueous solutions.

Substrate	<i>k</i> / litre mol ^{−1} s ^{−1}	<i>T</i> / °C	Ref.
2-Phenyl-1,2-benzoselenazol-3[2 <i>H</i>]-one ^a	2.0 × 10 ⁶	25	131
Mn(III) porphyrin ^b	1.8 × 10 ⁶ (see ^c)	22–24	132
Fe(III) porphyrin ^b	2.2 × 10 ⁶	37	133
Cistein	5.9 × 10 ³	37	83
Methionine	9.0 × 10 ²	25	125
	1.7 × 10 ³	25	117
	8.6 (see ^a)	25	117
4-Methylthio-2-oxo-butanoic acid	1.4 × 10 ³	25	125
Selenomethionine	2.0 × 10 ⁴	25	134
Tryptophan	1.3 × 10 ²	25	135
	1.8 × 10 ²	37	136
Cytochrome <i>c</i>	2.3 × 10 ⁵	25	137
Dimethyl sulfide	2.1 × 10 ³ (see ^d)	25	118
	0.23 (see ^c)	25	118
Dimethyl selenide	6.0 (see ^c)	25	118
Alcohol dehydrogenase	(2.6–5.6) × 10 ⁵	23	138
Myeloperoxidase	2 × 10 ⁷	25	139
Glutathione peroxidase ^f	8 × 10 ⁶	25	16
Aconitase	2.4 × 10 ⁵	25	140
Ascorbate	236	25	126
	1 × 10 ⁶	25	108
Carbon dioxide ^a	3.0 × 10 ⁴	25	141
	5.8 × 10 ⁴	25	142
Iodide anion	2.3 × 10 ⁴	27	119
Ni(II)-cyclam	3.3 × 10 ⁴	27	119

^a Reaction with peroxynitrite anion; ^b 5,10,15,20-tetrakis(*N*-methylpyridinium-4-yl)porphyrin; ^c at pH 7.4; ^d At pH 4.6; ^e at pH ~ 13; ^f for protein tetramer.

converted to the activated form ONOOH^* (k_{act}), which then rapidly interacts with the substrate (k^*) or produces nitrate (k_{N}). Therefore, even at very high concentration of substrate ($k^*[\text{S}] \gg k_{\text{N}}$), the yield of oxidation products in the indirect process is less than 50%. The nature of the reagent ONOOH^* is unknown. Competitive inhibition studies showed that in some cases the addition of free radical scavengers has no effect on the yields of products of indirect oxidation^{144, 145} or only partial inhibition is observed,¹¹⁹ which is weaker than that predicted from the known rate constants for the reactions of the scavengers with hydroxyl radicals. In those cases^{3, 100, 146} where the degree of inhibition correlated to the rate constants for hydroxyl radicals, the involvement of these species in indirect oxidation of substrates was excluded⁸⁴ based on the kinetic data and product yields.

The contributions of different oxidation routes strongly depends on the pH value (Fig. 5).^{3, 15, 22, 83, 127} In particular, the yields of products of DMSO oxidation following routes *c* and *d* decrease while the rate of oxidation of thiol group following route *a* increases with an increase in pH value.

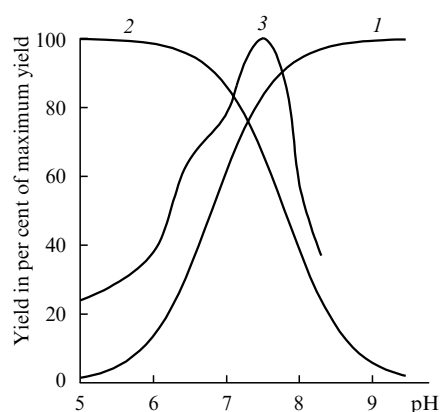


Figure 5. Oxidative reactivity of peroxynitrite plotted vs. pH values.^{15, 22} The results are presented in per cent of the maximum yield under optimum conditions.

(1) Oxidation of thiol group (100% yield), (2) $\text{HO}^{\cdot} \cdots \text{NO}_2^{\cdot}$ (yield 25%–35%), (3) nitration by NO_2^+ (8% with superoxide dismutase, 100% with Fe^{3+}).

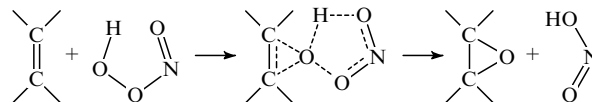
A great diversity of types of the chemical reactions of peroxynitrite is due to involvement (depending on reaction conditions) of various reactive species that are formed as a result of decomposition or activation of peroxynitrite and to unique properties of the peroxynitrite molecule that can simultaneously act as a strong one- and two-electron oxidant, an electrophile and a nucleophile.^{22, 38, 69, 147}

Now we will consider specific features of the mechanisms of the best studied peroxynitrite reactions in more detail.

2. Reactions with hydrocarbons; role of $\cdot\text{OH}$ -like species

The authors of the present review have found^{148–150} that the oxidation of alkanes and alkylbenzenes involves an intermediate step called ‘pre-activation’ of the reagent. At this step, reactive radical species, biradicals or metal complexes with a coordination vacancy are produced. The kinetics of reactions of hydrocarbons with various oxidants and radicals have been studied^{148, 150–152} so thoroughly that hydrocarbons are the best substrates for establishing the nature of the reactive species. Besides, investigations on the reactions of alkanes, alkenes and arenes with peroxynitrite are important for elucidating the mechanisms of oxidation of C–H bonds of alkanes and alkenes in cell membranes and arene- and sulfur-containing fragments of proteins. Prior to our publications, only the reactions of peroxynitrite with strong reducing agents (see Scheme 2) were studied. Only two experimental investigations concerning products of the oxidation of cyclohexane and cyclo-

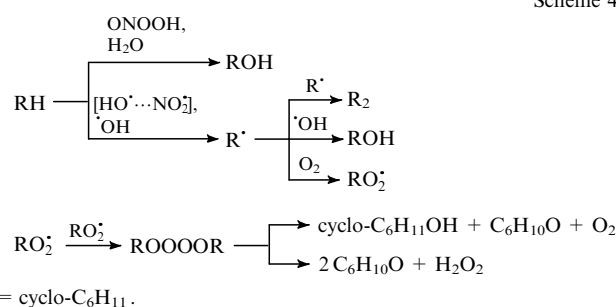
hexene¹²⁹ and arenes¹⁰⁵ in the H_2O_2 – HNO_2 system were available. According to quantum chemical calculations, the interaction of alkanes with peroxynitrous acid involves most probably production of OH radicals as intermediates¹⁵³ and the oxidation of alkenes involves *cis*- ONOOH and formation of a cyclic transition state^{68, 114, 154} similarly to epoxidation of olefins by organic peroxy acids.



We pioneered in systematic studies on the kinetics of peroxynitrite reactions with hydrocarbons as reducing agents and found¹⁵⁵ that alkanes, alkenes and alkylbenzenes are oxidised by aqueous solutions of peroxynitrous acid at $\text{pH} < 7.5$. In the case of cyclohexane, a number of products are formed simultaneously; these are cyclohexanone, cyclohexanol, bicyclohexyl and trace amounts ($< 1\%$) of nitrocyclohexane.^{155–157} Oxidation of alkylbenzenes under these conditions results in a mixture of phenols, nitrophenols and nitroarenes (see Scheme 3).¹⁰⁵ The oxidation of cyclohexene by peroxynitrous acid in phosphate buffer ($\text{pH} \sim 7$) and in the H_2O_2 – HNO_2 system ($\text{pH} 4.3$) gives a broad spectrum of products including cyclopentanecarbaldehyde, epoxycyclohexane, cyclohexanone, cyclohex-2-enol, cyclohex-2-enone, 2-hydroxycyclohexanone, 1-nitrocyclohexene and cyclopent-2-enecarboxylic acid that were identified by GC/MS.¹⁵⁸

The oxidation of cyclohexane by peroxynitrite in a three-phase system ‘aqueous solution–cyclohexane–gas phase’ (O_2 or He) proceeds in the aqueous phase and results in cyclohexanol, cyclohexanone and bicyclohexyl.¹⁵⁹ In both helium and oxygen atmospheres the alcohol is formed at a constant initial rate, whereas production of ketone is preceded by a rather long induction period due to the formation of O_2 in the decomposition of ONOOH . At $\text{pH} 4.7$ and $[\text{RH}]_{\text{aq}} = 7 \times 10^{-3} \text{ mol litre}^{-1}$, only 1% of ONOOH is consumed for the oxidation of hydrocarbon.¹¹⁶ This is due to fast decomposition of peroxynitrous acid. A decrease in the yield of cyclohexanol and an increase in the yield of cyclohexanone on going from the helium to oxygen atmosphere was explained by competition between the routes involving and not involving O_2 (Scheme 4).

Scheme 4



Thus, only a fraction of alcohol formed in the reaction is a product of primary oxidation of cycloalkane by peroxynitrite, whereas the remaining part of alcohol and the whole amount of ketone are products of the secondary radical reactions involving oxygen.

Extremely low solubility of hydrocarbons in water and rapid decomposition of ONOOH at $\text{pH} \sim 7$ make the use of conventional kinetic methods impossible. The problem was solved using the kinetic distribution method (KDM)¹⁴⁸ and a H_2O_2 – HNO_2 /acetate buffer model system ($\text{pH} 4.27$) where peroxynitrous acid is generated *in situ*. Of particular value is the fact that the method allows one to obtain not only the rate constants but also valuable thermodynamic data on the distribution of volatile reactants between the gas phase and solution.

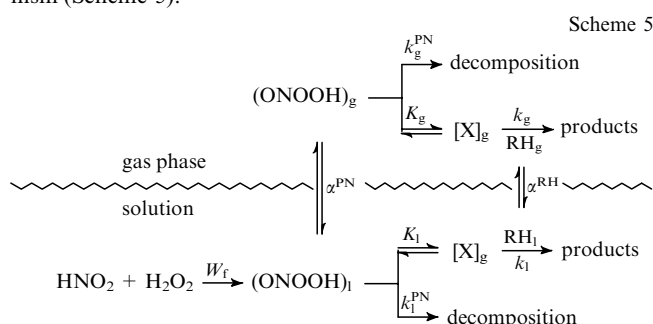
When studying the oxidation of hydrocarbons in aqueous solutions,^{148, 149} the apparent rate constants, k_{λ}^{RH} , for the loss of volatile substrate in the gas phase of a closed reactor are usually related to the liquid-phase rate constants k_1^{RH} as follows:

$$-\frac{1}{[\text{RH}]_{\text{g}}} \frac{d[\text{RH}]_{\text{g}}}{dt} = k_{\lambda}^{\text{RH}} = \frac{k_1^{\text{RH}}}{(1 + \alpha^{\text{RH}}\lambda)}, \quad (19)$$

where $\lambda = V_{\text{g}}/V_{\text{l}}$ is the ratio of the volume of the gas phase to the volume of the liquid phase in the reactor and $\alpha^{\text{RH}} = [\text{RH}]_{\text{g}}/[\text{RH}]_{\text{l}}$ is the distribution coefficient of the hydrocarbon between these phases. The relative liquid-phase rate constants for substrates A and B are related to the measured quantities $k_{\lambda}^{\text{A}}/k_{\lambda}^{\text{B}}$ as follows:

$$\frac{k_1^{\text{A}}}{k_1^{\text{B}}} = \frac{k_{\lambda}^{\text{A}}(1 + \alpha^{\text{A}}\lambda)}{k_{\lambda}^{\text{B}}(1 + \alpha^{\text{B}}\lambda)}. \quad (20)$$

However, the oxidation of hydrocarbons in the H_2O_2 – HNO_2 system cannot be described by Eqn (19) in a wide range of changes in λ . The apparent rate constants are unusual bell-shaped functions of λ and the relative liquid-phase rate constants $k_1^{\text{A}}/k_1^{\text{B}}$ for different pairs of substrates A and B change by 1.2 to 8 times for λ values ranging from 0.65 to 21.^{160, 161} Calculations using Eqn (20) gave an inverted order of selectivity (alkanes > alkenes > alkylbenzenes) and inversely proportional dependence of the relative rate constants on the solubility of hydrocarbons ($1/\alpha^{\text{RH}}$). These facts have no analogies with other hydrocarbon oxidation reactions;^{148, 150} they were explained^{160, 161} by the following mechanism (Scheme 5):



This includes the formation of peroxyxynitrous acid in solution at the rate $W_f = d[\text{ONOOH}]/dt$, the equilibrium distribution of the hydrocarbon (α^{RH}) and acid ($\alpha^{\text{PN}} = [\text{ONOOH}]_{\text{g}}/[\text{ONOOH}]_{\text{l}}$) between the gas and liquid phases, the decomposition of ONOOH (k_{g}^{PN} , k_1^{PN}), pre-activation of reagent (K_{g} , K_1) with production of a reactive species X (radical pair $[\text{HO}\cdots\text{NO}_2]$ or OH radical) and the interaction of X with the substrate RH (k_{g} , k_1) in both phases.

Kinetic studies of the H_2O_2 – HNO_2 system are complicated by simultaneous occurrence of reactions in solution and in the gas phase and by rapid decomposition of ONOOH. Therefore, even at large excess of reagent the loss of hydrocarbons does not obey the first-order kinetics with respect to substrate (Fig. 6). Calculations of Scheme 5 are simplified^{160, 161} at $[\text{H}^+] = \text{const}$ (buffer solutions) in two cases, namely, if $[\text{H}_2\text{O}_2]_0 \gg [\text{NO}_2^-]_0 \gg [\text{RH}]$ (system I) or $[\text{H}_2\text{O}_2]_0 = [\text{NO}_2^-]_0 \gg [\text{RH}]$ (system II).

In the case of system I the loss of substrate obeys¹⁶⁰ the following equation

$$\ln \frac{[\text{RH}]_{\text{g}}^0}{[\text{RH}]_{\text{g}}} = \frac{k_{\lambda}^{\text{RH}}}{k_{\lambda}^{\text{PN}}} [\text{NO}_2^-]_0 \left[1 - \exp(-k_{\text{f}}^{\text{I}}\tau) \right], \quad (21)$$

where $[\text{RH}]_{\text{g}}^0$ and $[\text{RH}]_{\text{g}}$ are the initial and current concentration of RH in the gas phase, respectively; k_{λ}^{RH} and k_{λ}^{PN} are the effective rate constants for the loss of substrate and decomposition of ONOOH, respectively,

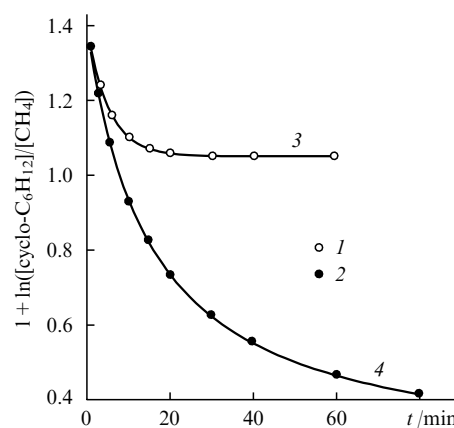


Figure 6. Kinetic curves of cyclohexane decay.¹⁶⁰

Open and solid circles denote experimental data obtained at pH 4.27, 25 °C, $\lambda = 2.31$: $[\text{H}_2\text{O}_2] = 0.1$, $[\text{NaNO}_2] = 0.01 \text{ mol litre}^{-1}$ (1) and $[\text{H}_2\text{O}_2] = [\text{NaNO}_2] = 0.042 \text{ mol litre}^{-1}$ (2); lines 3 and 4 correspond to data calculated from Eqns (21) and (24), respectively. Methane was used as internal reference that is stable under the reaction conditions.

$$k_{\lambda}^{\text{RH}} = \frac{k_1^{\text{RH}} + k_{\text{g}}^{\text{RH}}\alpha^{\text{RH}}\alpha^{\text{PN}}\lambda}{(1 + \alpha^{\text{RH}}\lambda)(1 + \alpha^{\text{PN}}\lambda)} \quad (22)$$

($k_1^{\text{RH}} = K_1k_1$, $k_{\text{g}}^{\text{RH}} = K_{\text{g}}k_{\text{g}}$ are the effective rate constants for the reaction of peroxyxynitrite with the hydrocarbon in the liquid and gas phases, respectively),

$$k_{\lambda}^{\text{PN}} = \frac{k_1^{\text{PN}} + k_{\text{g}}^{\text{PN}}\alpha^{\text{PN}}\lambda}{1 + \alpha^{\text{PN}}\lambda}. \quad (23)$$

The effective pseudo-first-order rate constant for production of ONOOH (k_{f}^{I}) is given by²⁰

$$k_{\text{f}}^{\text{I}} = \frac{W_{\text{f}}}{[\text{NO}_2^-]} = \frac{k_2k_3[\text{H}^+]^2[\text{H}_2\text{O}_2]}{k_{-2}[\text{H}_2\text{O}] + k_3[\text{H}_2\text{O}_2]}.$$

Taking the oxidation of cyclohexane as an example, it was shown that Eqn (21) is valid in the whole range of substrate decay (see Fig. 6, curve 3). The ratio $k_{\lambda}^{\text{RH}}/k_{\lambda}^{\text{PN}}$ is independent of the initial concentrations of H_2O_2 and NaNO_2 and the k_{f}^{I} values at a specified pH value depend only on $[\text{H}_2\text{O}_2]$ (Table 7). The k_2 and $k_3/k_{-2}[\text{H}_2\text{O}]$ values calculated from these data are similar to the estimates²⁰ obtained in basically different manner, from the kinetics of formation of ONOOH (see below).

$10^{-6} k_{\text{f}}^{\text{I}}/\text{litre}^2 \text{ mol}^{-2} \text{ s}^{-1}$	$k_3/k_{-2}[\text{H}_2\text{O}]/\text{litre mol}^{-1}$	Ref.
3.4 ± 0.6	3.6 ± 1.0	160
5.8	2.4	20

Table 7. Characteristics of cyclohexane oxidation in system I (pH 4.27, 25 °C, $\lambda = 2.31$): effect of the H_2O_2 and NO_2^- concentrations on the parameters of Eqn (21).¹⁶⁰

$[\text{H}_2\text{O}_2]_0/\text{mol litre}^{-1}$	$[\text{NO}_2^-]_0/\text{mol litre}^{-1}$	$10^3 k_{\text{f}}^{\text{I}}/\text{s}^{-1}$	$k_{\lambda}^{\text{RH}}/k_{\lambda}^{\text{PN}}/\text{litre mol}^{-1}$
0.1	0.014	3.1	30
0.1	0.010	3.2	35
0.1	0.007	3.3	38
0.1	0.005	3.0	36
0.15	0.01	4.0	34
0.2	0.01	5.2	37
0.3	0.01	6.4	33

Table 8. Dependence of the parameters of Eqn (24) on λ in system II (pH 4.27; 25 °C; $[\text{H}_2\text{O}_2]_0 = [\text{NO}_2^-]_0 = 0.042 \text{ mol litre}^{-1}$).^{160, 161}

λ	n-Hexane ($\alpha^{\text{RH}} = 65$)		Cyclopentane ($\alpha^{\text{RH}} = 7.7$)		Cyclohexane ($\alpha^{\text{RH}} = 8.0$)		Propene ($\alpha^{\text{RH}} = 11$)	
	$k_{\lambda}^{\text{RH}}/k_{\lambda}^{\text{PN}}$ /litre mol ⁻¹	$10^2 k_{\text{f}}^{\text{II}}$ /litre mol ⁻¹ s ⁻¹	$k_{\lambda}^{\text{RH}}/k_{\lambda}^{\text{PN}}$ /litre mol ⁻¹	$10^2 k_{\text{f}}^{\text{II}}$ /litre mol ⁻¹ s ⁻¹	$k_{\lambda}^{\text{RH}}/k_{\lambda}^{\text{PN}}$ /litre mol ⁻¹	$10^2 k_{\text{f}}^{\text{II}}$ /litre mol ⁻¹ s ⁻¹	$k_{\lambda}^{\text{RH}}/k_{\lambda}^{\text{PN}}$ /litre mol ⁻¹	$10^2 k_{\text{f}}^{\text{II}}$ /litre mol ⁻¹ s ⁻¹
0.32	24.5	2.3	—	—	—	—	—	—
0.66	25.0	2.5	18.0	2.3	26.0	2.4	98.6	2.6
1.20	24.8	2.4	21.0	2.5	27.4	2.4	108	2.3
2.31	23.6	2.6	20.8	2.2	28.0	2.6	107	2.8
5.61	21.0	2.5	18.2	2.4	26.0	2.5	91.9	2.7
8.46	—	—	16.5	2.4	24.0	2.8	81.7	2.5
12.2	14.6	2.6	14.8	2.0	21.0	2.6	72.5	2.6
21.0	15.0	2.4	—	—	—	—	—	—
	$(k_{\text{f}}^{\text{II}})_{\text{aver}} = (2.5 \pm 0.1) \times 10^{-2}$ /litre mol ⁻¹ s ⁻¹		$(k_{\text{f}}^{\text{II}})_{\text{aver}} = (2.3 \pm 0.1) \times 10^{-2}$ /litre mol ⁻¹ s ⁻¹		$(k_{\text{f}}^{\text{II}})_{\text{aver}} = (2.6 \pm 0.1) \times 10^{-2}$ /litre mol ⁻¹ s ⁻¹		$(k_{\text{f}}^{\text{II}})_{\text{aver}} = (2.6 \pm 0.1) \times 10^{-2}$ /litre mol ⁻¹ s ⁻¹	

For system II, the loss of substrate in the gas phase obeys the following equation

$$\ln \frac{[\text{RH}]_0}{[\text{RH}]_t} = \frac{k_{\text{f}}^{\text{II}} k_{\lambda}^{\text{RH}} [\text{NO}_2^-]_0^2 t}{k_{\lambda}^{\text{PN}} (1 + [\text{NO}_2^-]_0 k_{\text{f}}^{\text{II}} t)}, \quad (24)$$

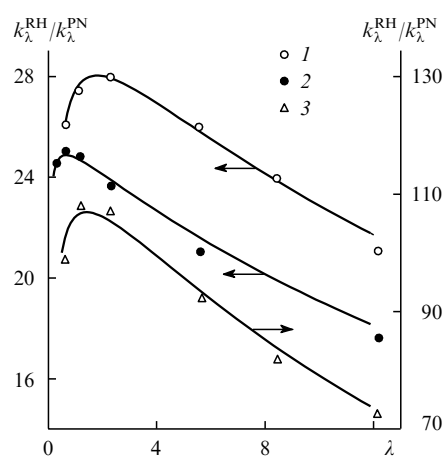
where k_{f}^{II} is the effective second-order rate constant for production of ONOOH at a specified pH value.

In system I the loss of hydrocarbons in the course of reaction is at most 30%.^{160, 161} On going to system II, it reaches 60% to 80%^{160, 161} (see Fig. 6, curve 4), which makes the determination of k_{f} and $k_{\lambda}^{\text{RH}}/k_{\lambda}^{\text{PN}}$ (Table 8) much more accurate.

The bell-shaped dependences of $k_{\lambda}^{\text{RH}}/k_{\lambda}^{\text{PN}}$ on λ (Fig. 7) were quantitatively explained in the framework of the extended KDM model (see Scheme 5).^{155–157, 160, 161} From Eqns (22) and (23) it follows that the dependence of the ratio $k_{\lambda}^{\text{RH}}/k_{\lambda}^{\text{PN}}$ on λ

$$\frac{k_{\lambda}^{\text{RH}}}{k_{\lambda}^{\text{PN}}} = \frac{(k_{\text{g}}^{\text{RH}} \alpha^{\text{RH}} \alpha^{\text{PN}} \lambda + k_{\text{f}}^{\text{RH}})}{(k_{\text{g}}^{\text{PN}} \alpha^{\text{PN}} \lambda + k_{\text{f}}^{\text{PN}}) (1 + \alpha^{\text{RH}} \lambda)} \quad (25)$$

includes terms proportional to λ in the numerator and terms proportional to λ and λ^2 in the denominator. At particular values of the parameters k_{f}^{RH} , k_{g}^{RH} , k_{f}^{PN} , k_{g}^{PN} , α^{RH} and α^{PN} , the plot of $k_{\lambda}^{\text{RH}}/k_{\lambda}^{\text{PN}}$ vs. λ passes through an extremum.

**Figure 7.** $k_{\lambda}^{\text{RH}}/k_{\lambda}^{\text{PN}}$ Ratios plotted vs. λ for the oxidation of cyclohexane (1), n-hexane (2) and propene (3) in the H_2O_2 – NaNO_2 /acetate buffer system (pH 4.27; 25 °C).¹⁶⁰

The lines correspond to data obtained from Eqn (25) for the $k_{\text{g}}^{\text{PN}}/k_{\text{g}}^{\text{RH}}$, $k_{\text{f}}^{\text{PN}}/k_{\text{f}}^{\text{RH}}$ calculated using the data from Table 9, at $(k_{\text{g}}^{\text{RH}} \alpha^{\text{RH}}/k_{\text{g}}^{\text{PN}}) \gg (k_{\text{f}}^{\text{RH}}/k_{\text{f}}^{\text{PN}} \alpha^{\text{PN}} \lambda)$.

The ratio (25) provides quite a correct description of the experimental data for alkanes, alkenes and alkylbenzenes in the whole range of changes in λ studied so far (see Fig. 7) and makes it possible to calculate^{160, 161} the ratios of the rate constants $k_{\text{g}}^{\text{PN}}/k_{\text{g}}^{\text{RH}}$ and $k_{\text{f}}^{\text{PN}}/k_{\text{f}}^{\text{RH}} \alpha^{\text{PN}}$:

$k_{\text{g}}^{\text{PN}}/k_{\text{g}}^{\text{RH}}$ /mol litre ⁻¹	$k_{\text{f}}^{\text{PN}}/k_{\text{f}}^{\text{RH}} \alpha^{\text{PN}}$
n-Hexane (1.4 ± 0.2) $\times 10^{-3}$	27 ± 4
Cyclopentane (1.7 ± 0.2) $\times 10^{-3}$	27 ± 3
Cyclohexane (1.2 ± 0.2) $\times 10^{-3}$	26 ± 2
Propene (3.3 ± 0.5) $\times 10^{-4}$	26 ± 5

Using a version of the KDM method for competitive processes, we calculated^{155–157} the relative rate constants for the oxidation of a large number of hydrocarbons in solution and in the gas phase (Table 9). Because of high α values in aqueous solutions (8–110), alkanes and alkenes at $\lambda > 1$ are mainly in the gas phase where they interact with ONOOH. For arenes, the reaction rates in two phases are comparable.

The reactive species in the reactions studied are hydroxyl radicals ($\text{X} = \cdot\text{OH}$ in Scheme 5), the contribution of the radical pair being insignificant.^{160, 161} The radical pair $[\cdot\text{OH} \cdots \text{ONO}]$ is 8 kJ mol^{-1} more stable than free radicals $\cdot\text{OH} + \text{NO}_2$ owing to formation of a hydrogen bond.⁶⁸ Therefore the rate constant for the reaction



cannot be higher than the rate constant for the following reaction



with free hydroxyl radicals (10^9 – $10^{10} \text{ litre mol}^{-1}$).^{148, 151, 152} For kinetic measurements, one has $[\text{RH}] < 10^{-4} \text{ mol litre}^{-1}$ and $k_{26}[\text{RH}] \leq 10^5$ – 10^6 s^{-1} . At the same time the estimate of the rate constant for decomposition of the radical pair to $\cdot\text{OH} + \text{NO}_2$ is $k_{\text{dif}} = 10^{10}$ – 10^{12} s^{-1} (assuming an activation energy of 8 kJ mol^{-1} and the pre-exponent $A = 10^{12}$ – 10^{14}). Since $k_{26}[\text{RH}]$ is 4–7 orders of magnitude lower than k_{dif} , it was concluded that the major route of transformation of the radical pair involves its decomposition and production of free hydroxyl radicals that are the reactive species in the oxidation of hydrocarbons.

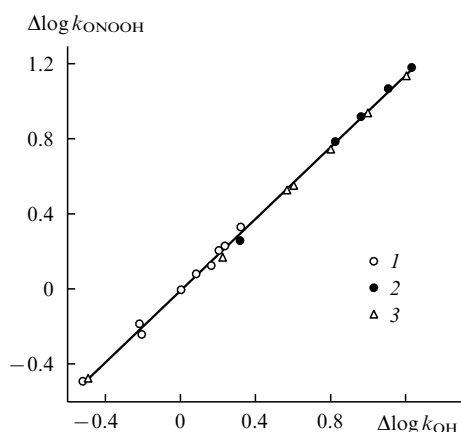
The mechanism (27) is also substantiated by (1) general correlation

$$\Delta \log k_{\text{g}}(\text{ONOOH}) = (0.98 \pm 0.01) \Delta \log k_{\text{g}}(\text{OH})$$

Table 9. Distribution coefficients, α , and relative gas-phase rate constants, $(k_g^{\text{RH}}/k_g^{\text{n-C}_5\text{H}_{12}})$, for oxidation of hydrocarbons by H_2O_2 – HNO_2 /acetate buffer system (pH 4.27) ^{155–158} and by OH radicals ^{148, 151, 152} at 25 °C.

Hydrocarbon	α	$k_g^{\text{RH}}/k_g^{\text{n-C}_5\text{H}_{12}}$		Hydrocarbon	α	$k_g^{\text{RH}}/k_g^{\text{n-C}_5\text{H}_{12}}$	
		H_2O_2 – HNO_2	$\cdot\text{OH}$			H_2O_2 – HNO_2	$\cdot\text{OH}$
Propane	29	0.32	0.33	Isobutene	13	12	13
n-Butane	37	0.65	0.66	n-Hexene	31	8.1	9.2
n-Pentane	49	1.0	1.0	Cyclohexene	3.3	16	14
n-Hexane	65	1.3	1.6	Benzene	0.23	0.33	0.32
n-Heptane	86	1.7	2.0	Toluene	0.26	1.4	1.7
n-Octane	110	2.2	2.3	<i>o</i> -Xylene	0.18	3.2	3.8
Isobutane	48	0.58	0.64	<i>m</i> -Xylene	0.29	5.4	6.4
Cyclopentane	7.7	1.2	1.3	<i>p</i> -Xylene	0.26	3.4	4.1
Cyclohexane	8.0	1.6	1.8	Pseudocumene	0.21	8.4	11
Ethene	12	1.8	2.1	Mesitylene	0.36	13	14
Propene	11	6.1	6.6				

that is valid for gas-phase oxidation of all the substrates studied (alkanes, alkenes and alkylbenzenes) (Fig. 8); ^{155–158} (2) similar products of the two reactions; ^{155, 158, 162, 163} (3) yield ratio ([cyclohexanol]:[cyclohexanone] $\approx$ 2) determined ^{155–157} for the reaction of cyclohexane with peroxyntous acid and characteristic of the reactions with $\cdot\text{OH}$ radicals (see Ref. 162); and (4) experimental proofs of high yield of OH radicals in the decomposition of ONOOH. ^{40, 62, 88, 98, 103, 104}

**Figure 8.** Generalised correlation between the relative rate constants for gas-phase oxidation of alkanes (1), alkenes (2) and alkylbenzenes (3) by the H_2O_2 – HNO_2 system (see Refs 155–158) and OH radicals (see Refs 148, 151, 152).

The calculated ratios $k_g^{\text{RH}}/k_g^{\text{PN}}$, $k_1^{\text{RH}}/k_g^{\text{PN}}\alpha^{\text{PN}}$ and $k_1^{\text{PN}}/k_g^{\text{PN}}\alpha^{\text{PN}}$ were used for estimating the rate constant for gas-phase decomposition of peroxyntous acid and the distribution coefficient α^{PN} . According to Scheme 5, the following reactions proceed in the two phases:



and also reaction (27). Based on the values of the free energy of homolysis of ONOOH, $\Delta G_{\text{hom}}^\circ = -RT \ln K_{28}$ (see Table 1), the equilibrium (28) in solution [$K_{28(\text{l})} = (0.01–1) \times 10^{-12}$ mol litre^{−1}] and in the gas phase [$K_{28(\text{g})} = (0.3–6) \times 10^{-6}$ mol litre^{−1}] is almost completely shifted to the left. With allowance for this fact the overall rate constant for the decomposition of ONOOH according to Eqns (28) and (29) in the gas phase or in solution is given by

$$k^{\text{PN}} = k_{28} + k_{29}. \quad (30)$$

Using the method of quasi-steady-state concentrations, for the effective second-order rate constant for the oxidation of RH according to Eqn (27) one gets

$$k^{\text{RH}} = \frac{k_{27}k_{28}}{k_{28} + k_{29}}. \quad (31)$$

From Eqns (30) and (31) it follows that

$$\begin{aligned} \frac{k_g^{\text{PN}}}{k_g^{\text{RH}}} &= \frac{(k_{28} + k_{29})^2}{k_{27}k_{28}}, \\ \frac{k_1^{\text{PN}}}{k_g^{\text{PN}}\alpha^{\text{PN}}} &= \frac{k_1^{\text{PN}}}{(k_{28} + k_{29})\alpha^{\text{PN}}}. \end{aligned} \quad (32)$$

From the known rate constants $k_1^{\text{PN}} = (k_{28} + k_{29})_0 = 1.2 \text{ s}^{-1}$ (Ref. 24) and $k_{28(\text{l})} = (0.34 \pm 0.08) \text{ s}^{-1}$ (Ref. 29) it is possible to determine the yield of OH radicals [$k_{28(\text{l})}/k_1^{\text{PN}}$] in the decomposition of peroxyntous acid in aqueous solutions at 25 °C, which is equal to 28%.

Taking into account the equilibrium constant $K_{28(\text{g})} = (0.3–6.0) \times 10^{-6}$ mol litre^{−1} and the rate constant for the reverse reaction $k_{-28(\text{g})} = 4 \times 10^8$ litre mol^{−1} s^{−1} (Ref. 164), the rate constant for homolysis, $k_{28(\text{g})} = K_{28(\text{g})}k_{-28(\text{g})}$, was estimated ^{160, 161} at $(0.1–2.4) \times 10^3 \text{ s}^{-1}$, which is much higher than for aqueous solutions.

If $\text{X} = \cdot\text{OH}$, one has $k = k_{27} = k_{\text{OH}}$ (see Scheme 5). Using the published data for n-hexane, cyclopentane, cyclohexane and propene ($k_{\text{OH}(\text{g})} = 3.6 \times 10^9, 2.8 \times 10^9, 4.0 \times 10^9$ and 16×10^9 litre mol^{−1} s^{−1}, respectively), ^{148, 151} experimental ratios $k_g^{\text{PN}}/k_g^{\text{RH}}$ and the value $k_{28(\text{g})} = (0.1–2.4) \times 10^3 \text{ s}^{-1}$, the constant k_g^{PN} was estimated ^{160, 161} from Eqn (31) at $(0.2–1) \times 10^5 \text{ s}^{-1}$. From comparison of the k_g^{PN} and $k_{28(\text{g})}$ values it follows that the yield of OH radicals in the gas-phase decomposition of ONOOH can range from 0.1% to 10%.

The ‘gas–solution’ distribution coefficient of peroxyntous acid estimated ¹⁶⁰ using Eqn (32) lies between the α values of H_2O_2 and O_2NOOH (calculated using the Henry law constants ^{165, 166} in aqueous solutions at 25 °C, $\alpha = 0.041/K_{\text{h}}$):

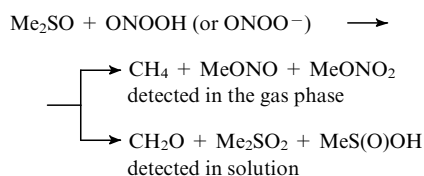
Compound	ONOOH	H_2O_2	O_2NOOH	MeCOOOH	MeOOH
$10^6 \alpha$	0.4–2	0.5	3	50	130

The α^{PN} value corresponds to the energy of solvation of peroxyntous acid in water $\Delta G_{\text{sol}}^\circ = -RT \ln \alpha^{\text{PN}} = 32.6–36.4 \text{ kJ mol}^{-1}$, which is in rough agreement with the estimate $\Delta G_{\text{sol}}^\circ = 25 \pm 12 \text{ kJ mol}^{-1}$ obtained from the free energies of formation of peroxyntous acid in the gas phase and in aqueous solution (see Table 1).

3. Oxidation of dimethyl sulfoxide

Dimethyl sulfoxide is an efficient scavenger of hydroxyl radicals, being converted to methanesulfinic acid MeS(O)OH (in 91% yield) and methyl radicals that can produce formaldehyde.¹⁶⁷ The oxidation of DMSO by peroxyxynitrite in neutral media results in the same products while the reaction in alkaline solutions yields dimethyl sulfone Me_2SO_2 .^{98, 104} The major reaction pathways are a radical route involving $\cdot\text{OH}$ at $\text{pH} < 7$ and bimolecular oxygen transfer from peroxyxynitrite to the substrate molecule in alkaline media.¹⁶⁸

In addition to formaldehyde, Me_2SO_2 and methanesulfinic acid the products of DMSO oxidation by peroxyxynitrite include methane, methyl nitrite and methyl nitrate, which are accumulated in the gas phase of a closed reactor.¹⁶⁹



Detection of these volatile products indicates a complex mechanism of the interaction of DMSO with peroxyxynitrite.

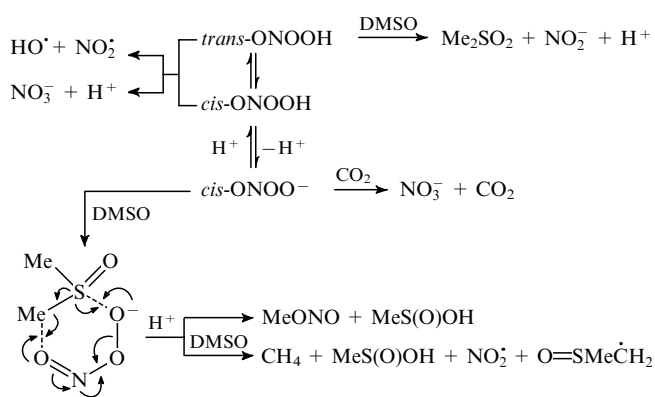
The dependence of yields of CH_4 , CH_2O and MeONO on acidity of the medium passes through maxima in the range of pH values 6.4–6.9 (Table 10). The major product formed under neutral conditions is methyl nitrite ($\sim 17\%$ with respect to initial peroxyxynitrite). The yield of methyl nitrate rapidly increases from 1% ($\text{pH} < 7$) to 17% ($\text{pH} \sim 10$) and then abruptly decreases. The yield of Me_2SO_2 monotonically increases from 2% to 45% as the pH value increases from 6.0 to 11.5. The dependences on the pH value show that methane, formaldehyde and methyl nitrite are produced in the reaction of DMSO with the same reactive species, whereas the formation of MeONO_2 and Me_2SO_2 involves other reaction routes.

Under neutral conditions, the yield of CH_2O reaches a maximum value (1.8% at 0.01 M DMSO) as the substrate concentration increases (see Table 10) and then slowly decreases. The yields of CH_4 , MeONO and Me_2SO_2 reach their maximum values at $[\text{DMSO}] \approx 1 \text{ mol litre}^{-1}$ while the yield of methyl nitrate depends only slightly on the DMSO concentration. The $[\text{CH}_4]:[\text{MeONO}]$ ratio is proportional to $[\text{DMSO}]$, thus indicating the involvement of two DMSO molecules in production of

methane. At pH 6.8, the yields of CH_4 and MeONO are linearly (that of MeONO_2 , quadratically) related to the peroxyxynitrite concentration (see Table 10). Under the same conditions the nitrite anions inhibit the formation of methane and methyl nitrite but have no effect on the yield of methyl nitrate. However, the introduction of NaNO_2 ($0.15 \text{ mol litre}^{-1}$) at pH 10.1 reduces the yield of MeONO_2 from 17% to 1%. In contrast to many other reactions involving peroxyxynitrite,^{120–122} the formation of methane and methyl nitrite (under neutral conditions) and methyl nitrate (at pH 10.4) is inhibited by adding NaHCO_3 . In the presence of a large excess of DMSO, the overall yield of the products ($\text{CH}_4 + \text{CH}_2\text{O} + \text{MeONO}$) with respect to peroxyxynitrite is $55 \pm 10\%$, being higher than the upper limit ($\sim 40\%$)¹⁰⁶ for the formation of OH radicals from ONOOH . It is impossible to explain all these results by considering the reaction route involving OH radicals.

It was assumed¹⁶⁹ that the reaction proceeds *via* a cyclic intermediate which can decompose into MeONO and MeS(O)OH and produce methane in the reaction with the second DMSO molecule (Scheme 6). Here, the role of the reactive species is played by *cis*- ONOO^- and the conversion of the intermediate to product is catalysed by the acid.

Scheme 6



trans-Peroxyxynitrite, which cannot form a cyclic intermediate, reacts with DMSO to give Me_2SO_2 . In the presence of CO_2 and NO_2^- , competing reactions of *cis*- ONOO^- with carbon dioxide proceed.^{120–122} Taking into account the quadratic dependence of the yield of methyl nitrate on the peroxyxynitrite concentration, it

Table 10. Product (P) yields in the reaction of DMSO with peroxyxynitrite in phosphate buffer (36 °C, $\mu = 0.15$) as functions of pH values and reagent concentrations (Ref. 169).^a

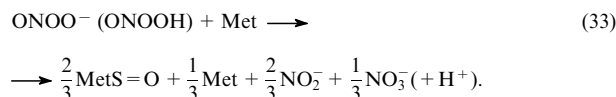
pH	$10^3 [\text{ONOO}^-]$	$10^2 [\text{Me}_2\text{SO}]$	$10^4 [\text{P}]$				
			$[\text{MeONO}]$	$[\text{CH}_4]$	$[\text{MeONO}_2]$	$[\text{CH}_2\text{O}]$	$[\text{Me}_2\text{SO}_2]$
5.66	7.8	7.2	4.1	0.72	0.1	—	—
5.95	7.8	7.2	—	—	—	1.1	1.8
6.80	2.4	7.2	3.1	0.14	—	—	—
6.80	4.7	7.2	7.9	0.38	0.5	—	—
6.80	7.8	7.2	12	0.94	1.6	—	—
6.80	14.3	7.2	20	1.4	5.0	—	—
6.95	8.6	1.8	1.1	0.043	0.26	1.6	2.0
6.95	8.6	4.0	3.5	0.28	0.30	—	—
6.95	8.6	7.2	6.3	0.86	—	1.5	5.0
6.95	8.6	30	18	2.8	0.40	—	—
6.95	8.6	120	22	9.5	—	1.4	7.0
7.10	7.8	7.2	5.8	0.4	—	—	—
7.75	7.8	7.2	1.8	0.02	4.6	0.95	3.3
10.4	7.8	7.2	0.7	0.001	13.2	< 0.02	—
11.2	7.8	7.2	0.4	0.001	5.4	—	30

^a Concentrations of reagents and products are given in mol litre^{-1} ; μ is the ionic strength.

was concluded¹⁶⁹ that MeONO_2 is formed in the interaction of DMSO with a complex between ONOO^- and ONOOH .^{16, 36, 38, 91}

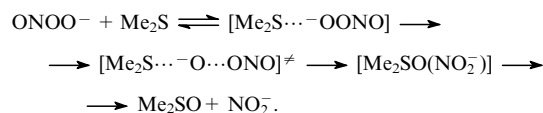
4. Oxidation of sulfides

Sulfides are oxidised by both peroxynitrous acid and its anion to give sulfoxides and NO_2^- (Refs 117, 118, 125, 170). The yield of DMSO and nitrite in the reaction of dimethyl sulfide with ONOO^- is 100% (with respect to peroxynitrite) and 80% in the interaction with ONOOH .¹¹⁸ The reaction of methionine (Met) with both forms of peroxynitrite is also stoichiometric but the reaction equation takes another form:¹¹⁷



The reactivity of peroxynitrous acid in the reactions with sulfides is more than two orders of magnitude higher than that of its anion (see Table 6). The activation enthalpy and activation entropy of the reaction of Me_2S with ONOOH are respectively $24.7 \pm 2.1 \text{ kJ mol}^{-1}$ and $-(96 \pm 13) \text{ J K}^{-1} \text{ mol}^{-1}$ [cf. $40.6 \pm 2.5 \text{ kJ mol}^{-1}$ and $-(121 \pm 13) \text{ J K}^{-1} \text{ mol}^{-1}$, respectively, for the reaction with ONOO^-].¹¹⁸ The reaction of Me_2S with ONOO^- is characterised by strong solvation effects.¹¹⁸ Namely, with an increase in the concentration of the organic component (EtOH, BuOH, MeCN, tetrahydrofuran, tetramethylenesulfone) in aqueous-organic media, the reaction rates decrease while the rate of the reaction of Me_2S with ONOOH remains unchanged.

According to quantum chemical calculations,⁷³ the reaction of Me_2S with *cis*- ONOO^- involves transfer of an oxygen atom (two-electron oxidation) *via* an equilibrium formation of a complex $\{\text{Me}_2\text{S} \cdots \text{OONO}\}$ followed by O—O bond cleavage at the rate-limiting step:



Gas-phase interaction between the negatively charged terminal oxygen atom of peroxynitrite and the sulfur atom bearing a partial positive charge is characterised by $\Delta H^\circ = -27$ and $\Delta G^\circ = -5.0 \text{ kJ mol}^{-1}$. The activation parameters, $\Delta H^\ddagger$ and $\Delta G^\ddagger$, of O—O bond homolysis in the transition state $[\text{Me}_2\text{S} \cdots \text{O} \cdots \text{ONO}]^\ddagger$ are 64 and 110 kJ mol^{-1} , respectively. The energy ΔH (ΔG) of the intermediate $[\text{Me}_2\text{SO}(\text{NO}_2^-)]$ is 215 (177) kJ mol^{-1} lower than those of the initial reagents. Dissociation of the intermediate to Me_2SO and NO_2^- is an endothermic process ($\Delta H^\circ = 72$, $\Delta G^\circ = 36 \text{ kJ mol}^{-1}$) with a low activation barrier. On the whole, the reaction of Me_2S with ONOO^- is exothermic, namely, $\Delta H^\circ = -143$ and

$\Delta G^\circ = -141 \text{ kJ mol}^{-1}$. Estimates⁷³ showed that solvation of ONOO^- increases the reaction rate, which is consistent with the experiment.¹¹⁸ The equilibrium complex between Me_2S and $(\text{H}_2\text{O})_n(\text{ONOO}^-)$ is destabilised with respect to the reagents at $n = 1, 2$; namely, $\Delta H^\circ(\Delta G^\circ) = -19$ (13) and 0.4 (26) kJ mol^{-1} , respectively. The activation enthalpy of O—O bond homolysis decreases from 64 ($n = 0$) to 62 ($n = 1$) and 56 kJ mol^{-1} ($n = 2$).

The reaction of Me_2S with *cis*- ONOOH can proceed⁷³ either as a stepwise or a concerted process that is much faster than the reaction with ONOO^- . The stepwise route involves homolysis of the ONO—OH bond and generation of free radicals ($\cdot\text{OH}$ and $\cdot\text{ONO}$), formation of the intermediate $[\text{Me}_2\text{S}(\text{OH})(\text{NO}_2)]$, which then can undergo either a barrierless endothermic transformation to radicals $[\text{Me}_2\text{S}(\cdot\text{OH})$ and $\text{NO}_2^\cdot$ or an exothermic proton transfer [$\Delta H^\ddagger = 48$, $\Delta G^\ddagger = 55 \text{ kJ mol}^{-1}$] to give DMSO and HONO. Parameters of the energy barrier to the concerted route involving O—O bond cleavage in the transition state $[\text{Me}_2\text{S} \cdots \text{HOONO}]^\ddagger$ were estimated as follows; $\Delta H^\ddagger = 25.5$ and $\Delta G^\ddagger = 26.4 \text{ kJ mol}^{-1}$. The stepwise reaction of Me_2S with ONOOH is more probable in the gas phase, whereas both routes are efficient in solution. Since H_2O interacts with ONOOH much weaker than with ONOO^- , solvation effects for the reaction of Me_2S with peroxynitrous acid are less pronounced.^{73, 118}

Methionine plays a key role in transfer of the unpaired electrons in peptides and proteins.¹⁷¹ The oxidation of this compound can proceed as reaction (33) resulting in methionine sulfoxide and as a one-electron oxidation by activated peroxynitrous acid ONOOH^* to give ethylene.¹²⁵ The second route is substantiated by nonlinear dependences of the rate constants on the concentration of methionine.^{84, 125}

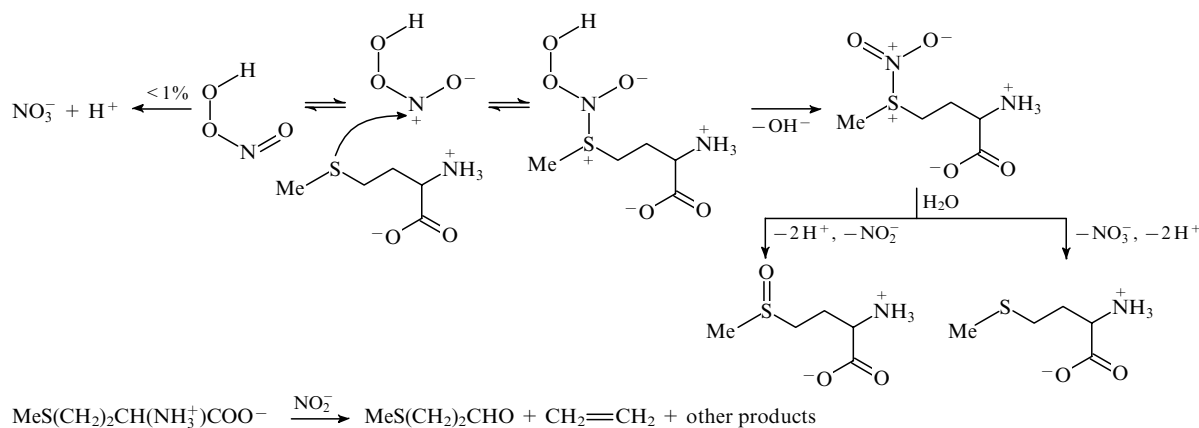
However, more recently¹¹⁷ this dependence was shown to be linear and the formation of nitrate (in addition to sulfoxide and nitrite) in accordance with Eqn (33) was established; *i.e.*, methionine catalyses the isomerisation of peroxynitrite to nitrate. The relative yields of products are independent of the pH value and substrate concentration. It was concluded that the reaction obeys Scheme 7 and that nitrite (either an impurity or the species formed in the reaction) is not chemically inert. Namely, it oxidises methionine in the one-electron process to ethylene and methional ($\text{MeSCH}_2\text{CH}_2\text{CHO}$).

Using the formation of acetaldehyde as a test for one-electron oxidation, it was found¹⁷⁰ that only 1.5% and 1.85% of threonylmethionine are oxidised in the one-electron process under anaerobic and aerobic conditions (pH 7.4), respectively, whereas the contribution of this route estimated from the yield of ethylene is at least 8%.¹²⁵

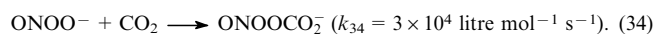
5. Interaction with carbon dioxide and carbonyl compounds

The reaction of peroxynitrite with bicarbonate buffer has long been known,²⁶ but attracted considerable attention of researchers only in 1993 when its biological importance was reported.¹⁴⁵ More

Scheme 7

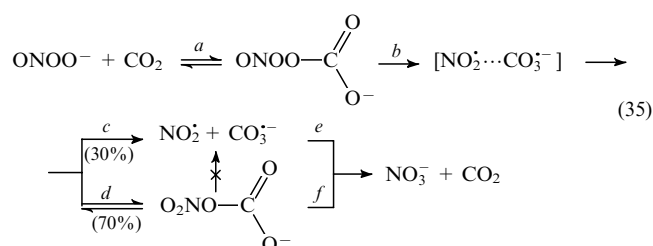


recently, it was shown¹⁴¹ that ONOO^- rapidly forms an unstable nitrosoperoxy carbonate with CO_2 :



The activation enthalpy and activation entropy are $45 \pm 3 \text{ kJ mol}^{-1}$ and $27 \pm 2 \text{ J K}^{-1} \text{ mol}^{-1}$, respectively. Using the stopped-flow technique, it was found^{172, 173} that ONOOCO_2^- is characterised by an absorption band at $\lambda_{\text{max}} = 650 \text{ nm}$. At present, reaction (34) is considered as the major route of peroxynitrite decomposition in biosystems because the physiological concentration of bicarbonate $(1-3) \times 10^{-2} \text{ mol litre}^{-1}$ (see Refs 96, 122, 141, 174–176) is sufficient for the process to proceed. Carbon dioxide affects many reactions involving peroxynitrite. Namely, it considerably accelerates nitration of arenes,^{142, 174, 175} DNA¹⁷⁷ and ethyl acetoacetate,¹⁷⁸ catalyses one-electron oxidation of metal complexes $\text{Fe}(\text{CN})_6^{4-}$, $\text{Mo}(\text{CN})_8^{4-}$, $\text{Os}(\text{bipy})_3^{2+}$, $\text{Fe}(\text{bipy})_3^{2+}$, $\text{Ru}(\text{bipy})_2^{2+}$ and I^- anion (see Ref. 121); partially inhibits the oxidation of thiols,¹⁴² DMSO,¹⁴² oxyhaemoglobin,¹⁴² DNA¹⁷⁷ and cytochrome c ;¹⁴² and completely inhibits the hydroxylation of benzoate anion.¹⁴²

In the absence of other reagents the reaction of CO_2 with peroxynitrite results in nitrate as the major product.^{120, 121} It is assumed^{120, 122, 123, 141, 142, 174, 176} that nitrosoperoxy carbonate formed in the reaction homolytically decomposes into a radical pair, which then transforms to nitrocarbonate ($\text{O}_2\text{NOCO}_2^-$)^{18, 120, 178–182} or decomposes into radical species, $\text{CO}_3^{\cdot-}$ and $\text{NO}_2^{\cdot}$.



The standard Gibbs energy diagram for the sequence of reactions (35)¹⁸² is shown in Fig. 9 and the rate constants for particular steps are listed in Table 11.

The rate of decomposition of $\text{O}_2\text{NOCO}_2^-$ to nitrate and CO_2 is 28 orders of magnitude higher than the rate of decomposition to

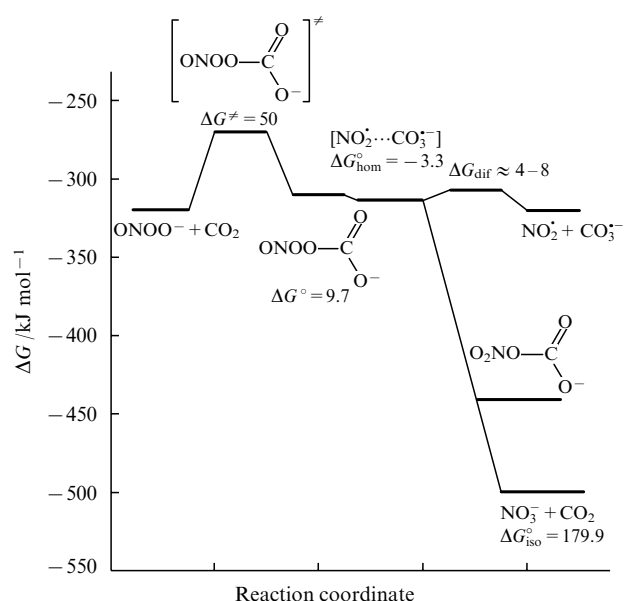


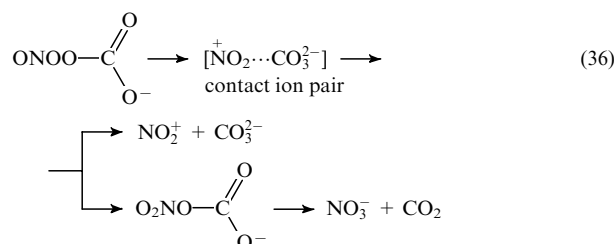
Figure 9. Standard Gibbs energy diagram of the reaction of peroxynitrite with CO_2 .¹⁸²

Table 11. Rate constants for particular steps of the reaction of peroxynitrite with CO_2 [reaction (35)] at 25 °C.

Stage	Rate constants	Ref.
$\text{ONOO}^- + \text{CO}_2 \rightleftharpoons$	$k_a = 3 \times 10^4 \text{ litre mol}^{-1} \text{ s}^{-1}$	141
$\text{ONOOCO}_2^- (a)$	$k_{-a} = 1.5 \times 10^6 \text{ s}^{-1}$	182
$\text{ONOOCO}_2^- \rightleftharpoons$	$k_{(b+c)} = 1.9 \times 10^9 \text{ s}^{-1}$	182
$\text{NO}_2^{\cdot} + \text{CO}_3^{\cdot-} (b + c)$	$k_{-(b+c)} = 5 \times 10^8 \text{ litre mol}^{-1} \text{ s}^{-1}$	182, 183
$\text{NO}_2^{\cdot} + \text{CO}_3^{\cdot-} \rightleftharpoons$	$k_e = 1.0 \times 10^9 \text{ litre mol}^{-1} \text{ s}^{-1}$	184
$\text{NO}_3^- + \text{CO}_2 (d)$		
$\text{NO}_2^{\cdot} + \text{CO}_3^{\cdot-} \rightleftharpoons$	$k_d = 5 \times 10^8 \text{ litre mol}^{-1} \text{ s}^{-1}$	182, 183
$\text{O}_2\text{NOCO}_2^- (e)$		
	$k_{-d} = 5.6 \times 10^{-15} \text{ s}^{-1}$	182
$\text{O}_2\text{NOCO}_2^- \rightleftharpoons$	$k_f = 4 \times 10^{13} \text{ s}^{-1}$	182
$\text{NO}_3^- + \text{CO}_2 (f)$	$k_{-f} = 8 \times 10^3 \text{ litre mol}^{-1} \text{ s}^{-1}$	182

$\text{NO}_2^{\cdot}$ and $\text{CO}_3^{\cdot-}$ (Table 11, steps f and $-d$, respectively). In a number of studies^{18, 59, 96, 111, 176, 185} nitrocarbonate is excluded from the sequence of reactions (35) assuming that the radical pair $[\text{NO}_2^{\cdot} \cdots \text{CO}_3^{\cdot-}]$ can either decompose into free radicals (30%–35%) or undergo intracage conversion to nitrate and CO_2 (65%–70%). The yield of radicals $\text{NO}_2^{\cdot}$ and $\text{CO}_3^{\cdot-}$ in the decomposition of nitrosoperoxy carbonate is $3 \pm 1\%$ (cf. $96 \pm 1\%$ for the yield of nitrate).¹⁷³

The catalytic effect of CO_2 in the nitration of arenes by peroxynitrite was explained^{120, 142, 175, 178–181} by heterolytic decomposition of nitrosoperoxy carbonate.

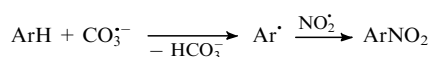


Although the formation of NO_2^+ cation in reaction (36) is thermodynamically allowed ($\Delta G^\circ = 16 \pm 29 \text{ kJ mol}^{-1}$), the very short lifetime in aqueous solutions (1.4 ns) (see Ref. 186) makes it a poor candidate for playing the role of the reactive species.^{96, 122} Nitrosoperoxy carbonate is a strong one-electron oxidant.¹⁸



Other possible reagents in the bicarbonate-catalysed processes included^{96, 120–122, 178–181} nitrocarbonate and $\text{NO}_2^{\cdot}$ and $\text{CO}_3^{\cdot-}$ radicals. However, instability of the ONOOCO_2^- and $\text{O}_2\text{NOCO}_2^-$ species (see the rate constants listed in Table 11) causes them to decompose much faster than to interact with the substrate.^{18, 121, 174, 185, 187, 188}

The most plausible reactive species are the $\text{NO}_2^{\cdot}$ and $\text{CO}_3^{\cdot-}$ radicals (Refs 18, 120, 123, 141, 142, 174, 175, 178–182). The carbonate radical anion is a strong oxidant [$E_{\text{CO}_3^{\cdot-}/\text{CO}_3^-}^\circ = 1.58 \pm 0.02 \text{ V}$ at pH 12.5 (Refs 188, 189) and $E_{\text{CO}_3^{\cdot-}/\text{HCO}_3^-}^\circ = 1.78 \pm 0.02 \text{ V}$ at pH 7.0 (Ref. 190)] capable of abstracting an electron from various substrates. The $\text{NO}_2^{\cdot}$ radical is a weaker one-electron oxidant ($E_{\text{NO}_2^{\cdot}/\text{NO}_2^-}^\circ = 1.04 \pm 0.02 \text{ V}$).¹⁹¹ A two-step mechanism was proposed for nitration of arenes (in particular, tyrosine, a compound of great biochemical value).^{111, 142, 174, 192}



The rate of the reaction of tyrosine with $\text{CO}_3^{\cdot-}$ is more than 300 times higher than that of the reaction with $\text{NO}_2^{\cdot}$.^{193, 194} In agreement with the redox potentials, direct interaction of the substrate

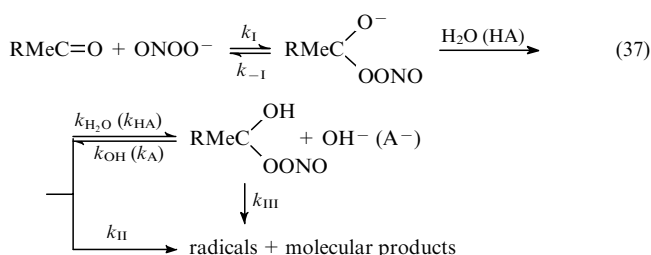
Table 12. Rate constants for different steps of reactions (37) in aqueous solutions at 22 °C.¹⁹⁸

Parameter	Reagent	
	acetone	acetaldehyde
k_I /litre mol ⁻¹ s ⁻¹	116 ± 7	(5.8 ± 0.4) × 10 ⁴
k_{-I} /s ⁻¹	~2 × 10 ⁹	~3 × 10 ⁹
K_I	~6 × 10 ⁻⁸	~2 × 10 ⁻⁵
k_{II} /s ⁻¹	~3 × 10 ⁵	~5 × 10 ⁶
k_{III} /s ⁻¹	~1 × 10 ⁶	~2 × 10 ⁶
k_{H_2O} /s ⁻¹	~2 × 10 ⁷	~6 × 10 ⁷
k_{OH} /litre mol ⁻¹ s ⁻¹	~3 × 10 ⁹	~3 × 10 ⁹
k_{HA} /litre mol ⁻¹ s ⁻¹ (see ^a)	~3 × 10 ⁹	~3 × 10 ⁹
pK_a (adduct)	~11.8	~12.3

^a HA refers to NH₄⁺.

with NO₂⁻ (and in other cases) proceeds much slower than with CO₃²⁻ (Ref. 18).

Nucleophilic addition of ONOO⁻ anion to carbonyl compounds^{97, 185, 195–198} proceeds similarly to reaction (34). It involves rapid equilibrium between the starting reagents and tetrahedral anionic adduct, which is strongly shifted towards the former (Table 12).^{185, 198}



R = H, Me.

The anionic intermediate in reactions (37) is rapidly protonated under the action of water or buffer components. The rate of the bimolecular reaction of ONOO⁻ with RMeCO strongly depends on the pH value and buffer concentration. Rapid homolysis of weak O—O bonds in the anionic and neutral adducts is followed by production of radical pairs in the solvent cage and subsequent formation of free alkoxy radicals and nitrogen dioxide (Scheme 8).

The yield of free radicals in the reactions of acetone and acetaldehyde with ONOO⁻ is ~15% at high and low pH values.¹⁹⁸

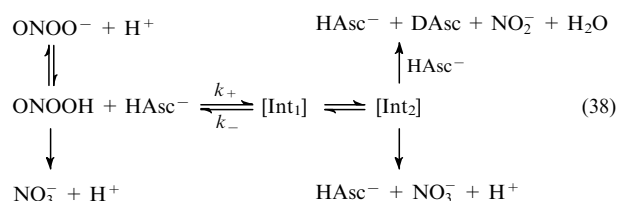
Like CO₂, aldehydes catalyse the oxidation of ABTS by peroxynitrite but, in contrast to carbon dioxide, have no effect on the rate of nitration of 4-hydroxyphenylacetate.¹⁹⁵ High rate constants for homolysis of peroxynitrite adducts with carbonyl compounds¹⁹⁸ indicate that they cannot act as reactive species, as was proposed earlier.¹⁹⁵

6. Reactions with other substrates, catalysis by metal ions

Ascorbic acid has two acidic protons characterised by pK_a values of 4.04 and 11.34 (see Ref. 199). This compound is an *in vitro* and *in vivo* antioxidant of paramount importance.²⁰⁰ Early studies^{123, 201} on the oxidation of hydroascorbate anion (HAsc⁻)

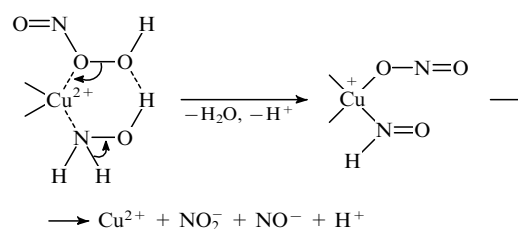
revealed that the reaction is first-order with respect to substrate and peroxynitrous acid ($k = 235$ litre mol⁻¹ s⁻¹). Based on the EPR spectra of ascorbyl radicals, it was concluded²⁰¹ that the reaction involves consecutive one-electron transfer.

According to recent data,^{38, 108} the rate constants are nearly 5000 times higher than those reported earlier (see Table 6). Kinetic, UV and EPR spectral studies and product analysis led to a mechanism that involves a rapid equilibrium formation ($k_+ = 1 \times 10^6$ litre mol⁻¹ s⁻¹, $k_- = 500$ s⁻¹ at 25 °C and pH 5.8; $k_+ = 1.5 \times 10^6$ litre mol⁻¹ s⁻¹, $k_- = 1 \times 10^3$ s⁻¹ at 37 °C) of a first intermediate (Int₁), which undergoes conversion to a second intermediate (Int₂) characterised by absorption maximum at 345 nm. At low concentration of HAsc⁻, the second intermediate decomposes into hydroascorbate and nitrate while at [HAsc⁻] > 4 mmol litre⁻¹ it reacts with the other substrate molecule to give hydroascorbate, dehydroascorbate (DAsc) and nitrite.

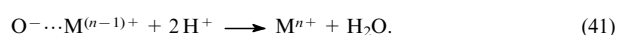
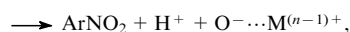
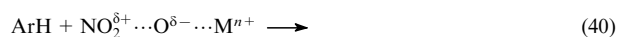
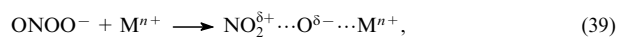


Intermediates Int₁ and Int₂ are treated¹⁰⁸ as 1:1 adducts of peroxynitrous acid with hydroascorbate. According to EPR data, the yield of ascorbyl radicals is 0.24% with respect to starting peroxynitrite and accumulation of these radicals in the course of reaction is accompanied by a decrease of absorption at 345 nm. Therefore, ascorbyl radicals are not primary products. No homolysis of ONOOH into hydroxyl radicals and nitrogen dioxide was detected under the experimental conditions.

Hughes and Nicklin²⁰² studied the oxidation of hydroxylamine in the presence of copper(II) salts. It seems that they were the first who observed catalysis of peroxynitrite reactions by metal ions. They also postulated the formation of a complex between Cu(II) and both reagents.

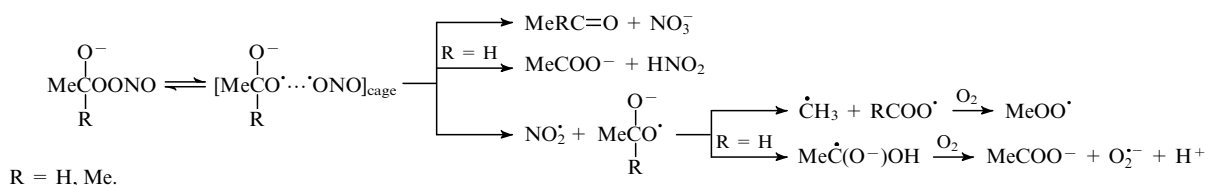


It is assumed^{5, 22} that nitration of phenols and aromatic acids catalysed by transition metal (Fe³⁺, Cu²⁺, Mn³⁺) complexes proceeds involving reactive species similar to nitroyl cation:

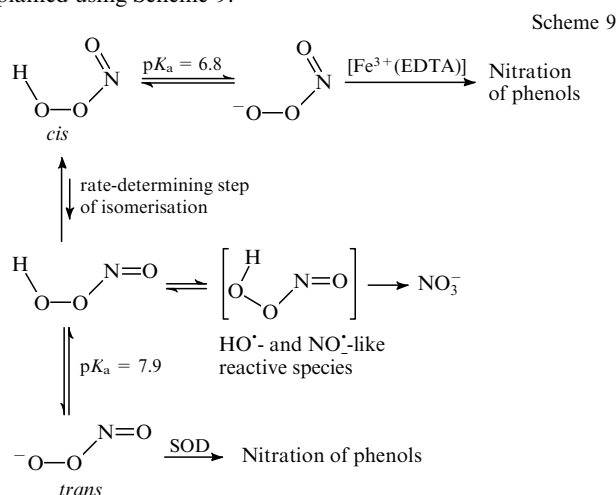


Nitration of phenols catalysed by superoxide dismutase (SOD) has been best studied.^{127, 203} The rate of the reaction of

Scheme 8

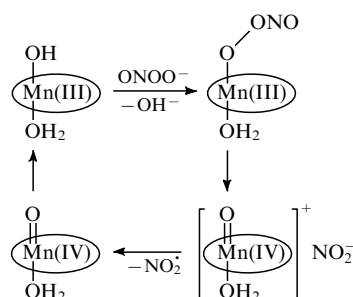


peroxynitrite with Cu,Zn-SOD is about 10^5 litre mol⁻¹ s⁻¹ and the maximum yield of nitrophenols ($\sim 8\%$) is observed at pH 7.5 (see Fig. 5). In the absence of other phenols, the tyrosine residue of SOD is transformed to nitrotyrosine²⁰³ and Cu,Zn-SOD retains its catalytic activity. In the first stage, peroxynitrite reacts with copper; removal of copper from the SOD molecule causes nitration to cease. A complex of Fe³⁺ with EDTA is less catalytically active, however the yield of products exceeds 90% with respect to the starting peroxynitrite at pH 7.5.^{127, 128} Nitration is not accompanied by production of free radicals involving 'nitroyl-like' species that are formed in reactions (39)–(41). The differences between SOD and the complex of Fe³⁺ with EDTA were explained using Scheme 9.¹²⁷



In the reaction with [Fe³⁺(EDTA)] the role of the reactive intermediate is played by *cis*-peroxynitrite. SOD interacts only with *trans*-peroxynitrite due to specific features of the structure of Cu,Zn-superoxide dismutase. The copper ion in SOD is in a deep narrow cavity, therefore only *trans*-ONOO⁻ can reach the active site. Positively charged amino acids near the active site facilitate the motion of peroxynitrite anion into the cavity. The rate-limiting step of this reaction is *cis*–*trans*-isomerisation.¹⁵

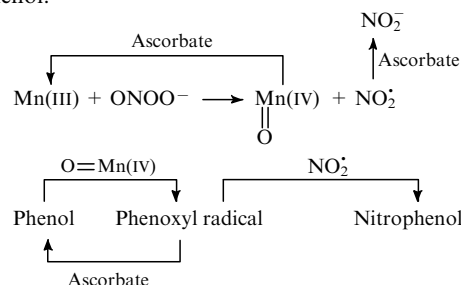
Another mechanism of catalysis is realised in the case of nitration of tyrosine in the presence of porphyrin complexes of manganese(III) and iron(III).^{204–207} Metal-containing porphyrins (MPs) are rapidly oxidised by peroxynitrite (rate constants depend on the porphyrin structure and range from 2.5×10^4 to 5×10^7 litre mol⁻¹ s⁻¹)^{204, 208–211} to relatively stable intermediates Mn(IV)=O and Fe(IV)=O from which Mn(III) and Fe(III) regenerate at the stage of catalytic decomposition of peroxynitrite.



Reduction of Mn(IV)=O and Fe(IV)=O in the presence of phenols is a fast process and MPs catalyse nitration of phenols and oxidation of peroxynitrite. The Mn- and Fe-containing porphyrins cause more than five-fold (pH 7.4) and twelve-fold (pH 9.1) increase in the yield of nitration products (see Ref. 204).

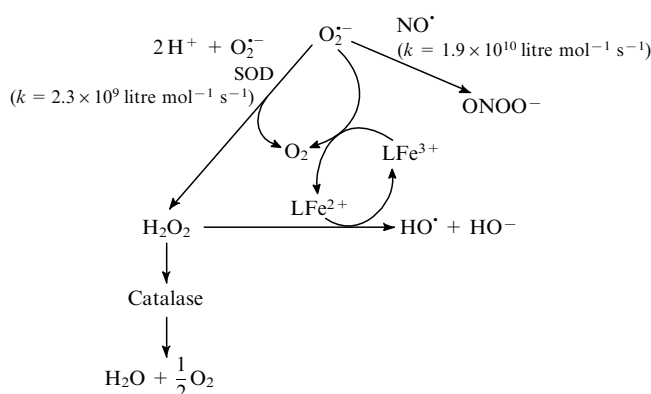
It was established^{204, 212} that the first stage of catalytic nitration of tyrosine and other phenols involves the oxidation of MP(3+) by peroxynitrite to MP(4+). The oxidised porphyrin rapidly reacts with phenols, thus regenerating MP(3+) and

converting phenols into phenoxyl radicals that recombine with nitrogen dioxide formed in the first stage at a high rate ($k = 3 \times 10^9$ litre mol⁻¹ s⁻¹).¹⁹⁴ Introduction of ascorbic acid into the system inhibits formation of nitrophenols, Mn(IV)=O and Fe(IV)=O are reduced to stable (3+) form, NO₂[•] radical is reduced to NO₂⁻ and phenoxyl radical is reduced to the starting phenol.²⁰⁴



VI. Biochemical role of peroxynitrite

The possibility of *in vivo* production of peroxynitrite in fast recombination [$k = (4.3–19) \times 10^9$ litre mol⁻¹ s⁻¹]^{32–38} of nitrogen monoxide (product of enzymatic oxidation of L-arginine)^{213, 214} and superoxide anion O₂^{•-} (conventional product of aerobic cell metabolism²¹⁵) was first reported by Beckman *et al.*³ Activated macrophages are assumed to be responsible for production of peroxynitrite.^{216–218} If the intracellular concentration of SOD is 10 μmol litre⁻¹ and the rate constant for the reaction of SOD with superoxide is 2.3×10^9 litre mol⁻¹ s⁻¹ (see Ref. 219), the loss rate of O₂^{•-} is 2×10^4 s⁻¹ and the whole superoxide is transformed to oxygen and hydrogen peroxide.^{16, 39} If the intracellular concentration of nitrogen monoxide is 10⁻⁸ mol litre⁻¹, the loss rate of superoxide in the reaction with NO is two orders of magnitude lower (2×10^2 s⁻¹) than in the reaction with SOD. No peroxynitrite is formed under these conditions. The local concentration of NO near activated macrophages is much higher ($5 \times 10^{-6}–10^{-5}$ mol litre⁻¹) and peroxynitrite is produced at a rate of $(2–4) \times 10^4$ s⁻¹, which is twice as high as the rate of the reaction of O₂^{•-} with SOD.

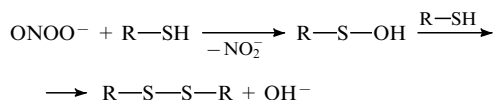


Since the extracellular concentration of SOD is probably lower than $5 \times 10^{-6}–10^{-5}$ mol litre⁻¹, it does not preclude formation of peroxynitrite near activated macrophages.^{16, 39} Nitration of SOD by peroxynitrite reduces its activity and, as a consequence, increases the yield of peroxynitrite, thus switching off the signal function of NO. Peroxynitrous acid and its anion can penetrate inside cells through lipid membranes moving along anion channels or by diffusion^{132, 220–222} and thus toxic effects of peroxynitrite can manifest themselves inside cells. Peroxynitrite is produced *in vivo* in the reaction of NO with superoxide; polluted air and cigarette smoke are also possible sources of this compound.²²³

Biological value of peroxynitrite is due to its high and polyfunctional reactivity with respect to various biomolecules.

The key mechanisms of biochemical action of peroxynitrite are as follows.

1. Interaction with sulfide and thiol groups^{24, 83, 117, 118, 224, 225}



mediates the activity of many enzymes and receptors.^{226–230} Toxic effects of peroxynitrite are often associated with its ability to oxidise the methionine residue in the active site of α -1-protease (elastase inhibitor), which causes inactivation of enzyme.²³¹

2. Protonation under physiological conditions and subsequent homolysis to hydroxyl radicals and NO_2 produces oxidative stress and apoptosis; this is related to neurotoxicity and molecular mechanisms of attack on immunocompetent cells.^{218, 226, 232–235}

3. Oxidation of the alkyl and alkene C–H bonds in polyunsaturated fatty acids causes oxidative damage of lipid membranes.^{132, 220, 221, 236, 237}

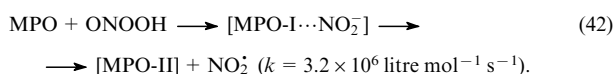
4. Metal-ion (Cu^{2+} , Zn^{2+} , Fe^{3+} , Mn^{3+}) catalysed nitration of phenols and aromatic amino acids. Many DNAs^{56, 177, 238, 239} and enzymes are nitrated and oxidised, e.g., SOD^{15, 218, 234, 240–242} (its activity reduces; the concentrations of superoxide and peroxynitrite increase, thus producing oxidative stress); actin and neurofilaments^{226, 243} (cytoskeleton and myofibrillae are damaged); cytochrome *c*, cytochrome P450 and mitochondrial ATPase^{137, 212, 243–246} (inhibition of oxidative phosphorylation).

Peroxyntirite in organisms is a carrier of the bound form of nitrogen monoxide, a key transmitter in central and peripheral nervous system, and can induce damage to neurons in the case of strokes and neurodegenerative disease.^{15, 216, 247, 248} The effect of peroxynitrite, a possible terminal neurotoxic agent, is responsible for neurotoxic action of NO .²⁴⁹ For instance, amyotrophic lateral sclerosis can be due to nitration and oxidation of proteins, which damage the nuclei of motor neurons in spinal cord.^{5, 250}

Oxidation of low density lipoproteins (LDLPs) in arterial walls is thought to be the key step leading to atherosclerosis. Peroxynitrite initiates the oxidation of lipids^{132, 220, 237, 251} and oxidises LDLPs^{6, 251–258} to a potentially active atherogenic form, which results in accumulation of cholesterol esters in cells. Besides, peroxynitrite rapidly oxidises α -tocopherol, which precludes the oxidation of LDLPs.²⁵³ Nitration of tyrosine at *ortho*-position is the major route of peroxynitrite attack on protein molecules, which manifests itself in increased content of *o*-nitrotyrosine in patients with atherosclerosis.^{6, 251, 257, 258}

Diffusion of peroxynitrite across cell membranes inhibits mitochondrial electron transfer²⁵⁹ and damages cation channels.²⁶⁰ High cytotoxicity of peroxynitrite to *Trypanosoma cruzi*²⁶¹ and bactericidal activity against *Escherichia coli*²⁶² are due to deactivation of thiol-containing enzymes and inhibition of cell respiration.²²⁹

Since peroxynitrite is produced *in vivo* and can damage cells, an enzyme system for deactivating or utilising it should exist. It was shown that myeloperoxidase (MPO), horse raddish peroxidase and lactoperoxidase rapidly react with peroxynitrite. For instance, the reaction with MPO results in compound MPO-II.¹³⁹



The character of the dependence of the rate for reaction (42) on the pH value indicates that the enzyme reacts only with peroxynitrous acid. Thus, MPO can reduce the concentration of peroxynitrite by converting it into important bactericidal agent NO_2^- and protect SOD from the action of peroxynitrite, thus increasing the lifetime of NO generated in neutrophils.

Another possible way of peroxynitrite utilisation is the reaction with hydroascorbate anion. The concentration of HAsc^- is $\sim 10^{-3} \text{ mol litre}^{-1}$ in lungs and neutrophils and $10^{-2} \text{ mol litre}^{-1}$ in neurons, ranges from 3×10^{-5} to

$1.5 \times 10^{-4} \text{ mol litre}^{-1}$ in plasma and is $7 \times 10^{-3} \text{ mol litre}^{-1}$ in leucocytes and $1.3 \times 10^{-3} \text{ mol litre}^{-1}$ in liver.^{263–266} Therefore, with allowance for the rate constant for reaction (38), ascorbate can be treated as efficient intracellular scavenger of peroxynitrite.

Increasing interest in chemistry of ONOOH and nitrogen oxides is due to very important role played by these compounds in physiological processes (respiration, regulation of blood pressure and sexual function, growth of malignant cells, etc.). Both positive role (bactericidal and antimicrobial effects) and negative role of peroxynitrite are considered.^{4–11, 226, 247, 251, 258, 262, 267}

VII. Conclusion

The chemistry of peroxynitrite emerged more than 100 years ago. However, systematic, comprehensive investigations of the kinetics and mechanisms of reactions involving this compound began only in the last decade. Complexity of the studies of peroxynitrite reactions is due to its instability at physiological pH values, diversity of transformation pathways and to the influence of impurities (nitrite, hydrogen peroxide, metal complexes, CO_2) on the rates and mechanisms of reactions. Recently, application of methods for studying fast reactions and the kinetic distribution method made it possible to achieve some advances in studies of the kinetics and mechanisms of peroxynitrite decomposition and isomerisation, its reactions with hydrocarbons and DMSO, catalytic action of CO_2 and metal complexes. Considerable literature is devoted to biochemical aspects of the action of peroxynitrite.

At the same time a number of key problems concerning the mechanisms of influence of peroxynitrite are still to be solved. Pathways of isomerisation and decomposition of the compound belong to the most debatable issue. Recently, the homolytic mechanism of isomerisation involving intermediate formation of $\cdot\text{OH}$ and NO_2 radicals, which was accepted in earlier studies, has cast some doubt.^{38, 104} Experimental and theoretical arguments *pro et contra* the homolytic mechanism in different types of reactions are available. Undoubtedly, this is due to polyfunctional reactivity of peroxynitrite, which underlies high chemical and biochemical activity of the compound.

An interesting classification of the mechanisms of peroxynitrite reactions with a broad spectrum of organic substrates was reported¹⁴⁷ by researchers from Japan. It includes five reaction classes. These are (1) electron transfer with involvement of the reactive species NO^+ , NO_2 and $\cdot\text{OH}$ (nitration, hydroxylation and dimerisation of phenols, oxidation of phenols to quinones, dealkylation of *N,N*-dialkyl-*p*-toluidine); (2) *O*-electrophilic substitution involving ONOOH (formation of *N*-oxides in the oxidation of amines, oxidative cleavage of $\text{C}=\text{C}$ double bond and oxidation of alcohols to ketones); (3) *N*-electrophilic substitution (formation of triazoles from aromatic 1,2-diamines and *S*-nitrosation); the reactive species are ONOOH and NO^+ ; (4) *O*-nucleophilic substitution involving ONOO^- and HOQ^- (epoxidation of quinones and oxidation of aldehydes); and (5) radical mechanisms involving NO_2 and $\cdot\text{OH}$ (oxidation of lipids and alcohols, hydroxylation of activated aromatic compounds).

Analysis of the results presented in the present review and obtained in our kinetic studies of the reactions of peroxynitrite with hydrocarbons and DMSO (see Sections V.2 and V.3) suggest the following.

1. High oxidation potential and high electrophilic and nucleophilic activity allows peroxynitrite to react with a broad spectrum of substrates.

2. The variety of pathways and mechanisms of peroxynitrite reactions and the nature of the active centers in the peroxynitrite molecule are determined by not only the reaction conditions (pH, presence of transition metal impurities, CO_2 , hydrogen peroxide, nitrite) but also the properties of substrates:

- (a) with highly reactive substrates, whose reactions with peroxynitrite proceed faster than the latter decomposes, either peroxynitrous acid or its anion can act as reactive species;

(b) reactions with substrates of low reactivity proceed by radical mechanisms involving $\cdot\text{OH}$ -like reactive species (hydroxyl radical, radical pair or the excited form of peroxynitrous acid), which was proved taking the oxidation of inert alkane molecules under mild conditions as examples.

It is the reactivity of substrates that can reconcile the research group headed by Koppenol^{16, 38, 61, 108} (they assume a bimolecular interaction of peroxynitrite with many substrates) with the groups headed by Goldstein^{40, 62, 65} and Hurst^{64, 88} who prefers the mechanisms involving $\cdot\text{OH}$ -like reactive species.

3. Volatile substances, e.g., low-molecular-mass hydrocarbons, can react with peroxynitrous acid (but not its anion!) not only in solution, but also in the gas phase.

4. The ability of ONOOH to distribute between different phases (aqueous, gas phase and lipophilic phase) and generate OH radicals in each phase is of great importance for understanding the mechanisms of peroxynitrous acid initiated oxidation of lipid fragments in cells and diffusion of peroxynitrite across cell membranes.

High chemical and biological activity of peroxynitrite requires further systematic studies on the kinetics and mechanisms of reactions, including the reactions with biomolecules and their models under physiological conditions.

The authors express their gratitude to Dr. Yu V Geletij (Emory University, Atlanta, USA) for help in providing access to recent literature on the subject and for numerous discussions on the material, Prof. I V Komissarov (Donetsk Medical University) and Dr. V P Tretyakov (L M Litvinenko Institute of Physical Organic and Coal Chemistry, Ukraine) for valuable comments.

This review has been written with the financial support of the INTAS (Grant Nos 93-1060 and 99-209).

While the manuscript was in preparation, a new review²⁶⁸ has appeared. This indicates incessant interest of researchers in the subject in question.

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^a — *Theor. Exp. Chem. (Engl. Transl.)*

^b — *Russ. J. Org. Chem. (Engl. Transl.)*

^c — *Kinet. Catal. (Engl. Transl.)*

Piezoelectric immunosensors: analytical potentials and outlooks

T N Ermolaeva, E N Kalmykova

Contents

I. Introduction	397
II. Some functional characteristics of gravimetric piezoelectric immunosensors in gaseous and liquid media	398
III. Types of immunoassay	399
IV. Methods for immobilisation of biomolecules	401
V. Conditions for regeneration of bioselecting coatings	404
VI. Applications of piezoelectric immunosensors	404
VII. Conclusion	407

Abstract. The state-of-the-art in the design of piezoelectric immunosensors is analysed. The analytical conditions, types of immunochemical reactions detected by piezogravimetric sensors and methods for immobilisation of bioreceptor molecules on the electrode surface of piezoelectric resonators are considered. Special attention is given to the use of immunosensors for the detection of microorganisms and low- and high-molecular-mass compounds in liquid media. The bibliography includes 172 references.

I. Introduction

In the past decade, the use of immunosensors has become one of the most attractive and promising trends in bioanalytical chemistry. A distinguishing feature of this type of analytical devices is their ability to determine compounds of interest in complex mixtures with a high degree of sensitivity and selectivity and without any sample pretreatment. Immunosensors, like any other bioprobes, are built up of two major closely interconnected operational units, *viz.*, a bioselective material (a receptor) and a detector (a physical transducer). The receptor comes into contact with the tested substance, while the detector transduces the signal generated in the course of the biochemical reaction into an analytical response which can further be transformed and presented in a digital form.

High selectivity and high sensitivity of immunoassays are attained through the use, as key reagents, of antibodies (Ab), *i.e.*, protective proteins formed in the organisms of higher animals in response to external stimuli (antigens, Ag).^{1,2} The neutralising effect of Ab is based on their ability for highly specific recognition of complementary antigens and formation of immune Ag–Ab complexes with their subsequent elimination from the organism.

Traditional immunological methods enable determination of even minute concentrations of antibodies or antigens (high-molecular-mass immunogens and low-molecular-mass haptens);

however, they require complex time-consuming procedures. In contrast, immunobiosensors detect antigen–antibody interactions within a course of tens of seconds. The processes accompanying the operation of immunosensors are very similar to those occurring in living organisms. The formation of immune complexes is concomitant with changes in the voltage, current, optical (*e.g.*, refractive index) and acoustic characteristics, *etc.*; therefore, biochemical interactions can be recorded with the help of a vast array of physical, *e.g.*, optical, electrochemical, acoustic (including piezoelectric), *etc.*, transducers.

The interaction of an analyte with a piezoelectric sensor is associated with changes in the frequency (f), amplitude and phase of the transducer oscillations.³ Piezoelectric sensors are highly sensitive to changes in both mass and some physicochemical properties (*e.g.*, viscosity, density, elasticity, conductivity, *etc.*) of the receptor layer and the fluid in contact with the sensor.^{4,5} Especially well-studied are immunosensors operating on a microbalance principle. In order to enhance the stability and accuracy of measurements and to reduce the acquisition time from sensors operating at high damping fluid loads, modern devices employ high-precision sensitive digital systems for measuring frequency signals and efficient noise filtration methods. However, this trend demands special consideration and is beyond the scope of the present review.

The role of analytical signals in gravimetric sensors is played by the decrease in the oscillation frequency of the sensor (Δf) caused by the increasing mass of the receptor layer in the course of selective immunochemical coupling.

Apart from very high (at the picogram level) sensitivity of gravimetric immunosensors, the latter enable direct on-line detection of biochemical reactions without the use of labelled (fluorescent, enzymatic, radioactive, luminescent, *etc.*, probes) materials employed in classical solid-phase immunoassays, *e.g.*, Enzyme-Linked Immunosorbent Assay (ELISA), and related processes. The presence of non-polar organic solvents, which usually diminish the sensitivity of procedures that employ labelled materials, is not critical for the direct interaction of antibodies with antigens sensed with piezoelectric detectors.⁶ Other advantages of gravimetric immunosensors include fast response, handling ease, portability and possibility to be incorporated into multisensor and information gathering and processing systems.

Piezoelectric detection compares favourably and even exceeds in sensitivity many popular optical, spectrophotometric, electrochemical, fluorescent, immunoenzymatic, *etc.*, procedures for monitoring immunochemical reactions and is only slightly inferior

T N Ermolaeva, E N Kalmykova Lipetsk State Technical University, ul. Moskovskaya 30, 398060 Lipetsk, Russian Federation.
Fax (7-4742) 31 04 73, tel. (7-4742) 32 81 55,
e-mail: ermolaeva@stu.lipetsk.ru (T N Ermolaeva),
kalmyken@stu.lipetsk.ru (E N Kalmykova)

Received 31 March 2005

Uspekhi Khimii 75 (5) 445–459 (2006); translated by R L Birnova

to reflexometry.^{7,8} In contrast to solid-phase immunoanalysis based on the use of non-recoverable reagents, immunosensors can easily be regenerated for repeated use. This capability makes their broader application in routine assays more expedient, primarily because the cost of a single assay is significantly reduced.

Some theoretical aspects of performance of piezoelectric biosensors and their specific applications for the detection of a vast array of analytes were reviewed.^{6,8–19} Two processes are taken into consideration in estimating analytical responses of biosensors, *viz.*, the increase in the coating weight due to formation of heterogeneous immune complexes and the transformation of this weight increase into electrical signals.

The development of various types of gravimetric sensors (*e.g.*, test systems, detectors for flow-injection analysis, *etc.*) based on highly specific interactions [antibodies–antigens, enzymes–substrates, receptors–ligands (hormones, cytokines), avidin–biotin, protein A–antibodies, DNA–DNA or RNA, transport proteins–various molecules and ions] will significantly expand the area of their application. Such sensors can find use in medicine, food industry, perfume production, pharmaceutical chemistry, agriculture (veterinary medicine, horticulture, plant growing), biotechnology, mining industry, military engineering and ecological monitoring of toxicants as well as soil and waste water pollutants of bacterial origin.

Unfortunately, in Russia the theoretical aspects of the design of mass-sensitive immunosensors are still very poorly investigated, whereas in other countries this trend of research is developing rapidly.

The present review is devoted to the description of different types of immunoassay based on the use of piezoelectric transducers with special reference to conditions for their implementation and methods for immobilisation of bioreceptor molecules. Special attention is given to the efficiency and outlooks in the application of gravimetric immunosensors for the detection of microorganisms as well as high- and low-molecular-mass biologically active substances in liquid media.

II. Some functional characteristics of gravimetric piezoelectric immunosensors in gaseous and liquid media

An acoustic microbalance is a piezoelectric quartz resonator, which operates on the bulk acoustic wave principle. It represents a thin disc from a natural or synthetic crystal of quartz with metal (gold, silver, aluminium, nickel, chromium) electrodes plated on both sides of the disk by thermal spraying.^{18–21} To minimise thermal effects, the disc is cut up along the shear plane of the crystal (the so-called AT-cut) manifesting the highest thermal stability in the temperature range 10–50 °C.¹²

Only the area between the electrodes appears to be piezoelectrically active; the mass sensitivity of a piezoelectric resonator decreases appreciably with an increase in the distance from the centre. Especially popular are crystals with a quartz plate diameter of 10–16 mm and gold (less often, silver) electrodes operating at intrinsic oscillation frequencies from 5 to 15 MHz. Some literature reports describe the use of resonators with improved frequency characteristics of the order of 30 (see Refs 22 and 23), 70 and even 110 MHz.^{24,25} Thin crystals resonating at high frequencies are more sensitive to mass fluctuations, but suffer from drawbacks of fragility and high noise levels.

The application of an external alternating electric potential to a piezoelectric material produces internal mechanical stress between the electrodes which leads to the deformation of the crystal. The resonance is achieved by including the crystal in an oscillation circuit where electric and mechanical oscillations are near to the fundamental frequency of the crystal. The intrinsic frequency of a resonator depends on many factors some of which are constant, *e.g.*, size and structure of the plate (thickness, density, roughness, type and shape of the cut, *etc.*), while some

are variable, *e.g.*, masses of metal electrodes and external factors (density or viscosity of gaseous and liquid media in which the measurements are performed, composition, ionic strength and pH of test solutions, *etc.*).^{4,5,10,11} The oscillation frequency of an AT-cut crystal decreases linearly with an increase in the mass of the materials deposited on the electrode surface in accordance with the Sauerbrey equation:²⁶

$$\Delta f = -\frac{2.3f_0^2 10^6 \Delta m}{A},$$

where Δf is the change in the oscillation frequency of the crystal (in Hz), f_0 is the intrinsic oscillation frequency of the crystal (in MHz), Δm is the mass of the receptor layer coated onto the electrode surface (in g) and A is the surface area of the electrode (in cm²).

However, this ratio is valid only for small mass increments. Overloading not only diminishes the sensitivity of assays, but also results in the stripping of signals; therefore, commercial piezoelectric microbalances are usually set to operate in the range from $\sim 1 \text{ ng cm}^{-2}$ to $\sim 100 \text{ } \mu\text{g cm}^{-2}$.

1. Specificity of immunosensors in gaseous media

The first attempt to use antigens as electrode coatings for piezoelectric microbalances dates back to 1972;²⁷ however, the interest of investigators in this field was awakened some time later. A report²⁸ on a highly sensitive (at the ppb level) detection of the pesticide parathion in air, which was based on the use of anti-parathion antibodies immobilised on a piezoelectric crystal, was published in 1986. Traces of moisture present in the thin-film coating of a sensor favoured the occurrence of immunochemical reactions in the gaseous phase. Piezoelectric sensors based on immobilised proteins (antibodies) were successfully employed for the detection of atmospheric pollutants including sulfur dioxide, carbon monoxide, hydrogen chloride, nitrogen dioxide, ammonia, organophosphorus pesticides, *etc.*^{28–32}

However, some literature reports refuted the occurrence of specific immunochemical reactions in antibody-based dry films used as biosensor coatings for detecting pesticide content in the air.³³ It is noteworthy that piezoelectric immunosensors are no longer employed for the analysis of gases due to the difficulty of analytical signal recording resulting from minute changes in the mass of the biosensor coatings during direct detection of low-molecular-mass compounds.

2. Some functional features of biosensor systems in liquid media

Early attempts to use piezoelectric biosensors for conducting measurements in liquid media were unsuccessful, since the crystals ceased to oscillate after being immersed into a solution. To overcome this problem, the mass gain was measured in the gaseous phase after incubation of the sensor with the test solution and subsequent drying. In this case, the frequency shifts were governed by the Sauerbrey equation. This procedure is commonly referred to as the dip-and-dry method.^{10,27,34,35} An alternative approach includes the construction^{36,37} of a different in principle excitation circuit for the analysis of fluids; this is based on the use of a flow detection cell where the test solution is exposed to only one side of the crystal.^{5,21,38,39}

The resonance frequency of a crystal immersed into a solution is strongly affected by the properties of the liquid phase; in this case, the Sauerbrey equation is not fulfilled. There exists no general equation which would take into account the contribution of all environmental factors to the overall response of a piezoelectric sensor in a liquid medium. Such a signal depends on the structure of the interface between the sensor coating and the surrounding solution. Such boundary effects are levelled off when only one side of the resonator is exposed to the solution and if crystal optically polished are used.

With consideration of the above limitations, piezoelectric immunosensors are used either as analytical test systems or as detectors for flow-injection analysis.

The pioneering studies that used piezoelectric immunosensors for a comparison of activities and specificities of antibodies in liquid media were carried out using the dip-and-dry method.²⁷ Since the 1980s, this trend was developing more intensively culminating in the elaboration of several methods for the detection of different subclasses of antibodies⁴⁰ and an indirect/competitive procedure for identification of antigens.⁴¹ In the 1990s, the range of detectable compounds increased considerably at the expense of biosensors for the detection of a vast array of microorganisms,^{42–52} blood cells,^{53–56} albumin,^{38,57} atrazine,^{17,58,59} human transferrin,⁶⁰ insulin,⁶¹ cocaine⁶² and immunoglobulin M (IgM).^{63,64} The major problems in conducting routine assays by this method are related to the conditions of exposure of biosensors to test solutions and their subsequent drying as well as the nature of the solvent adsorbed onto the sensor coating.

The range of substances detected by piezoelectric sensors in liquid media is rather broad and includes high- and low-molecular-mass compounds and cells. An original procedure was developed⁴² for the detection of microconcentrations of *Candida albicans* in the range from 10^6 to 5×10^8 cells ml^{-1} . High specificity of assay was confirmed by the absence of interactions of other yeast species or other antigen types with the sensor coating. Later, this approach was used for the detection of a vast array of pathogenic microorganisms (*Salmonella typhimurium*,⁴⁴ *Salmonella paratyphi*,⁴⁵ *Listeria monocytogenes*,^{46,47} *Vibrio cholera*⁴⁸), viruses (diarrhea,⁴⁹ herpes^{50,51}) and blood cells (human granulocytes,⁵³ T-lymphocytes,⁵⁴ erythrocytes^{55,56}).

Despite the relatively low reproducibility of experimental results due to hydration and the differences in the degree of the solvent adsorption on the receptor surface, the dip-and-dry method did not lose its significance to this day. Some recent publications describe different applications of this technique for the detection of microorganisms,^{52,65,66} proteins^{67–69} and toxicants.^{70,71} Its main advantage is in the possibility to use immunosensors as convenient quick-operating test systems for extralaboratory diagnostics and screening of environmental objects. The reliability of determination increases, while the limit of detection decreases with an increase in the time of exposure of the biosensor to the test sample, proper washing and drying of the biolayer to the constant weight.

A two-component sensor system one component in which is a detector and the other one is a reference sensor was developed in order to minimise the non-specific interactions between the sample components and the receptor layer of the sensor.⁶⁹ In this system, immobilisation of bioreceptor molecules on the sensor surface is preceded by the blockage of the sensitive area of the reference sensor.

The use of piezoelectric immunosensors in flow-injection analyses seems to hold more promise. In this case, the time required for a single assay is reduced to several minutes and the signal is followed in real time.⁷² This enables much higher reproducibility of the experimental data (measurement of relative changes in the frequency shift) and reduces the effects of non-specific interactions, since compounds adsorbed on the biosensor surface are easily removed by washing with the carrier solution. This, in its turn, allows re-usability of biosensors after regeneration of the biosensitive layer at the end of each measurement cycle.

The measurements are performed in a low-volume flow cell through which the test solution is pumped at a predefined speed. The cell volume varies from 35 to 100 μl .^{5,39,73}

More recent developments include a vast array of flow-type immunosensors for the detection of high- (bacteria, viruses, phages; antibodies, protein antigens, nucleic acids) and low-molecular-mass analytes (drugs, metabolites, ecotoxins).

III. Types of immunoassay

Immunoanalytical techniques based on piezoelectric immunosensors are classified according to the following criteria:

- nature of the receptor layer (antibodies, antigens, hapten–protein conjugates);
- type of biochemical reactions that induce the analytical signal (direct, competitive or displacement detection; mass amplified assays based on analyte modification);
- mechanism of generation of the analytical signal (increase or decrease in the mass of the bioreceptor layer);
- measurement technology (one- or two-step detection; dip-and-dry method, flow-injection analysis).

The classifications based on the type of the biochemical reaction and mechanism of generation of the analytical signal are especially popular. Among those, immunological methods based on the use of piezoelectric quartz transducers for conducting direct, indirect/competitive and displacement assays are among the most extensively studied techniques.^{13,16} Sandwich assay and approaches aimed at increasing the masses of adsorbed molecules and, hence, the analytical signal of the sensor, were developed for augmenting the sensitivity of immunoassays.

1. Direct detection

This one-step procedure is the simplest among other methods and is based on the interaction of the receptor layer of the biosensor with the analyte. The decrease in the resonance frequency due to formation of an immune complex on the electrode surface is directly proportional to the concentration of the analyte (Fig. 1). This kind of analysis is performed both in dip-and-dry and flow formats. Sensor electrodes are modified by antigens, monoclonal antibodies or polyclonal antibody-containing sera.

To increase the selectivity of assays, the sensor is pretreated with a solution of a non-ionic detergent or an inactivated protein which does not cross-react with test sample components [bovine serum albumin (BSA), gelatin, *etc.*], but is bound to the non-specific sites localised on the receptor surface of the biosensor. For example, the receptor layer of a DNA-based biosensor only weakly reacts with BSA molecules to produce a feeble frequency signal. In contrast, the analytical signals generated by anti-DNA antibody-containing sera from patients with autoimmune disease amounted to hundreds of Hertz.⁷⁴

Direct detection is the most efficient approach to identification of high-molecular-mass objects (somatic cells, microorganisms, protein macromolecules, antibodies, nucleic acids, glycoproteins, glycolipids and other antigens), since their sorption is accompanied by a significant increase in the mass of the receptor layer.

It is believed that direct binding of small molecules cannot be detected by piezoelectric immunosensors. For example, the sorption of a substance (4.4 ng cm^{-2}) onto a crystal with the intrinsic oscillation frequency of 10 MHz and the sensitivity of $0.227 \text{ Hz ng}^{-1} \text{ cm}^{-2}$ was accompanied by frequency changes that amounted to 1 Hz.¹³ The antibody monolayer (capacity of 500 ng cm^{-2}) contained 7×10^{-12} moles of binding sites. The

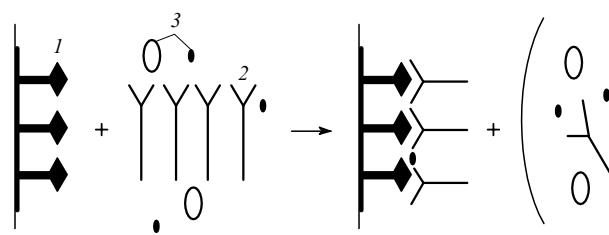


Figure 1. A schematic representation of a direct antibody assay.

(1) Antigen (hapten), (2) antibody, (3) non-specific components of the mixture.

maximum binding of a low-molecular-mass (~ 1000 Da) antigen corresponds to 2.7×10^{-12} mol cm $^{-2}$ and can induce only minor changes in the resonance frequency of the biosensor equal to several Hertz, which corresponds to the noise level. Nevertheless, the use of direct detection for identification of low-molecular-mass compounds, such as the herbicide atrazine⁷¹ and 2,4-dichlorophenoxyacetic acid^{13,75} having the detection limits from 0.24 to 0.27 $\mu\text{g litre}^{-1}$, has been described. The discrepancies between the magnitudes of experimentally determined and calculated frequency shifts can be attributed to changes in the viscoelastic properties of boundary layers of the fluid as a result of complexation with low-molecular-mass analytes.

Indirect/competitive, sandwich and other assay types are routinely used for the detection of low-molecular-mass molecules.

2. Competitive analysis

The first single-step indirect/competitive analysis of haptens based on piezoelectric sensors was carried out⁴¹ in 1980 and had a number of specific features. Whereas in routine immunochemical assays the competition for binding sites usually takes place between free and radiolabelled analytes, in the case of piezoelectric immunosensors the role of competing reagents is played by the free (non-bound) analyte, which is present in the solution, and the hapten–protein conjugate immobilised onto the bioreceptor layer (Fig. 2). The magnitude of the analytical signal of the sensor is inversely proportional to the hapten concentration in the test sample.

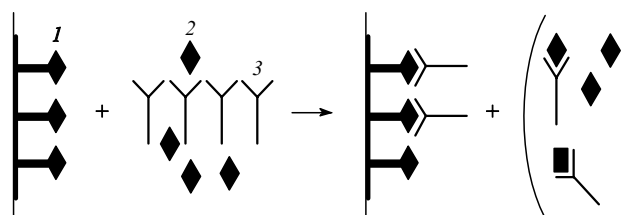


Figure 2. A schematic representation of an indirect/competitive assay. (1, 2) Immobilised and free haptens, respectively; (3) antibody.

This approach is especially convenient for the detection of low-molecular-mass haptens, *e.g.*, vitamins, drugs, hormones, metabolites, herbicides, *etc.* Competitive assays exceed direct detection in sensitivity,^{18,58} however the range of measured concentrations is narrower by one or two orders of magnitude.

Not only hapten–protein conjugates, but also antibodies can be used for the formation of receptor layers in competitive assays. In the latter case, a fixed amount of the hapten–protein conjugate is added to each test sample; such modification has got the name ‘alternative competitive analysis’ (Fig. 3). The conjugated and free haptens are equiprobably bound to the active sites of the immobilised antibodies; therefore, the lower the concentration of the free analyte in the sample, the greater the amount of the conjugated hapten bound to the receptor layer of the sensor. In this way, sorption of a conjugated analyte contributes to a significant enhancement of the frequency response.

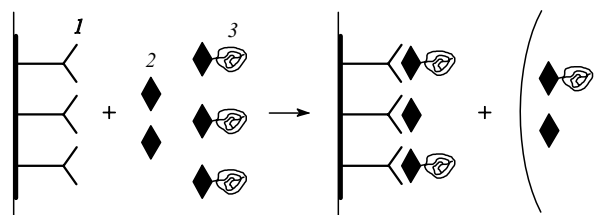


Figure 3. A schematic representation of an alternative competitive assay. (1) Antibody, (2) hapten, (3) hapten–protein conjugate.

This type of immunoanalysis was successfully employed¹⁷ for the quantitation of triazine derivatives. The magnitude of the frequency shift induced by the binding of the triazine–protein conjugate to the receptor layer was inversely proportional to the triazine concentration in the range from 0.01 to 1 $\mu\text{g litre}^{-1}$. Despite its obviously lower sensitivity, the alternative method offers a broader concentration range in comparison with the competitive approach.

3. Two-stage sandwich assay

This assay is based on the use of secondary or species-specific antibodies which interact with the antibodies of the immune complex as with antigens specifically raised against them.^{40,76} Thus secondary antibodies enhance the analytical signal by forming sandwich complexes with test antibodies (Fig. 4), which significantly increases the selectivity and sensitivity of the assay. The sandwich technology was successfully employed⁷⁷ for determination of cholera toxin concentration in solutions (1×10^{-4} nmol litre $^{-1}$).

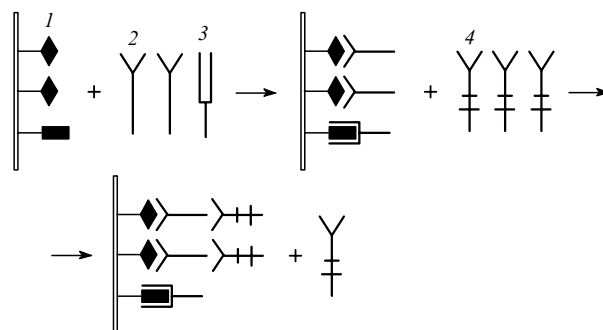


Figure 4. A schematic representation of a sandwich assay. (1) Antigen, (2) specific antibody, (3) non-specific antibody, (4) secondary antibody.

Sandwich assays are performed in two steps. In the first step, the antibodies (both specific and non-specific) are bound to an immobilised antigen. This is followed by an addition of secondary antibodies which react only with their specific antibodies to form sandwich-like complexes. The detection of allergen-specific immunoglobulin (IgE) in blood sera of patients with allergic dermatitis is a classical example of clinical application of this technique.⁶⁸ The allergenic protein (Der p) isolated from dermatophagoids was immobilised on the electrode surface of a biosensor. The interaction of the sensor with an antigenic blood serum from an allergic patient resulted in the binding of different antibody classes to the receptor layer; this was followed by differentiation of adsorbed antibodies upon exposure of the sensor to secondary anti-human IgE. The ability of secondary antibodies for specific recognition enables the differentiation between bound allergen-specific antibodies and representatives of other classes of blood serum immunoglobulins (*e.g.*, IgG, IgM).

A method⁷⁸ for determination of human serum albumin (HSA) based on the complexation of HSA with two types of antibodies is yet another illustrative example of a successful application of sandwich analysis. Noteworthy, the analytical signal generated by the sensor exceeded that obtained by the direct detection method threefold.

If direct detection of antigens is performed by the competitive method, the sandwich assay is complete in one step. This approach was used to determine the testosterone content ($13.6 \mu\text{g ml}^{-1}$) in a biological fluid.^{13,76}

4. Mass amplified assay

In addition to sandwich assays, the sensitivity of low-molecular-mass assays can be enhanced through the use of other approaches.

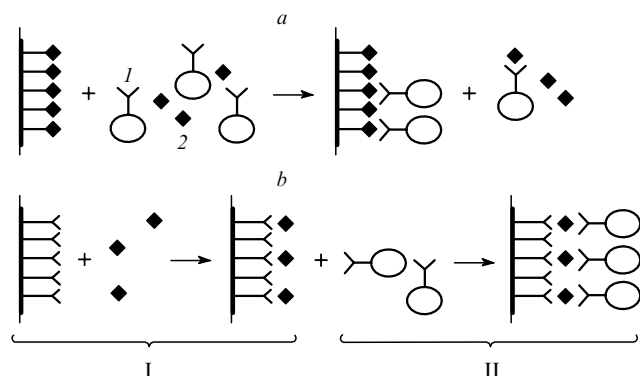


Figure 5. A schematic representation of a modified antibody assay. (a) Competitive assay, (b) sandwich assay, (1) modified antibody, (2) analyte.

One of them includes modification of sorbates by colloidal,^{79,80} latex, *etc.*, particles.^{81–83} Such methods are singled out into an independent group termed as ‘mass amplified assay’ and are based on the increment in the analyte mass.¹³ A schematic representation of such analyses is shown in Fig. 5.^{82,83} Modification of antibodies by colloidal particles caused significant increases in the sizes and masses of the adsorbed molecules. The assays were performed in the competitive (Fig. 5a) and sandwich (Fig. 5b) formats.

In the former case, the antibody molecules modified by solid colloidal particles could bind either to free analyte molecules (in solution) or to analyte molecules immobilised on the surface of the sensor electrode. Thus, the binding of the antibodies to the receptor layer was inhibited by high concentration of the analyte. The magnitude of the analytical response was inversely proportional to the concentration of the test antigen.

In the latter case, the reaction was complete in two steps (I and II); the protein molecules modified by colloidal particles interacted, similarly to secondary antibodies, with the analyte molecules bound to the receptor layer. In both cases, the frequency signal of the sensor was strongly enhanced by the colloidal particles deposited on the sensor surface. Gold, lead, cadmium and zinc sulfide sols as well as chromium, titanium and iron oxide sols are generally used as colloidal particles.

Latex agglutination is a convenient procedure for enhancing analytical signals. This approach was used³⁸ for the detection of *Escherichia coliform* species in solution within the concentration range 10^6 – 10^8 cells ml^{-1} . Latex particles able to modify *E. coli* specific antibodies were added to the reaction mixture.⁸⁴ After conjugation of the cells with antibodies immobilised on the sensor electrode, the anti-*E. coli* antibodies immobilised onto latex particles formed sandwich complexes with the cells bound to the antibodies on the electrode surface.

5. Displacement analysis

This format is especially suitable for determination of stabilities of affinity complexes (Ab–Ag, DNA–protein, DNA–RNA, *etc.*) in kinetic dissociation studies and for measurement of analyte concentrations. Whereas competitive analysis is a method of choice in determining minor concentrations of small molecules, macromolecules are more conveniently detected by displacement analysis. The method is based on the measurement of decrement in the mass of heterogeneous complex in the course of its dissociation induced by excess concentration of one of the reaction components. The analysis is performed in two steps (Fig. 6).

Determination⁴⁷ of *Listeria monocytogenes* in milk (2.5×10^5 – 2.5×10^7 cells ml^{-1}) is an example of this type of an immunoassay. The antibodies present in the sample were conjugated to a protein antigen isolated from *Listeria* sp., which was

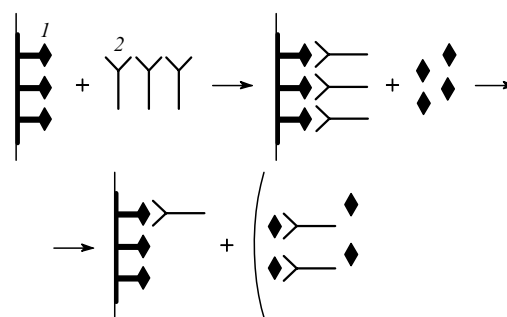


Figure 6. A schematic representation of a displacement immunoassay. (1) Antigen, (2) specific antibody.

previously immobilised on the sensor electrode. This caused a decrease in the oscillation frequency of the sensor. Then, a displacement of the antibodies from the heteroimmune complex by *Listeria* cells added to the sample occurs. The amount of the displaced antibodies was directly proportional to the concentration of *Listeria* cells in the sample. A similar approach was used to determine the content of *Pseudomonas aeruginosa* in milk and drinking water.⁸⁵

IV. Methods for immobilisation of biomolecules

The sensitivity, selectivity and reproducibility of the assays of high- and low-molecular-mass compounds based on piezoelectric immunosensors strongly depend on the method used for the immobilisation of receptor molecules on the electrode surface.

The main requirements to the quality of bioreceptor layers are as follows:⁸⁶

- firm fixation of receptor molecules on the electrode surface;
- retention of high activity of immobilised biomolecules;
- uniform distribution of active binding sites on the electrode surface;
- physical and chemical stability (including regeneration stability) of the electrode layer in contact with the fluid during the measurement cycle;
- minimum mass of the receptor layer (the smaller the mass of the coating, the greater the mass increment of the analyte that can be established with the help of a microbalance).

The nature of the metal electrode should also be taken into consideration in deciding upon the immobilisation technique. Owing to their high chemical stability, piezoelectric resonators with gold electrodes are the most frequently used type; therefore, virtually all immobilisation techniques have been designed to operate with gold electrodes. However, in the past decade crystals with silver electrodes were gaining increasing attention by virtue of their low cost and higher sorptive capacity.^{87,88} It was found⁶⁸ that immunosensors with silver electrodes modified by lipoic acid with *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride as a coupling reagent manifested 1.5 times higher sensitivity than sensors with gold electrodes. However, silver electrodes suffer from the disadvantage of being highly reactive and demands additional protection. This can be achieved, for example, through the use of polyethyleneimine supports able to form uniform layers and affording complete coverage of the electrode surface.

All currently known methods used for immobilisation of protein molecules may conventionally be divided into three groups:^{13,16} physical sorption, incorporation into matrices and chemical sorption.

Each of these techniques has advantages and drawbacks of their own. Very often, different methods are used in combination, but the choice of a procedure best suited for meeting a specific goal is always arbitrary. The degree of immobilisation of biomolecules

and the stability of the receptor layer should always be checked experimentally.

1. Physical sorption

Physical sorption is the simplest and fastest method for immobilisation of protein molecules on the surface of crystal electrodes under mild conditions. This is ensured by non-specific interactions or hydrogen bonds,⁸⁹ which enable the preservation of high functional activity of protein molecules^{70, 73, 90} and the formation of low-density layers.⁹¹ The number of active antibody sites is usually kept constant, although in some cases^{92–94} their functional activities can decrease as a result of conformational changes in the protein molecules. The amount of the adsorbed protein and, as a consequence, the sensitivity of the sensor are determined by the nature of the metal and the hydrophobicity of the protein, which, in its turn, depends on pH, ionic strength, temperature⁹⁵ and time of exposure of the sensor in the solution with antibodies. It was found⁹⁶ that after 4-day incubation the receptor layer could withstand up to 20 measuring cycles without any decrease in the analytical response.

Physical sorption is often used, *e.g.*, for the preparation of receptor coatings based on goat anti-ricin antibodies,⁷³ *Vibrio cholera*⁴⁸ and herpes virus antibodies,^{49, 50} recombinant fragments of specific antibodies against human immunodeficiency virus (HIV),^{97, 98} *etc.* The quantity of immobilised antibodies and cells can be estimated with a sufficient degree of accuracy from the difference between the frequency shifts in modified and pure piezoelectric quartz crystals.

The main disadvantages of such immobilisation include low sorptive capacity and low stability of coated surfaces, which diminishes the reproducibility of immunoassays and reduces the service lives of immunosensors. As the method in question does not provide well-developed surfaces required for covalent immobilisation, the sensitivities of biolayers are rather low.⁹¹

The use of physical sorption is not confined to the direct formation of bioreceptor coatings of sensor electrodes; it also favours the formation of intermediate protein layers which provide strong binding to both the metal surface of the electrode and the immunoreagent molecules. Protein A,^{61, 86, 87, 90, 98–100} which forms stable complexes with gold in neutral media (its binding constant is equal to 10^8 litre mol⁻¹) (see Ref. 101), is often used for the formation of intermediate layers. At the same time, protein A, which represents a polypeptide constituent of *Staphylococcus aureus*, can actively and specifically bind to immunoglobulins (to IgG, in particular) without affecting the active sites of antibodies which retain their high activities in the immobilised state.^{90, 102} Such immobilisation ensures not only high sensitivity and high binding capacity of the bioreceptor layer, but also its high elasticity, which is especially important for stable performance of piezoelectric immunosensors.¹⁰³ Immunosensors designed for the detection of insulin¹⁰⁴ and some viral and bacterial species¹⁰⁵ the bioreceptor coating in which was formed by protein A molecules demonstrated high sensitivity and stable performance even after a period of several months.

Further improvements of this technique included structural modification of proteins aimed at increasing the strength of binding of protein molecules to the gold surface. To achieve this, amino acid residues (*e.g.*, cysteine) containing SH groups were incorporated into the structure of the recombinant protein A (B5C1) by genetic engineering methods.¹⁰² The resulting intermediate layer based on the synthetic protein manifested higher binding capacity in comparison with the native protein A, which made it possible to increase the service life of the immunosensor without any loss in activity.

2. Incorporation into matrices

Incorporation of proteins into gels^{106–108} or polymeric matrices,^{51, 53, 54, 109, 110} which enables immobilisation at the expense of physical interactions, is rather a popular approach.

To obtain a polymeric matrix, a drop of a polymer solution in an organic solvent is placed onto the surface of a cleaned electrode and let dry until complete evaporation of the solvent. Immobilisation of antibodies is achieved by immersion of the sensor into an antibody-containing solution; then, antibodies are included into the polymeric layer. Such immobilisation was used³⁵ to determine the content of HSA. In earlier studies, biosensors based on polymeric matrices were actively employed for determination of blood cells, *e.g.*, human T-lymphocytes,⁵⁴ erythrocytes^{55, 56} and granulocytes;⁵³ however, the analytical signals generated by them were unstable in repeated measurements. The strength of binding of biomolecules can be increased through additional use of glutaraldehyde. To obtain a receptor layer, a solution of polyethyleneamine (PEA)^{70, 111} or polyethyleneimine (PEI)⁷⁰ in methanol is added dropwise to the surface of a crystal electrode and, after removal of the solvent, is incubated sequentially with glutaraldehyde and appropriate biomolecules, *e.g.*, antibodies or hapten–protein conjugates. In this case, the selective layer of the sensor retains its activity up to a period of 38 days.

Polymeric matrices prepared by electropolymerisation⁴⁵ or by the glow discharge method²¹ (which excludes the use of toxic solvents) are more efficient, but are still seldom used. Protein molecules in such polymeric films are linked by covalent bonds.^{21, 45, 112, 113}

Natural biopolymers (*e.g.*, proteins, polysaccharides) are also used for immobilisation of receptor molecules. A method for the formation, on the electrode surface, of hydrogels based on proteins (BSA) and antibodies has been described.⁷⁰ The biosensitive layer thus prepared was distinguished for high sensitivity and stability.

In recent years, polymeric films were especially often used as electrode modifiers (base layer) increasing the adhesion of biomolecules, since hydrophobisation and functionalisation of receptor surfaces enhance the stability of the bioreceptor layer.

3. Chemical sorption

This method is used for the preparation of dense and strong saturated layers that manifest high stabilities in liquid media.¹¹⁴ It is especially suitable for flow or flow-injection analyses. Covalent coupling provides firm fixation of biolayers on the electrode surface, which minimises the losses upon long-term exposure to fluid media, provides higher reproducibility of analytical signals and improves re-usability of immobilised solid phases after regeneration. Besides, chemical sorption allows preservation of functional activities of proteins over long periods of time (up to two years). However, in some cases the number of active sites in covalently coupled antibodies decreases under toxic effects of chemical reagents.¹¹⁵ Chemisorption usually employs gold (less often, silver) electrodes, and never aluminium or chromium electrodes.

Cross-linking, which is singled out into a separate group by some authors,^{108, 109, 116} represents a modified version of chemical sorption. It makes use of a vast array of mono- and heterobifunctional cross-linking reagents, such as hydrazide- and succinimide-containing derivatives. Glutaraldehyde, which reacts smoothly with amino groups to form additional methylene bridges in the protein molecule, is used more often than other reagents.^{68–71, 77, 111, 117–120}

Cross-linking is performed using different procedures. After short-term incubation of antibodies with a cross-linking reagent at room temperature, a drop of the reaction solution is added to the surface of a crystal electrode and air-dried.¹¹⁸ In the alternative approach, a drop of an antibody solution placed onto the electrode is exposed in a closed cell saturated with glutaraldehyde vapour at low temperature.⁷⁰ The fundamental difference between these two techniques is in different effects of the cross-linking reagent in homogeneous and heterogeneous media. Whereas after mixing of experimental solutions methylene bridges are formed throughout the whole bulk of the fluid, glutaraldehyde reacts exclusively with protein molecules on the surface of the liquid

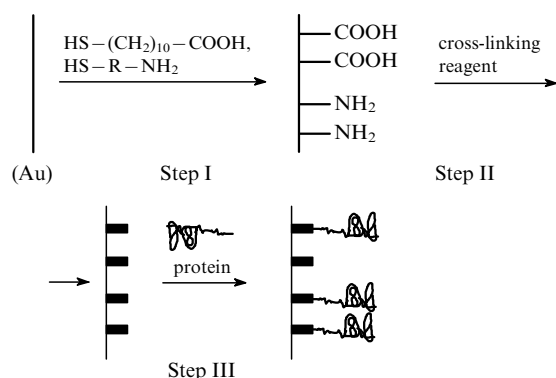


Figure 7. A scheme of immobilisation of biomolecules by chemical sorption.

Immobilisation steps: I, activation of the metal surface; II, modification of functional groups; III, immobilisation of the protein molecule.

phase. This enables preservation of the native conformation of the active sites of the antibodies inside the layer and increases the sensitivity of the receptor coating of the sensor.

Virtually all chemical immobilisation procedures are complete in three steps (Fig. 7).

The surface of sensor electrodes is activated by application of a thin film (base layer) which is firmly fixed on the metal surface and contains reactive functional groups essential for subsequent immobilisation of protein molecules. In addition, the film coating protects the surface of metal electrodes from oxidation and premature destruction by corrosive media.

The formation of base layers from self-assembled monolayers (SAM) is of particular interest. Its advantages include homogeneity of base layers, their uniform distribution and spatial accessibility of their active sites and functional groups for the binding to receptor molecules as well as high mechanical strength and chemical stability.^{119, 120} An ideal monolayer consists of densely packed filaments firmly bound to smooth (*e.g.*, metal) surfaces.^{121, 122}

Treatment with siloxane derivatives, *e.g.*, (γ -aminopropyl)-triethoxysilane (APTS) and (γ -glycidoxypentyl)trimethoxysilane (GOPS) containing reactive amino and hydroxy groups, respectively, is widely used^{36, 71, 123–127} for the formation of SAM-based base layers. The surfaces thus modified bind biomolecules either directly (as in the case of GOPS) or after treatment with glutaraldehyde. The coupling of antibodies to siloxane films *via* amino and hydrocarbon groups of bifunctional cross-linking reagents¹¹⁶ favours the formation of dense ($74\text{--}220\text{ ng cm}^{-2}$) surface layers. High (from 78% to 92%) binding capacity of the latter in reactions with antigens is responsible for the wide applicability of this immobilisation technique.

The use of sulfur-containing compounds (*e.g.*, thiols and disulfides) that are adsorbed irreversibly on gold surfaces by coordination bonds between sulfur and gold atoms is yet another popular approach to the preparation of SAM. Alkanethiol-based films are among the most extensively studied types of SAM. As the orientation and stabilisation of monolayers is provided by van der Waals interactions between the methylene groups, the use of alkanethiol chains containing more than ten methylene groups permits one to obtain highly ordered monolayers of the crystal type.¹²¹

A similar approach was used to prepare SAM based on poly-L-lysine,¹²⁸ hydrophobic lipids,^{129, 130} cysteamine,¹³¹ cysteine⁷² and *p*-aminophenol,⁴⁵ which provide amino groups for modified layers; thiopropionic and lipoic acids,^{68, 72, 121} mercaptoundecanol¹³² containing reactive carboxy and hydroxy groups and dithiobis(succinimidylpropionate)^{72, 132} the NHS groups in which are directly involved in the binding of biomolecules.

High elasticity, which imparts conformational mobility to receptor molecules during their interactions with test objects and ensures successful transmission of signals to piezoelectric transducers, is a crucial requirement to piezoelectric sensor coatings. Therefore, in the second chemisorption step the activated surface of the sensor electrode is modified with a cross-linking reagent, such as glutaraldehyde, cyanogen bromide, thiol acids, hydrazine, 1,4-diepoxybutane, *etc.*¹¹⁵ To prepare more elastic bilayers with enhanced ligand-binding properties, high-molecular-mass biopolymers, *e.g.*, proteins A and G,⁷⁰ BSA⁷⁰ or polysaccharides: dextran¹³² or periodate-oxidised dextran,⁷² are used as cross-linking reagents. The formation of a receptor layer where covalently linked dextran is used as a spacer is schematically represented in Fig. 8.

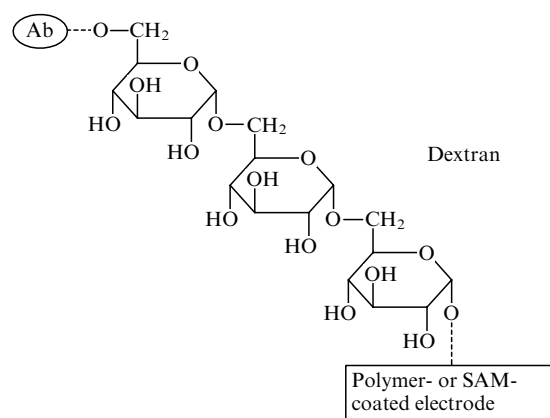


Figure 8. A scheme of formation of a receptor layer where dextran is used as an intermediate layer between the electrode coating and the protein molecule.

Carbohydrate chains covalently attached to the protective coating on the sensor confer conformational 'flexibility' on the biomolecules that are bound to them.^{109, 115} Dextran activated by periodate oxidation were used^{72, 133} to prepare three-dimensional dense base layers with enhanced ligand-binding properties. However, this method has a number of disadvantages: it is time- and labour-consuming and requires the use of toxic reagents.

Biomolecules (protein A, lectins, avidin–biotin complex) used for modification of electrode surfaces present additional interest as flexible spacers. Therefore, the assignment of immobilisation methods to different groups is always arbitrary and combinations of various methods are used more and more often for the preparation of bioreceptor layers. The formation of the avidin–biotin complex is described by an affinity constant equal to $10^{15}\text{ litre mol}^{-1}$, which points to its stronger ($\sim 10^3$ -fold) binding in comparison with immunochemical fixation. Moreover, biotin is endowed with the ability to bind easily and firmly to antibodies without any appreciable loss of activity. Therefore, bioreceptor layers based on the avidin–biotin complex, which retains stability over a broad range of pH upon long-term exposure to liquids, are widely employed in immunochemical studies.^{57, 132, 134}

The third step includes direct covalent binding of protein molecules to reactive groups of spacers.

To salient advantages of chemical sorption of biomolecules one can relate the great diversity of immobilisation techniques and the possibility to use them in combination, which, in its turn, favours the development of strategic approaches to the preparation of highly selective layers with predefined characteristics and the design of biorecognising receptors for the detection of analytes.

The disadvantages of the above-considered immobilisation methods (cross-linking, covalent binding, incorporation into

polymeric matrices, immobilisation on biomolecules) include relatively high masses of receptor layers and, as a consequence, the need for step-by-step control over mass increases in order to prevent the losses in the assay sensitivity and to provide stable performance of piezosensors. In some cases, continuous monitoring of receptor layers may be required, since no versatile procedure exists allowing the attainment of high immobilisation levels with simultaneous preservation of activities of immobilised antibodies. Therefore, immobilisation conditions should be optimised individually for each specific measurement.

V. Conditions for regeneration of bioselecting coatings

Re-usability of biolayers after each measurement cycle is a valuable feature of immunosensors, especially those designed for flow-injection screening of large panels of test samples where the same crystal has to be used many times.

It is known that formation of heterogeneous immune complexes is a reversible process; therefore, regeneration is confined to their dissociation under the influence of various factors that cause a shift in the reaction equilibrium towards the initial compounds. The increase in the ionic strength is one of such factors. Considering that immune complexes are stabilised by hydrogen bonds and van der Waals interactions, any increase in the ionic strength brings about conformational changes in the active sites of antibody molecules with simultaneous desorption of the analyte from the bioreceptor layer and restoration of the initial number of binding sites in the immobilised biomolecules. Acid or alkaline solutions [0.2 M glycine/HCl buffer (pH 2.5),^{58, 67, 68, 134} 0.2 M glycine,⁶ 0.001 M HCl,^{13, 67, 68} 0.1 M HCl,⁶ 0.5 M H₂Cr₂O₇,¹³ 1 M HCOOH,⁷¹ 0.001–0.1 M NaOH (see Ref. 6)] as well as 30%–50% methanol⁶ and denaturing reagents [6–8 M (NH₂)₂CO (see Ref. 44) and guanidine⁶] are generally used for regeneration; their action suppresses the interactions of the active sites with the analyte. It is found that dilute solutions sometimes fail to induce complete dissociation of immune complexes, whereas more concentrated reagents can diminish the sensitivity of biosensors as a result of damage of the layer consisting of immobilised ligands. From this standpoint, restoration of their initial sensitivities and preservation of mass after each measurement are the main requirements to regeneration of biolayers. The regenerating effect of 0.15–3 M KSCN, which depends on the nature of the immunoreagents and enables up to 20-fold utilisation of the bioreceptor layer without any detriment to its activity, has been described.^{126, 127}

Selective biochemical interactions, which yield more stable complexes than those formed upon immunochemical coupling, can be used, along with chemical reagents, for decomposition of immune complexes. Thus synthetic peptides able to react with adsorbed antigens (*e.g.*, viruses) and to be easily eliminated from the receptor surface can be used for regeneration of biolayers.⁵¹ In this case, the biosensors retained their activities over 18 measurement cycles. A sorbed protein analyte can be eliminated on treatment with a proteinase. For example, a solution of non-specific proteinase K induced hydrolytic elimination of antibody molecules in a neutral medium without any effect on the immobilised ligands of the biolayer.⁶

When long-term performance causes partial inactivation and destruction of the sensor biolayer as a result of which the reproducibility of analytical signals diminishes, the metal surfaces of sensor electrodes should be cleaned and washed properly with highly concentrated solutions of alkali and acids, *e.g.*, 0.5–1.2 M NaOH (pH 11–13); 0.5–1.2 M HCl (pH 1–2), or concentrated hydrochloric acid. The choice of conditions for complete regeneration of the sensor surface depends on the nature of the metal electrode and the method used for the formation of the base layer. For example, if antibodies are immobilised on a gold electrode using protein A, the protein layer is completely eliminated by sequential washing of the sensor with 1.2 M NaOH,

1.2 M HCl and concentrated HCl.⁵⁸ Siloxane films are easily destroyed by treatment with concentrated HCl. A solution of H₂Cr₂O₇, which allows complete purification of gold electrodes of piezoelectric resonators from thiol within a course of 15 min, can be used as an efficient regenerating reagent. The elimination of (γ-aminopropyl)triethoxysilane-containing base layers requires long-term incubation of the sensor in a hot solution of H₂Cr₂O₇.¹³ (γ-Aminopropyl)triethoxysilane- and tetraethoxysilane layers are easily eliminated from the surfaces of silver electrodes with 0.1 M HCl (pH 2), which acts directly on the oxide film of the metal.^{13, 125–127, 135} After washing and drying, piezoelectric resonators can be repeatedly used for the formation of biosensitive layers of another specificity.

Thus, the choice of conditions for regeneration of bioreceptor layers and complete purification of metal surfaces of resonator electrodes depends on the nature of the metal and the method used for immobilisation of biomolecules; in each case, the conditions are selected experimentally. The possibility of performing two-level regeneration of resonators is a salient advantage of piezoelectric immunosensors, since it enables their repeated application and versatile performance, which eventually reduces the cost of the analysis.

VI. Applications of piezoelectric immunosensors

The areas of application of piezoelectric immunosensors for the detection of high- and low-molecular-mass analytes in liquid media are extremely diverse and include biochemical, clinical and analytical studies; certification of foodstuffs and pharmaceutical substances; monitoring of environmental objects and so on (Table 1).

The majority of modern piezoelectric immunosensors are designed for the detection of 'large-sized' analytes, such as protein molecules, lipid–protein complexes, nucleic acids and viruses as well as for identification of somatic and bacterial cells in biological fluids, drinking water and foodstuffs. Determination of concentrations of such objects with the help of piezoelectric immunosensors proved to be more convenient in comparison with traditional microbiological or immunological methods. Piezoimmunosensors are used in the clinical diagnostic practice for identification of blood constituents (erythrocytes, T-lymphocytes, granulocytes) and the most common pathogenic bacteria.^{5, 6, 11, 13, 16, 17} Design of sensors for detecting pathogenic viruses (*e.g.*, herpes,^{50, 51, 139} hepatitis,^{136–138} human immunodeficiency,^{97, 98} *etc.*) is yet another promising trend. A good correlation with the results obtained by ELISA was established upon screening of blood sera for the human immunodeficiency virus.^{67, 68, 97} Piezoelectric immunosensors are used in veterinary medicine for identification of infectious pathogens in animals^{65, 96} and poultry⁵² and monitoring the quality of agricultural products.^{13, 96}

An important role in the variability of microorganisms residing in human body and environmental objects is played by bacteriophages. Therefore, phages are presently used for the solution of many practical tasks including deciphering of the human genetic code, prophylaxis and treatment of infectious diseases and detection of pathogenic microorganisms in environmental objects. The most recent trends are towards the development of highly sensitive piezoimmunosensors based on resonators with intrinsic oscillation frequencies from 39 to 110 MHz; they are designed for the direct detection of phages M13 in liquids²⁵ and screening of phage libraries.^{140, 141}

New, in principle, applications for piezoelectric immunosensors are described in the review.¹⁴² A highly selective immunosensor was proposed based on immobilised monoclonal antibodies for discrimination of serogroups A, B and D of *Salmonella*. Such sensors manifest extremely high specificities in the recognition of antigens differing structurally at the level of immunodominant monosaccharides, *viz.*, optically isomeric 3,6-dideoxyhexoses (paratose, abequose, tyvelose). These findings open up fresh opportunities for the use of gravimetric immunosensors for

Table 1. Use of piezoelectric immunosensors in clinical diagnostics and ecological monitoring.

Analyte	Type of assay, method for immobilisation of biomolecules	Detection limit	Ref.
Microorganisms			
Hepatitis A and B viruses	direct assay, Ab were immobilised by protein A	10^5 particles ml^{-1}	136, 137
Hepatitis C virus	hepatitis C virus RNA was immobilised on cysteamine SAM through avidin (streptavidin)	—	138
Herpes virus	direct assay, Ab were immobilised by protein A	5×10^4 particles ml^{-1}	50, 51, 139
Potato X-virus	direct assay, chemisorption of Ab on a siloxane substrate	4×10^{-8} – 6×10^{-3} mg ml^{-1}	125
Phage library	displacement analysis, biotinylated antigens were immobilised by streptavidin	$(1-5) \times 10^{11}$ particles ml^{-1}	140
Bacteriophages M13	direct assay, antibodies were immobilised by a bifunctional cross-linking reagent	10^9 particles ml^{-1}	25
Bacteriophages	—	5×10^{12} particles ml^{-1}	141
<i>Salmonella</i> sp. from serogroups A, B and D	direct assay, antibodies were immobilised by a bifunctional cross-linking reagent	10^5 – 10^8 cells ml^{-1}	142
Proteins			
Immunoglobulin G (IgG)	direct assay, Ab were bound to protein A	10^{-6} – 10^{-2} mg ml^{-1}	143
Human IgG	direct assay, chemisorption of the protein complex IgG–Ab on a polystyrene substrate	$5 \mu\text{g ml}^{-1}$	144
HSA	Ab were immobilised on an ethylene diamine substrate, obtained by the glow discharge method	16 – $128 \mu\text{g ml}^{-1}$	21
	direct assay, Ab were immobilised on polystyrene	5 – 100 mg ml^{-1}	35
Immunoglobulin M	direct assay, chemisorption of Ab on poly(2-hydroxyethyl methacrylate)	10 ng ml^{-1}	145
Antibodies to human immunodeficiency virus	direct assay, immobilisation of a synthetic HIV-peptide or recombinant human proteins	tests yes/no	97, 98
Staphylococcal enterotoxin B (SEB)	competitive method, Ab were adsorbed on gold	$0.1 \mu\text{g ml}^{-1}$	146
Cholera toxin	sandwich method enhanced by ganglioside-modified liposomes	10^{-4} nmol litre $^{-1}$	147
C-Reactive protein	latex agglutination	20 – $66.7 \mu\text{g litre}^{-1}$	81
Ricin	direct assay, Ab were immobilised by physical sorption	$0.5 \mu\text{g litre}^{-1}$	73
Complement factors C1, C6	direct assay, chemisorption of Ab on a polyethyleneimine substrate	$0.83 \text{ nmol litre}^{-1}$	148, 149
Ferritin	direct assay, Ab were immobilised on a cysteamine monolayer by cross-linking	0.1 – 100 ng ml^{-1}	131
α -Fetoprotein	direct assay, Ab were immobilised on a cysteamine monolayer by cross-linking	$1.5 \text{ nmol litre}^{-1}$	150
Surface antigen of hepatitis B	the same	$4.7 \text{ nmol litre}^{-1}$	151
Immunoglobulin E	direct assay, physical sorption of the protein antigen	0 – 300 IU ml^{-1} , 0.15 – 17.5 IU ml^{-1}	67, 68
	direct assay, affinity attachment to an aptamer based on single-stranded DNA	$0.05 \text{ nmol ml}^{-1}$	152
Anti-DNA antibodies	direct assay, native and denatured DNA were immobilised by chemisorption	0.1 – $25 \mu\text{g ml}^{-1}$, 0.03 – 8 IU ml^{-1}	74
Insulin	sandwich format, adsorption of Ab	$0.17 \text{ nmol litre}^{-1}$	104
Transferrin	agglutination enhanced by poly(ethylene glycol)	$2.1 \text{ nmol litre}^{-1}$	153
Immunoliposomes	competitive assay, immobilisation of hapten	10^{-8} – $10^{-5} \text{ mol litre}^{-1}$	154
Low-molecular-mass compounds			
Oxalic acid	competitive assay, Ab were covalently immobilised on polyethylenamine substrate	$1.9 \mu\text{g ml}^{-1}$	70
	Ab were immobilised into a BSA-based hydrogel	50 ng ml^{-1}	70
2,4-Dichlorophenoxyacetic acid	competitive assay, Ab were covalently immobilised on an aminobenzenethiol substrate	0.24 – $0.27 \mu\text{g litre}^{-1}$	155
Cortisol	direct assay, Ab were bond to protein A	$36 \mu\text{g litre}^{-1}$ ($100 \mu\text{mol litre}^{-1}$)	117
3-Indolylacetic acid	competitive assay	$3 \text{ nmol litre}^{-1}$	156
Atrazine	the same	0.025 ng ml^{-1} ($5 \times 10^{-4} \mu\text{mol litre}^{-1}$)	58, 59
	direct assay	0.01 ng ml^{-1}	71
Cocaine	direct assay, Ab were bond to protein G	$33 \mu\text{mol litre}^{-1}$	62
	competitive assay, the hapten was attached to the monolayer of mercaptoundecanoic acid	$10^{-4} \mu\text{mol litre}^{-1}$	157
β -Estradiol	immobilisation of an estrogen component capturing the receptor–estradiol complex	$8 \text{ nmol litre}^{-1}$	158

Table 1 (continued).

Analyte	Type of assay, method for immobilisation of biomolecules	Detection limit	Ref.
Atropine	—	0.05 nmol litre ⁻¹	159
Polynuclear aromatic hydrocarbons	competitive assay, Ab were covalently immobilised on a siloxane substrate	0.01 µmol litre ⁻¹	160, 161
Nonylphenol	the same	0.8 ng ml ⁻¹	162
Cotinine	"	0.1 µmol litre ⁻¹	74
Salicylic acid	"	2.9 µmol litre ⁻¹	126
Sulfamethoxazole	"	6 × 10 ⁻⁴ µmol litre ⁻¹	127

validation of structural data for carbohydrate-containing biopolymers and design of diagnostic systems.

Piezoelectroimmunosensors are used for identification of protein molecules, *e.g.*, of antibodies in blood serum (IgG, IgM, IgE). In order to promote efficient treatment of allergic and autoimmune diseases, patients' blood sera are screened for immunoglobulins (IgE)^{67, 68, 152} and anti-DNA antibodies. Receptor layers containing native or denatured DNA were used⁷⁴ in direct flow-injection assays of anti-DNA antibodies in blood sera of patients with systemic lupus erythematosus.

Piezoelectroimmunosensors were used as valuable tools for the detection of a vast variety of clinically important analytes, such as α -fetoprotein¹⁵⁰ and ferritin,¹³¹ the tumour-associated protein markers. Unfortunately, the recently developed sensors cannot be used for the analysis of human blood samples because the range of quantifiable ferritin concentrations is very narrow. Further experiments should be aimed at expanding the quantifiable concentration range, since normal blood levels of this protein in healthy females and males are usually equal to 90 and 200 ng ml⁻¹, respectively.

DNA-Based piezoelectroimmunosensors are used for hybridisation of nucleic acids.^{163–165} A recently developed gravimetric immunosensor^{166, 167} proved to be the instrument of choice in the estimation of genetically modified organisms.

Not only protein molecules and DNA, but also carbohydrate-lipid biopolymers [lipopolysaccharides (LPS)], are used as receptor layers. Biologically active LPS, which represent the major outer membrane constituents of Gram-negative bacteria, are responsible for the O-antigenic specificity and toxicity of bacteria. A method for the study of interactions between immobilised bacterial endotoxins (LPS) and synthetic LPS-binding peptides has been developed.¹³⁵ The data obtained point to a high potential of gravimetric immunosensors based on immobilised LPS in estimating the efficiency of antitoxic agents (antidotes).

The widening assortment of competitive immunoanalytical techniques based on piezoelectric sensors gave a new impetus to the appearance of publications devoted to the analysis of low-molecular-mass substances (drugs, hormones, alkaloids, pesticides and their metabolites, ecotoxins, vitamins, *etc.*).^{168, 169}

Residual concentrations of pesticides, which belong to one of the most widespread classes of low-molecular-mass toxicants, can also be controlled with the help of piezoelectroimmunosensors.⁶

Considering that veterinary antibiotics are used as widely as pesticides and that accumulation of drug components and their toxic metabolites in agricultural products is a potential hazard to human health, the use of piezoelectroimmunosensors for the monitoring over the content of toxic substances in foodstuffs (milk, meat, eggs) and environmental objects (waste waters; rivers, brooks, subterranean waters) is a currently central task. Immunosensors for detecting antimicrobial sulfamide drugs in aqueous solutions and milk have been developed.^{127, 170} In addition, piezoelectroimmunosensors can be used in drug tests for adulterants.

A gravimetric immunosensor for measuring the content of cotinine (a nicotine metabolite and a specific marker of the functional status of smokers in sociological tests) in urine samples

has been designed.⁷⁴ Screening of analytes revealed that cotinine content in the urine of active smokers varied from 4 to 6 mg litre⁻¹, while that in non-smokers was as low as 0.5–0.7 mg litre⁻¹. The sensitivity of the new piezoelectroimmunosensor was comparable to those attained in polarisation immunofluorescent studies.

The operating characteristics of piezoelectroimmunosensors for detecting hydrophobic ecotoxins (*e.g.*, polyaromatic hydrocarbons^{160, 161}) were improved in the presence of organic solvents.^{6, 155}

The broad application of nonylphenol ethoxylates as detergents and emulsifying agents in the commercial production of cleansers, dyes, some herbicides and tanning agents led to the pollution of the environment with their degradation products. Especially hazardous and toxic is nonylphenol possessing carcinogenic, estrogenic, *etc.*, activities. A flow-injection method for measuring the nonylphenol content in water aimed at monitoring industrial effluents and water reservoirs has been developed.¹⁶²

The possibility of ecological monitoring of toxicants (*e.g.*, ocadaic acid) produced by some algae species has been demonstrated.⁷⁰

The ever increasing number of publications illustrates the strong inclination of investigators to expand the area of application of piezoelectroimmunosensors. It is of note that flow-type immunosensors are efficient tools not only for the detection of analytes of different molecular masses, but also for monitoring the changes in the viscoelastic properties of boundary layers in immune reactions carried out in solutions⁷⁵ and for following biochemical reactions in real time. This unique capability of piezoelectroimmunosensors enables kinetic studies of affinity reactions, such as antigen–antibody and protein–nucleic acid interactions, hybridisation of complementary DNA chains, receptor–ligand interactions, *etc.* Recent investigations in this field are documented in the reviews.^{6, 15, 126} Besides, piezoelectroimmunosensors hold much promise as potent tools for quantitation of cross-linking reactions between structurally related antigens and antibodies,¹⁷⁰ hybridisation of DNA^{163–165} and epitope mapping.¹⁷¹

Combination of piezoelectroimmunosensors with impedance measurements is a useful approach to the study of viscoelastic properties of films and fluids exposed on the surface of piezoelectric crystals. In this case, the alternating voltage having a frequency close to the intrinsic frequency of the resonator is applied to the piezoelectric crystal and the auxiliary electrode. The electrode potential and the current passing through the crystal are measured simultaneously. Their ratio (impedance) permits real-time monitoring of degradation processes in thin polymeric films in the presence of biomolecules; conformational changes; phase transitions, swelling and other immunochemical reactions.^{22, 172}

Moreover, the possibility to combine piezoelectroimmunosensors with other (*e.g.*, optical and electrochemical) methods including surface plasmon resonance and atomic force microscopy will further extend our knowledge of the actual events related to biochemical interactions at the cell level.

VII. Conclusion

The analysis of publications of the past decade demonstrates that the novel scientific trend related to the development and practical applications of piezoelectric immunosensors in bioanalytical chemistry has aroused an ever increasing interest of investigators all over the world.

The combination of a low cost with enhanced sensitivity, selectivity and re-usability makes piezoelectric immunosensors a valuable alternative to existing optical, electrochemical, etc., devices for conducting routine tests. As regards long-range outlooks, piezoelectric immunosensors can occupy a more prominent place as analytical tools for flow-injection detection of analytes of different molecular masses and genetically modified products, monitoring of immunochemical interactions and control over the growth of bacterial populations and changes in viscoelastic properties of liquid media. The development of diagnostic kits that are based on piezoelectric immunosensors and are specifically designed for early diagnosis of infectious, autoimmune and oncological diseases is still a topical task in modern clinical and veterinary medicine. Especially promising is the use of piezoelectric immunosensors for detecting drugs (doping control) and screening of urine, saliva and other biological fluids for alkaloids, hormones and other abused drug components.

In Russia, investigations aimed at the development of mass-sensitive immunosensors are still in their infancy. It remains to be hoped that the data presented herein will shed additional light on the broad prospects for future applications of piezoelectric immunosensors and will demonstrate their major advantages including real-time monitoring of molecular interactions without the use of any labels and complicated sample pretreatment procedures.

This review has been written with the financial support of the Russian Foundation for Basic Research (Project No. 06-03-32226).

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^a — *J. Anal. Chem. (Engl. Transl.)*

^b — *Russ. J. Phys. Chem. (Engl. Transl.)*

Mesoporous titanium silicates as catalysts for the liquid-phase selective oxidation of organic compounds[†]

O A Kholdeeva, N N Trukhan

Contents

I. Introduction	411
II. Types of mesoporous titanium silicates and their synthesis	412
III. Methods of physicochemical characterisation of mesoporous titanium silicates	415
IV. Catalytic properties	422
V. Conclusion	429

Abstract. The data on the synthesis, physicochemical and catalytic properties of mesoporous titanium silicate materials published to date are surveyed. The relationship between the structure of these materials and their catalytic properties in the liquid-phase selective oxidation of organic compounds with peroxides is considered. The emphasis is placed on the problems of stability of mesoporous titanium silicate catalysts and the possibility of their recycling. The bibliography includes 264 references.

I. Introduction

Oxygen-containing organic compounds are important intermediates and products of both base and fine organic syntheses.^{1–9} Nearly a quarter of the major chemicals in the modern chemical industry are produced through the catalytic oxidation processes and the share of such processes is constantly increasing.^{8,9} Meanwhile, the stoichiometric ‘environmentally unfriendly’ oxidation of substrates with such agents as manganese or chromium oxides, metal permanganates or bichromates, nitric acid, *etc.*, still remains the major route to oxygen-containing products in the fine industrial synthesis.^{7,10–17} The stoichiometric oxidation consumes large amounts of expensive and toxic oxidants, which unavoidably gives rise to the problem of hazardous waste utilisation.

However, over the last decade, there has been a marked trend towards replacement of traditional stoichiometric oxidation procedures by catalytic ones, which are substantially more environmentally friendly and cost-effective. Among them, catalytic processes based on the environmentally safe oxidants, such as molecular oxygen and hydrogen peroxide, arouse the greatest interest.^{6–25} The active oxygen content in H₂O₂ is 47% and mere water is the only by-product of the H₂O₂ reduction. Although hydrogen peroxide is more expensive than oxygen (100% H₂O₂ costs 0.7 USD per kg),²⁵ the use of H₂O₂ often proves preferable in small-scale fine organic synthesis. First, the process equipment required for the oxidation with hydrogen peroxide is less expensive than that for the oxidation with oxygen, since the latter is

typically operated at elevated temperatures and pressures.^{7–10,26} Second, the processes based on the oxidation with aqueous H₂O₂ are commonly considered to be safer than those utilising oxygen under pressure. The feasibility of the implementation of hydrogen peroxide as an oxidant for a number of large-scale processes, such as caprolactam synthesis (Sumitomo Chemical Co.) or propylene oxidation (BASF and The Dow Chemical Co.) is currently surveyed by leading chemical companies.²⁵

Presently, water-soluble metal salts or complexes are dominantly used as catalysts for the liquid-phase oxidation.^{4–10,27} However, available catalysts for the selective homogeneous oxidation typically provide high activity and selectivity but low productivity due to the degradation of the catalytic sites in oxidative media. Furthermore, the separation of reaction products from the catalyst and recycling of the latter become a challenging task. Even in the case of two-phase oxidation, *i.e.*, when the catalyst is initially present in the aqueous phase, whereas the substrate and product are in an organic medium, contamination of the target product with toxic transition metal derivatives cannot be completely suppressed, since the interaction of the catalyst (or products of its decomposition) with organic components of the reaction mixture (*i.e.*, solvent or oxidation products) can yield metal complexes soluble in the organic phase.

The problem of the catalyst separation from the reaction products can be, in principle, solved only by the use of heterogeneous catalytic processes. However, it is known that the liquid-phase oxidation is often accompanied by the leaching of active components from solid catalyst, such that the oxidation process actually proceeds homogeneously in the bulk of the solution and all the above issues related to the product isolation and purification remain.^{10,13,16,28–33} Therefore, the development of novel solid catalysts providing the high activity and selectivity simultaneously with the stability against the action of reaction media is one of the most current challenges to the modern liquid-phase catalytic oxidation. The incorporation of transition metal ions or their complexes into frameworks or cavities (channels) of ordered micro- and mesoporous materials, *i.e.*, the design of so-called redox molecular sieves composed of isolated active sites homogeneously distributed over a solid matrix represents a promising possible route to the solution of this problem.^{7–10,13,16,28,29,34–37}

O A Kholdeeva, N N Trukhan G K Boreskov Institute of Catalysis, Siberian Branch of the Russian Academy of Sciences, prosp. Acad. Lavrent'eva 5, 630090 Novosibirsk, Russian Federation.
Fax/tel. (7-3833) 30 95 73, e-mail: khold@catalysis.nsk.su
(O A Kholdeeva), tel. (49-621) 605 52 98,
e-mail: natalia.trukhan@basf.com (N N Trukhan)

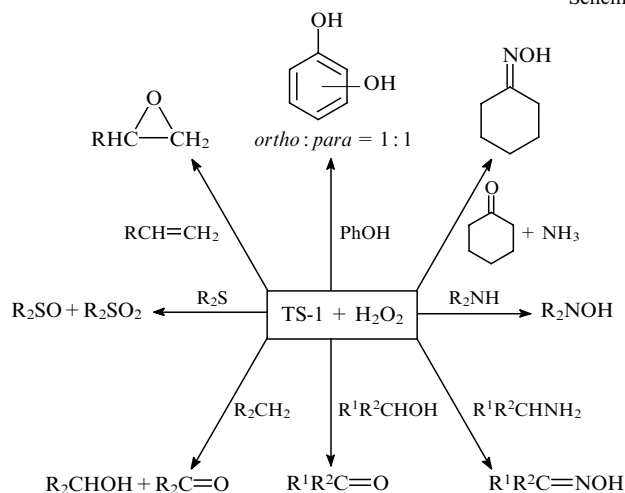
Received 19 May 2005

Uspekhi Khimii 75 (5) 460–483 (2006); translated by Ya V Zubavichus

[†] The review is dedicated to the memory of V N Romannikov, who stimulated activities on the synthesis and studies of mesostructured silicate and metal-silicate materials at the Institute of Catalysis of the Siberian Branch of the RAS in the end of 1990s.

A real breakthrough in the liquid-phase catalytic oxidation was achieved in the mid-1980s by the Italian company Enichem with the invention of a microporous titanium silicate catalyst TS-1.³⁸ This catalyst is characterised by the structure of silicalite ZSM-5 (structural type MFI), in which the titanium(IV) ions are isomorphously substituted for a part of silicon atoms. This structure contains a three-dimensional framework of channels with a diameter of 5.3–5.6 Å. TS-1 was followed by another microporous titanium silicate catalyst, TS-2 (ZSM-11, structural type MEL, channels of 5.3–5.4 Å).^{39,40} Presently, TS-1 is still the best catalyst for the heterogeneous liquid-phase oxidation of various classes of organic compounds with aqueous hydrogen peroxide (Scheme 1).^{41–49} The oxidation of phenol with hydrogen peroxide over TS-1 was implemented industrially in 1987; using this process, about 10 000 t of hydroquinone and pyrocatechol are produced yearly.^{41,45} The main drawback of the microporous titanium silicates is the small size of the pores, which prevents their utilisation for the conversion of large organic molecules. In particular, the system TS-1–H₂O₂ is an active oxidant only for substrates with a kinetic diameter smaller than 6 Å (which includes unbranched alkanes and olefins, phenols, *etc.*).^{41–45} The problem of the selective catalytic oxidation of large organic molecules remains unsolved.

Scheme 1



Over the recent years, several titanium-containing zeolites and disordered titanium silicates with pores larger than in TS-1 have been synthesised, *viz.*, Ti-Beta (6.4 × 7.6 Å),^{50,51} Ti-APSO-5 (7.3 × 7.3 Å),⁵² Ti-MOR (6.7 × 7.0 Å),^{53,54} ITQ-7 (6.1 × 6.5 Å),⁵⁵ Ti-MWW (7.1 × 18.2 Å),^{56–59} Ti-DMS1 (11.2 Å),⁶⁰ *etc.* They were successfully utilised in the catalytic oxidation of some cyclic alkenes and alkanes (*e.g.*, cyclohexene, cyclooctene, norbornene, methylcyclohexane, *etc.*) and unsaturated alcohols,^{50–56,59–67} which cannot be oxidised over TS-1. Nevertheless, these catalysts are unable to overcome the problem of oxidation of larger molecules. Furthermore, some of them are sensitive to the action of aqueous hydrogen peroxide.^{28,29,31,68}

Over the last decade, a new class of materials, *viz.*, mesoporous silicates containing ions of various transition metals, including titanium, has become in the focus of interest: the number of publications devoted to their synthesis, characterisation and application as oxidation catalysts is rapidly increasing.^{32,45,69–91} The specific surface area of such materials can be as high as 1000 m² g^{−1} or even more. Large organic molecules can freely penetrate into the pores of these materials under the conditions of liquid-phase heterogeneous catalysis, in contrast to the pores of microporous materials. The design of such materials takes the first place among the current strategic tasks of fine organic synthesis oriented on the use of hydrogen peroxide.¹⁶

A number of reviews^{32,33,45,74,76–79,81–85,90,91} (not mentioning numerous original papers) devoted to the synthesis and elucidation of the properties of mesoporous metal silicates have

recently appeared. The first one was published in 1996.^{74,76} In the same year, a detail review devoted to microporous titanium silicates by Notari appeared,⁴⁵ which generalised rather scarce experimental data on mesoporous silicate materials available by that time. In 1997, two reviews by Corma^{77,78} on the synthesis of mesoporous molecular sieves (including metal silicates) and their applications in catalysis and another review by Schneider and Baiker,⁸¹ who considered mixed titanium–silicon oxides (aerogels), were published.

In the present review, we undertake an attempt to generalise and analyse the experimental results published to date (prior to the beginning of 2005) concerning the synthesis of mesoporous titanium silicates (both structurally ordered and amorphous) and analysis of their physicochemical properties and consider possible applications of these materials as catalysts for the selective liquid-phase oxidations. The emphasis is placed onto the relationship between the physicochemical characteristics of mesoporous titanium silicates and their catalytic properties and onto the problems of their stability and possibility of their recycling.

II. Types of mesoporous titanium silicates and their synthesis

There are two fundamentally different types of mesoporous metal silicate (including titanium silicate) materials, *viz.*, ordered and disordered. The first type includes various mesostructured materials (MMM, MCM-41, MCM-48, HMS, FSM-16, SBA-15, *etc.*), which are often referred to as mesoporous molecular sieves (Fig. 1*a*). The second type includes amorphous mixed oxides (*i.e.*, aerogels and xerogels) (Fig. 1*b*). Titanium can be either incorporated into the porous silicate matrix during its synthesis^{41,66–77} or grafted onto the surface of a preprepared matrix using the so-called post-synthesis, which means a treatment of a mesoporous silicate with titanium salts or complexes, such as TiCl₄, Ti(OPr)₄, [(C₅H₅)₂TiCl₂], [Ti₆(μ₃-O)₆(μ-O₂CC₆H₄OPh)₆.(OEt)₆], *etc.*^{7,28,92–99}

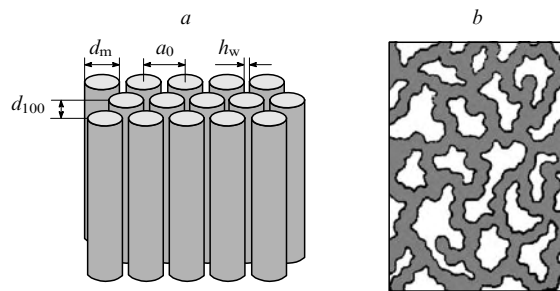


Figure 1. A schematic representation of the structure of a mesostructured material with hexagonally packed cylindrical mesopores (channels) (*a*) and of an aerogel (*b*);

a_0 is the lattice parameter, d_m is the diameter of a mesopore, h_w is the thickness of the silicate wall ($h_w = a_0 - d_m$), d_{100} is the interplanar spacing.

1. Mesostructured titanium silicate materials

Mesostructured silicates are known starting from the early 1990's.^{100,101} They represent highly ordered systems produced through the hydrothermal synthesis from inorganic precursors and surfactants.^{70–78,82,83,86–91} The mesopores emerging in such materials following the removal of surfactants by calcination or extraction have precisely determined sizes in the nanometre range (typically, from 20 Å to 200 Å) and form channels. The packing of the mesopores can be either hexagonal (MCM-41, HMS, MMM, FSM-16 or SBA-15) (see Fig. 1*a*), or cubic (MCM-48 or SBA-1) or lamellar (MCM-50), depending on the surfactant : Si ratio and conditions of the hydrothermal synthesis.^{74–77,83} The silicate

walls separating the channels of mesopores from each other are amorphous, but nevertheless the structure of these materials is characterised by long-range ordering[‡] owing to the ordered arrangement of the hollow channels. The specificity of the structure of these materials is reflected in the terms 'mesophase' or 'mesostructured', which imply long-range ordering (in the distance range from 1 nm to 1000 nm) at the absence of short-range ordering (at the atomic level). This feature distinguishes these materials from zeolites that are both short-range and long-range ordered.

Mesoporous mesophase metal silicates (and titanium silicates, in particular) are typically prepared through the hydrothermal synthesis by the crystallisation of a gel containing a source of the structural element (an Si compound), a structure-forming agent (*i.e.*, a surfactant) and a transition metal compound. The crystallisation is often carried out under elevated pressures and temperatures (25–200 °C). The duration of the crystallisation can vary from a few hours to several weeks.

The first report on the synthesis of an ordered mesoporous titanium silicate material, Ti-MCM-41, was published in 1994.⁶⁹ Later, several methods for the synthesis of a number of mesostructured titanium silicate materials (*e.g.*, Ti-MCM-41,^{69, 70, 72, 77} Ti-MCM-48,^{95, 102, 103} Ti-HMS,^{73, 87, 104} Ti-MMM,^{88, 105, 106} KIT-1,⁹³ Ti-TUD-1,¹⁰⁷ Ti-MSU-1,¹⁰⁸ Ti-FSM-16,¹⁰⁹ Ti-SBA-15,^{95, 96, 99, 110–113} Ti,Al-SBA-15,¹¹⁴ Ti-SBA-1,¹¹⁵ Ti-MMM-2,¹¹⁶ *etc.*) have been elaborated. The basic types of mesostructured titanium silicate materials are summarised in Table 1.

The type of interaction between the inorganic component (I) and the surfactant (S) is the key factor governing the formation of a mesophase material with a specific structure. The following interaction types are possible: electrostatic (S^+I^- or S^-I^+),^{76, 77, 82, 83, 88, 104} indirect electrostatic (S^+A-I^+ or $S^-C^+I^-$, where A^- and C^+ are auxiliary anions and cations, respectively),^{104, 117, 118} hydrogen ($S^0 \cdots I^0$)^{73, 87, 104, 108} and covalent (S^0-I^0)¹¹⁹ bonding.

The synthesis of mesostructured silicate and metal silicate materials (MCM-41, MCM-48, MMM, *etc.*) mediated by the electrostatic interactions between cationic surfactants (S^+) and polysilicate anions (I^-), *i.e.*, through the reaction pathway S^+I^- , is realised in alkaline media.^{69, 70, 77, 88, 102–106} The first mesostructured silicates of the structural type MCM-41 were synthesised in 1992 by the R&D team of the Mobil company using exactly this method.^{100, 101}

Alkyltrimethylammonium halides or hydroxides with the common formula $C_nH_{2n+1}(CH_3)_3NX$ ($n = 12–18$; $X = Cl^-$,

Br^- , OH^-) are usually employed as surfactants. The value of n determines the diameter of the resultant mesopores. Trimethylcetylammmonium bromide $n-C_{16}H_{33}(CH_3)_3NBr$ is used most frequently giving rise to the mesopores of 3–4 nm. If the reaction pathway S^+I^- is utilised, at least a part of oxygen atoms in the inorganic walls of the material carry a negative charge. In contrast to uncharged SiOH groups, charged SiO^- groups cannot take part in the formation of strong Si–O–Si siloxane bonds through the polycondensation under the hydrothermal treatment, which gives rise to discontinuities within the silicate walls and to a low stability of the materials against hydrolysis.^{88, 120} Due to the low hydrolytic stability, such a catalyst degrades structurally during the liquid-phase oxidation thus losing its activity.^{88, 106, 121–126} Attempts aimed at the additional structural stabilisation of the MCM-41 type catalysts with various chemical means (in particular, by addition of water-soluble organic or inorganic salts to the reaction mixture during the synthesis) often resulted in the collapse of the mesostructure and formation of disordered materials (see, for example, Refs 127 and 128).

The thermo- and hydrostability of MCM-41 can be enhanced by an additional hydrothermal treatment of the starting material with water.^{129, 130} This procedure, however, leads to an increase in the thickness of the silicate walls (h_w), which is unacceptable for metal silicate catalysts, since a part of active sites can be trapped within the walls and thus become inaccessible for the substrates (see Section III). Alternatively, the stability of the silicate walls towards the reaction (aqueous) medium can be enhanced by their surface silylation with hydrophobic species, such as $(CH_3)_3SiCl$, $(CH_3)_3SiNHSi(CH_3)_3$, *etc.*,^{131–138} or by specific doping, for instance, with aluminium.⁸⁸ The surface hydrophobicity of Ti-MCM-41 can also be increased by the removal of the template using extraction under supercritical conditions ($CO_2 + MeOH$).¹³⁹ Recently, a micromesoporous titanium silicate Ti-MMM-1, which combines structural motifs of TS-1 and Ti-MCM-41 in one phase, was synthesised using two types of surfactants, *viz.*, tetramethylammonium hydroxide and trimethylcetylammmonium bromide on the first and second steps of the synthesis, respectively.¹⁴⁰

The HMS type mesoporous silicate materials are formed at a pH close to 7 owing to the van der Waals interaction of uncharged surfactants (most typically, amines) with silicate particles (*i.e.*, the interaction type is $S^0 \cdots I^0$).^{73, 80, 87, 104, 141} The synthesis of Ti-HMS is usually carried out at room temperature.^{73, 87, 104} These materials are characterised by larger thickness (and, respectively, by higher strength) of the silicate walls as compared to those synthesised through the reaction pathway S^+I^- . The small size of particles constituting the HMS type materials is responsible for the so-called 'texture mesoporosity'.⁷³ It has to be stressed, however, that the degree of structural ordering in such materials is rather low.^{74, 104, 105}

[‡] The long-range ordering can be reliably detected using X-ray diffraction at small angles (less than 6–8 deg), high-resolution electron microscopy and adsorption techniques (see Section III).

Table 1. The main types of mesoporous mesostructured titanium silicate materials.

Material	Surfactant	Lattice type	Mesopore diameter /nm	Wall thickness /nm	Ref.
Ti-MCM-41	$C_{16}H_{33}(CH_3)_3NOH$ or $C_{16}H_{33}(CH_3)_3NBr$	hexagonal	2.9–3.5	1.0–1.5	69, 72, 104
Ti-MMM	$C_{16}H_{33}(CH_3)_3NBr$	"	3.4–3.8	0.8–1.0	88, 106
Ti-MMM-2	$C_{16}H_{33}(CH_3)_3NBr$	"	3.2	1.0	116
Ti-MCM-48	$C_{16}H_{33}(CH_3)_3NBr$	cubic	2.3	—	102, 103
Ti-HMS	$C_{12}H_{25}NH_2$	hexagonal	2.7	1.9	73, 87, 104
Ti-SBA-1	$C_{16}H_{33}(CH_3)_3NBr$	cubic	2.0	—	115
Ti-SBA-15	$(EO)_{20}(PO)_{70}(EO)_{20}$ (see ^a)	hexagonal	10.6–10.9	1.6–2.0	110
Ti-MSU-1	$C_{11}H_{23}O(CH_2CH_2O)_{12}H$	"	3.0	—	108
Ti-TUD-1	$(C_2H_5O)_3N$	see ^b	4.5–5.7	2.5–4.0	107

^a Triblock copolymer polyethylene oxide–polypropylene oxide–polyethylene oxide (Pluronic P123). ^b A disordered three-dimensional framework of mesopores with similar sizes.

Recently, mesoporous silicate materials were synthesised through the reaction pathway $S^{0...I^0}$ with polyethylene oxide-based (PEO) oxygen-containing polymers as non-ionogenic surfactants.^{108, 142} These surfactants are substantially less expensive than ionogenic alkylammonium salts and non-ionogenic alkylamines and, furthermore, they are non-toxic. Mesoporous titanium silicate Ti-MSU-1 was synthesised by addition of tetraethyl orthosilicate (TEOS) to a solution of amphiphilic surfactant Tergitol 15-S-12 [$C_{11-15}H_{23-31}O(CH_2CH_2O)_{12}H$] containing 5% of Ti.¹⁰⁸ The catalyst Ti-MSU-1 possesses a disordered hexagonal-like system of mesopores with a mean diameter of 3.0 nm. An alternative method for the synthesis of Ti-MSU-1 consists of the preparation of an aqueous solution of sodium silicate at pH > 9 followed by its mixing with acidic aqueous solution of non-ionogenic surfactant, *i.e.*, an amphiphilic diblock copolymer A_nB_m (A is a hydrophilic fragment, B is a hydrophobic fragment).⁸ The required heteroelement is then added to the reaction mixture (at a pH from 4 to 10). The materials obtained by this method are characterised by disordered arrangements of mesopores with similar diameters (from 1.5 nm to 30 nm, depending on the type of the surfactant used) separated from each other by walls with a thickness of >0.5 nm; the specific surface area of these materials is 300–1400 m² g⁻¹. Such materials are thermostable but no information on their hydrolytic stability is available.

Mesoporous silicate materials SBA-3 and SBA-15 are synthesised in strongly acidic media at pH ≤ 1.5 (Refs 75, 104, 118, 143–146) through the reaction pathway $S^+A^-I^+$ using the electrostatic interaction of surfactant cations and uncharged silicon dioxide particles with partly protonated surface silanol groups [*i.e.*, I^+ can be formulated as $H_2O^+Si(OH)_3$] mediated by auxiliary anions ($A^- = Cl^-$ or other anions). Alkylammonium salts,^{75, 104, 118} oligomeric alkylpolyethylene oxide with the general formula $C_nH_{2n+1}(EO)_mH$ ($n = 12–18$, $m = 2–25$) and block copolymers of oligomeric polyalkylene oxides $(EO)_n(PO)_m(EO)_p$ ($0 < n < 100$, $5 < m < 150$, $0 ≤ p < 100$) can be used as surfactants.^{118, 142–147} This approach makes it possible to achieve nearly the same degree of ordering of the mesostructure and control over the structural parameters as in the systems produced by the reaction pathway S^+I^- . The resulting materials are characterised by exceptionally high hydrostability,^{86, 142–146} since silicon dioxide particles involved into the formation of the mesostructure contain no ionised oxygen atoms that prevent complete polycondensation of siloxane links within the silicate walls.

Therefore, according to the available literature data, the silicate walls of mesoporous mesophase materials, which are stable against the action of water, can be formed only in strongly acidic media. However, the introduction of metal cations (Ti, Al, V, *etc.*) into silicate matrices becomes a problem in these media.^{86, 95, 104, 113} In particular, aluminium remains virtually unbound within the silicate walls being present in the forms that are readily leached.⁸⁶ The synthesis of Ti-MCM-41,¹⁰⁴ Ti-SBA-15¹¹³ and Ti-SBA-1¹¹⁵ in strongly acidic media requires a large excess of titanium, since its incorporation into the silicate walls is hindered by high solubility of Ti-containing species at this pH.¹⁰⁴ This issue can be overcome only by increasing pH to a value that provides sufficient level of the hydrolysis of dopant transition metal ions. In the majority of cases, this is achieved at a pH from 2.5 to 4.

The first attempt to incorporate titanium into a silicate matrix at a pH of 2.6–3.2 was undertaken in the beginning of 2000 with the synthesis of Ti-SBA-15 using $(EO)_{20}(PO)_{70}(EO)_{20}$ as a surfactant.¹¹⁰ Recently, a novel mesophase material, Ti-MMM-2, which manifests both thermohydrostability and resistivity to the leaching of the active component (titanium), has been synthesised using this approach with $C_{16}H_{33}(CH_3)_3NBr$ as a surfactant.^{116, 148} The

Ti-MMM-2 structure is generated in two steps. In the first step, a mixture containing positively charged silicon hydroxy complexes, titanium compounds and a surfactant is prepared while the pH is maintained in the range of 0.5–1.5. In the second step, a certain amount of a basic sodium silicate solution is added to the reaction mixture to increase and maintain the pH to a value in the range from 2.5 to 7.0. Then the mixture is subjected to a hydrothermal treatment.

Recently, two new methods for the synthesis of Ti-SBA-15 have been reported, the first one combines the hydrothermal treatment with the microwave irradiation,¹¹¹ the second is based solely on the microwave irradiation.^{149, 150} Most frequently, titanium is grafted onto the surface of presynthesised silicate SBA-15 in the post-synthesis step.^{95, 96, 99, 111, 112}

In the vast majority of published works, expensive tetraethyl orthosilicate was employed as a source of silicon. In recent years, there have been several reports on the use of less expensive and more available silicon sources, *viz.*, water-soluble inorganic sodium silicates $Na_2Si_2O_5$ and Na_2SiO_3 ,^{106, 110, 116, 142, 144, 145} and 'liquid glass' (28%–30% of SiO_2 and 9%–10% of Na_2O).¹²¹ Alternatively, H_2SiF_6 (Ref. 151) and colloidal dispersions of SiO_2 (Refs 121, 130) can be used. As a titanium source, titanium alkoxides, $Ti(OEt)_4$, $Ti(OPr)_4$, $Ti(Obu)_4$, and so on were utilised. The hydrolysis of organotitanium derivatives has to be strictly controlled in order to prevent their polymerisation.^{152, 153}

Inorganic titanium compounds, *e.g.*, $TiCl_3$,¹¹³ $TiCl_4$, $K_2TiO(C_2O_4)_2$, $(NH_4)_2TiF_6$,¹⁵⁴ $(NH_4)_3[Ti(O_2)F_5]$,¹⁵⁵ $Ti(SO_4)_2$ (Refs 110, 116, 148, 154) have recently started to be used in the synthesis of mesoporous mesophase titanium silicates. However, partial formation of oligomerised particles of titanium oxide was observed in all those cases except for the use of $(NH_4)_3[Ti(O_2)F_5]$ in the synthesis of Ti-MCM-41¹⁵⁵ and of the system $Ti(SO_4)_2-H_2SO_4$ in the synthesis of Ti-MMM-2.¹¹⁶ The addition of complex-forming agents (*e.g.*, H_2O_2 , acetylacetone, polyalcohols, aminoalcohols, *etc.*) often decelerates the hydrolysis and, respectively, suppresses the undesired polymerisation of titanium species.^{107, 113, 145, 153} Additionally, this technique makes it possible to increase the content of titanium in the silicate matrix up to an Si:Ti ratio of 1.9.¹⁵³ A synthesis of Ti-MCM-41 from a structure-forming precursor simultaneously from silicon and titanium, *viz.*, a copolymer of diethoxysiloxane with diethyltitanate $[(C_2H_5O)_2SiO]_n[(C_2H_5O)_2TiO]_m$, has recently been reported.¹³¹

The question on the formation mechanism of mesoporous mesostructured silicates remains a subject of debate.^{74, 76, 77, 82, 83, 88–90, 101} The model of 'liquid crystalline ordering' was one of the first mechanisms proposed.¹⁰¹ According to this mechanism, surfactant molecules self-assemble first into spherical micelles and then into cylinders. The latter are further arranged to form a hexagonal packing. The resultant 'liquid crystals' are then covered with a shell of inorganic particles.

According to another hypothesis,¹⁵⁶ no ordered phase of 'liquid crystals' is involved. The surfactant molecules assembled into cylinders interact with inorganic particles, which gives rise to the growth of a silicate layer atop the external surface of micelles and only after that the cylinders are arranged into a hexagonal packing.

Nevertheless, the majority of authors adopt the cooperative mechanism, which implies that electrostatic interactions between inorganic ions and surfactant molecules play the key role and govern the morphology of the resultant mesostructure.¹⁵⁷ This mechanism is depicted schematically in Fig. 2. In the first step (Fig. 2a), the ion pairs combining inorganic particles and surfactant molecules are formed due to the electrostatic interactions. In the second step (Fig. 2b), the ion pairs self-assemble into cylindrical micelles. Depending on the conditions, the cylinders are further arranged yielding a hexagonal (Fig. 2c), cubic or lamellar structure. In the last step, the inorganic particles are condensed giving rise to the emergence of a strong framework.

According to an alternative suggestion, the inorganic silicate particles self-assemble into layers separated from each other by

§ Triblock copolymers polyethylene oxide–polypropylene oxide–polyethylene oxide, such as $(EO)_{20}(PO)_{70}(EO)_{20}$ or $(EO)_{20}(PO)_{30}(EO)_{20}$, are most typically used as non-ionogenic surfactants.

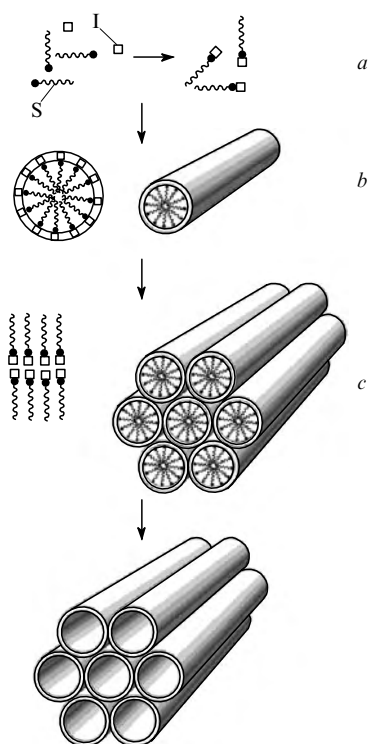


Figure 2. A scheme depicting the cooperative mechanism of the formation of mesostructured silicates; (a–c) — see text.

rows of cylindrical micelles formed by the surfactant molecules.¹⁵⁸ Upon ageing, the layers become puckered and undergo cross-linking around the micelles thus yielding a hexagonal packing. Yet another model assumes that layers of surfactant and inorganic silicate particles are initially formed in the synthesis of MCM-41.¹⁵⁹ In the course of the polymerisation of silicate particles, the charge density is redistributed, which gives rise to the contortion of the layers and transformation of the lamellar mesostructure into the hexagonal one. However, the detailed consideration of modern concepts concerning the mechanisms of the mesostructure formation lies beyond the scope of the present review.

2. Amorphous mesoporous mixed oxides $\text{TiO}_2\text{—SiO}_2$

Amorphous mixed oxides $\text{TiO}_2\text{—SiO}_2$ (*i.e.*, aerogels and xerogels) represent another important class of mesoporous titanium silicate materials.^{81, 84, 85, 160–172} In terms of the structure, aerogels and xerogels can be described as long chains composed of primary silica particles (globules) touching each other only in a few points (see Fig. 1b).¹⁷³ Aerogels are characterised by a mean pore size of > 100 Å, whereas the mean pore size of xerogels is 5–20 Å. The typical specific surface area of xerogels is 300–700 $\text{m}^2 \text{g}^{-1}$. Aerogels manifest larger specific surface areas ($> 1000 \text{ m}^2 \text{g}^{-1}$) and simultaneously very high porosity (the specific volume of pores can be as high as 3–3.5 $\text{cm}^3 \text{g}^{-1}$).

Mixed oxides $\text{TiO}_2\text{—SiO}_2$ are routinely prepared by the sol–gel technology^{81, 173–175} that includes five major steps: (1) hydrolysis of silicon and titanium alkoxides, (2) polycondensation of alkoxides and growth of sol particles, (3) sol aggregation into an alcogel network, (4) gel ageing and (5) drying. The significant difference between the hydrolysis rates of silicon and titanium alkoxides makes certain problems in the preparation of materials with a homogeneous distribution of titanium ions over the silicon sol–gel matrix. These difficulties can be overcome by the utilisation of prehydrolysed TEOS^{84, 160, 161, 171} or tetramethyl orthosilicate (TMOS), which is more reactive towards hydrolysis, or by modification of titanium tetraisopropoxide with peroxide or

chelating agents, such as acetylacetone, cyclohexane-1,4-diol, *etc.*^{164, 165, 167–171, 176}

Aerogels are produced from alcogels by their drying under the conditions of a gradual increase in the temperature and solvent vapour pressure up to supercritical values. This results in the elimination of the ‘liquid–vapour’ interface and the related reduction of capillary pressure, which under the normal drying conditions in narrow pores can reach values equivalent to hundreds atmospheres and thus decrease the initial volume of the gel several-fold. The supercritical drying can be classified into high-temperature and low-temperature ones.^{81, 163, 167} In the former case, alcohols are used as solvents, whereas CO_2 is utilised in the latter case. The drying under the supercritical conditions makes it possible to avoid significant structural modifications of the starting alcogel. Xerogels are produced by the ordinary thermal drying of alcogels.

Prior to the 1980s, mixed oxides $\text{TiO}_2\text{—SiO}_2$ were synthesised with the use of either acidic or basic catalysis. The use of basic catalysts gives rise to gels composed of large particles with wide pores between them, whereas, finely structured gels composed of small particles separated from each other by narrow pores are formed under the conditions of acid catalysis. The latter structure is extremely fragile and breaks down to a significant extent even upon drying in supercritical CO_2 . As a result, the specific volume of pores in aerogels prepared with the use of acidic catalysts typically does not exceed 1 $\text{cm}^3 \text{g}^{-1}$.¹⁶⁸

In 1982, a new convenient method for the control over the structure of synthetic silica gels was suggested. It employs a two-step sol–gel procedure with the subsequent utilisation of acidic and basic (amine) catalysts in the first (partial hydrolysis and condensation) and second (polycondensation) steps, respectively.¹⁷⁷ This synthetic scheme enables stricter control over the structure of the resultant gel. In the first step, the chain-length distribution of alkoxide oligomers can be efficiently adjusted and various forms of particles can be deliberately generated (from active monomers to virtually completely condensed colloidal particles). In the second step, further growth of particles generated and the gel formation process can be finely tuned. The use of basic catalysts in this step provides more efficient polycondensation and enhances both the strength of the resultant material and its porosity. This technique was successfully applied to the synthesis of mixed aerogels $\text{TiO}_2\text{—SiO}_2$ affording materials with the specific pore volume of 2 $\text{cm}^3 \text{g}^{-1}$.^{178, 179} As has been established recently,^{126, 180, 181} a partial or complete replacement of traditional silicon alkoxides by less expensive ethyl silicate-40 (ES-40, the commercially available form of ethoxypolysiloxane; acidic hydrolysis of ES-40 yields low-molecular-weight polysilicate hydroxide¹⁷⁴) enables the preparation of aerogels $\text{TiO}_2\text{—SiO}_2$ with the specific pore volume as high as 3 $\text{cm}^3 \text{g}^{-1}$.

A substantial drawback of mixed oxides (primarily, of aerogels) is the collapse of their porous structure under the action of polar solvents (water, in particular). As has been demonstrated in a number of studies, the surface hydrophobisation of aerogels or the introduction of hydrophobic additives during the sol–gel synthesis often increases their activity and stability towards the reaction media.^{182–187} Methods for the production of composite mesoporous materials utilising presynthesised TS-1 as a component for the subsequent step of the sol–gel synthesis¹⁸⁸ are currently under development.

III. Methods of physicochemical characterisation of mesoporous titanium silicates

1. X-Ray diffraction

X-Ray diffraction (XRD) gives valuable information in studies of the hydrothermostability of mesostructured titanium silicates.^{88, 110, 116, 121, 125} XRD patterns of mesostructured materials, such as Ti-MCM-41, Ti-MMM, Ti-HMS and Ti-SBA-15, which are characterised by the hexagonal packing of cylindrical (or hexagonal prismatic) mesopores, reveal an intense peak (100)

and three weaker reflections, (110), (200) and (210).^{72, 77, 83, 86, 87} These reflections are indexed in a hexagonal lattice with the unit cell parameter given by $a_0 = 2d_{100}/\sqrt{3}$. Owing to the high degree of structural order in the mesoporous mesophase materials, the lattice parameter a_0 is constant. For the mesostructured systems under consideration this means that the diffraction patterns reveal narrow peaks with full widths at half maximum ($w_{h/2}$) of $(0.07-0.09)^\circ 2\theta$, which is close to the instrumental broadening. According to the experimental finding, the structure of Ti-MMM is more ordered than that of Ti-MCM-41 and Ti-HMS, as described in the literature.¹⁰⁴⁻¹⁰⁶ The peaks observed in the XRD pattern of Ti-MMM are substantially narrower with $w_{h/2} = (0.08-0.18)^\circ 2\theta$ and have symmetrical shapes. Meanwhile, the widths of the (100) reflection are $w_{h/2} = (0.40-0.70)^\circ 2\theta$ and $> 0.50^\circ 2\theta$ for Ti-MCM-41 and Ti-HMS, respectively; in the latter case, only one reflection is observed in the pattern, whereas the former also reveal feebly marked (110), (200) and (210) peaks (Fig. 3).^{75, 104}

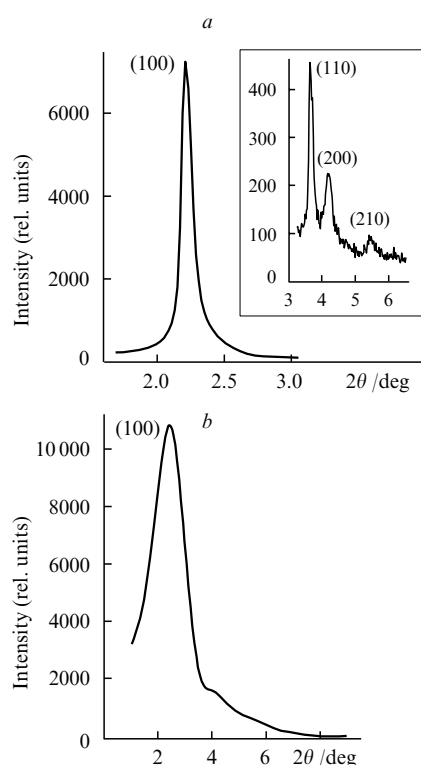


Figure 3. The X-ray diffraction patterns of the mesostructured titanium silicates Ti-MMM (a) and Ti-HMS (b).^{104, 105}

It was established that the lattice parameters of calcined ordered titanium silicates (TS-1, Ti-ZSM-48, Ti-MCM-41 and Ti-HMS) linearly increase with an increase in the titanium content (up to 2%–2.5%).^{35, 45, 87, 104} This experimental fact can be rationalised assuming that the substitution of titanium for silicon is isomorphous. Since the ionic radius of titanium is larger than that of silicon, the substitution should give rise to a dilatation of the unit cell. Based on this observation, it was concluded¹⁸⁹ that the maximum titanium content, which can be accommodated in the TS-1 silicate matrix, is 2.5 mass %. A further increase in the titanium content does not result in a lattice dilatation, which indicates the appearance of non-structural titanium in TS-1. An increase in the titanium content in Ti-MMM and Ti-MCM-41 above 3 mass% gives rise to a significant loss in their structural order, which is manifested in the broadening of peaks in the XRD patterns.^{88, 105, 190} It is of note that this is not accompanied by any noticeable changes in the lattice parameter a_0 .¹²⁵

A recently developed method of structure simulation based on the quantitative analysis of intensities of diffraction reflections made it possible to recover the electron density distribution maps for a number of hexagonal mesostructured materials and reveal important information on the shape of the mesopores, the thickness and electronic structure of the silicate walls and the structure–chemical composition relation for these materials.^{88, 120, 191}

Mixed oxides $\text{TiO}_2\text{--SiO}_2$ are amorphous as regards X-ray diffraction due to the both lack of short- and long-range order.

2. Low-temperature nitrogen adsorption

Low-temperature (at 77 K) N_2 adsorption gives quantitative information concerning the texture of titanium silicate mesoporous materials, including specific surface area (A_m), specific volume (V_m) and mean diameter of the mesopores (d_m). The cylindrical shape of the mesopores in titanium silicates Ti-MCM-41, Ti-MMM, Ti-HMS and Ti-SBA-15 determines a characteristic shape of the adsorption isotherm,^{73, 74, 77, 83, 192} which is classified as type IV according to the IUPAC nomenclature (Fig. 4). Assuming zero scatter in the pore diameters, the range of pressures $\Delta(P/P_0)$, at which the capillary condensation should occur upon nitrogen adsorption, is rather narrow (0.06–0.08). Exactly these small values of $\Delta(P/P_0)$ are typical of type Ti-MMM materials (Fig. 4a), which fully supports the higher degree of their ordering as compared to, for instance, Ti-HMS, where $\Delta(P/P_0) > 0.2$ (Fig. 4b).^{105, 106} The strict constancy of the diameters of all cylindrical mesopores along their lengths requires the adsorption and desorption curves of nitrogen adsorption isotherms to be identical, at least, for $d_m \leq 4.5$ nm.^{88, 193} Investigations into the N_2 adsorption demonstrated that the texture porosity of Ti-HMS is substantially higher than that of Ti-MCM-41. In particular, the specific volumes of mesopores (with a diameter of 10–30 nm) between fine particles of Ti-HMS and Ti-MCM-41 are 1.11 and 0.03 $\text{cm}^3 \text{g}^{-1}$, respectively.⁷³

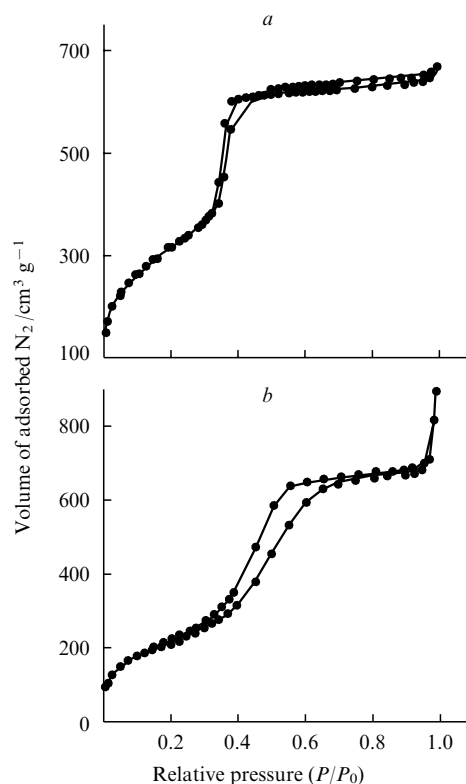


Figure 4. The isotherms of N_2 adsorption on the mesostructured titanium silicates Ti-MMM (a) and Ti-HMS (b).¹⁰⁵

Most typically, aerogels (they also manifest the type IV adsorption isotherms) do not contain micropores, whereas both micro- and mesopores are usually present in xerogels. Most frequently, xerogels manifest the type I isotherms. In order to estimate the texture parameters of mixed oxides $\text{TiO}_2\text{--SiO}_2$ (including aerogels and mesoporous xerogels), which are characterised by a broad size distribution of pores (Fig. 5), a modification of the Kelvin equation is normally applied, which takes into account the thickness of the multilayer of adsorbed molecules (it is the so-called BJH, or Barrett–Joyner–Halenda, method). This calculation, however, neglects pores smaller than 17 Å.⁸⁴

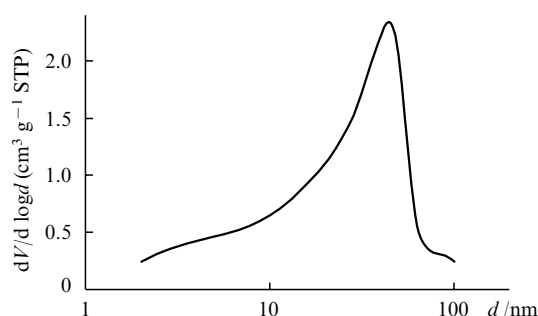


Figure 5. The size distribution of pores in the aerogel $\text{TiO}_2\text{--SiO}_2$ (20% TiO_2) calculated from the desorption part of the N_2 adsorption isotherm (273 K, 1 atm).¹⁶⁴ STP is standart temperature and pressure.

The BJH method is employed by the majority of authors for the calculation of texture parameters of mesostructured titanium silicates. Nevertheless, Fenelonov *et al.*¹⁹⁴ proposed a more accurate method for estimating the specific surface area, volume and size of the mesopores in such materials based on the combined structural and adsorption approach. It assumes that the following relations are held for a hexagonal (honeycomb) structure:

$$a_0 = d_m + h_w,$$

$$d_m = a_0(\varepsilon_m)^{1/2},$$

where ε_m is the porosity determined from the specific area of mesopores and real density (ρ) according to the equation

$$\varepsilon_m = \frac{V_m \rho}{1 + V_m \rho}.$$

The specific volume of mesopores can be estimated from the nitrogen adsorption isotherms measured at 77 K by standard procedures. For the determination of the specific volume V_m , external surface area (A_{ext}) and total surface area (A_{Σ}), the widely adopted comparison method is utilised.¹⁹⁴ The specific surface area of mesopores (A_m) is calculated by the equation

$$A_m = A_{\Sigma} - A_{\text{ext}}.$$

Table 2 lists the values of the texture parameters of four titanium silicates, *viz.*, Ti-HMS, Ti-MMM, Ti-MMM-2 and Ti-SBA-15 with the hexagonal packing of the mesopores, determined by the method described above. These results unambiguously indicate that the degree of structural ordering decreases along the series $\text{Ti-SBA-15} \sim \text{Ti-MMM} > \text{Ti-MMM-2} > \text{Ti-HMS}$. It was found that the size of the mesopores and the thickness of the silicate walls in Ti-SBA-15 are substantially larger than those in Ti-MMM and Ti-MMM-2. The thickness of the walls in Ti-MCM-41 increases with an increase in the titanium content.¹⁹⁵

3. Water adsorption

The adsorption and, consequently, catalytic properties of titanium silicates (*i.e.*, their activities and selectivities) as well as their stability against reaction media are determined to a large extent by their surface structures. According to the published data,^{45, 74, 77, 87, 101, 196, 197} microporous TS-1 possesses a hydrophobic surface, in contrast to mesoporous materials, such as Ti-MCM-41, Ti-HMS, *etc.*, which are characterised by hydrophilic surfaces owing to the presence of a large amount of the SiOH groups. Several types of such groups can occur on the surface of mesostructured silicates, in particular, free, H-bonded and coupled ones.¹⁹⁸ Only free and coupled SiOH groups are active towards the silylation upon hydrophobisation.

The surface hydrophobicity (or hydrophilicity) of titanium silicates can be evaluated using thermogravimetry by measuring mass losses due to water removal from the surface upon controlled heating.^{133, 134} Another modification of the thermogravimetric analysis consists of measuring the mass gain by evacuated or calcined samples in air with a certain humidity.¹³² According to this method, the ability of mesoporous materials to absorb water decreases in the series aerogel $\text{TiO}_2\text{--SiO}_2 > \text{Ti-MMM-2} > \text{xerogel } \text{TiO}_2\text{--SiO}_2 > \text{Ti-SBA-15} > \text{Ti-MMM} \gg \text{hydrophobised aerogel } \text{TiO}_2\text{--SiO}_2$ (Fig. 6). The saturation of identical

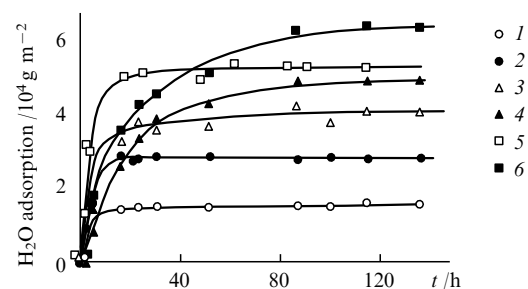


Figure 6. The kinetics of water adsorption on mesoporous titanium silicates (20 °C, relative humidity of 100%).¹³² (1) Hydrophobised aerogel $\text{TiO}_2\text{--SiO}_2$, (2) Ti-MMM, (3) Ti-SBA-15, (4) xerogel $\text{TiO}_2\text{--SiO}_2$, (5) Ti-MMM-2, (6) aerogel $\text{TiO}_2\text{--SiO}_2$.

Table 2. Structural and texture parameters of selected titanium silicate materials calculated from the results of the combined structural-adsorption method.¹⁹⁴

Material	Ti content (mass %) (Si : Ti ratio)	pH ^a	Texture parameters					Structural parameters		Ref.
			A_m /m ² g ⁻¹	A_{ext} /m ² g ⁻¹	V_m /cm ³ g ⁻¹	d_m /nm	h_w /nm	a_0 /nm	$w_{h/2}$ /deg 2θ	
Ti-HMS	2.60 (30)	7.0	627	170	0.89	—	—	—	> 0.5	105
Ti-MMM-2	1.67 (46)	3.0	1147	51	0.74	3.2	1.0	4.2	0.36	116
Ti-MMM	1.53 (49)	9.0	1059	53	0.91	3.8	0.8	4.6	0.078	105
Ti-SBA-15	2.05 (38)	3.2	573	30	1.34	10.6	1.7	12.2	0.054	110

^a pH of the reaction mixture during the synthesis.

cylindrical pores with water proceeds faster and thus the adsorption equilibrium is established over a shorter time.

4. ^{29}Si NMR with the magic-angle spinning

The ^{29}Si nuclear magnetic resonance spectroscopy with line narrowing by the magic-angle spinning (NMR-MAS) provides important supplementary information on the structure of walls in titanium silicates, in particular, on their surface hydrophobicity (hydrophilicity) and the degree of polymerisation of siloxane links (including the possibility of the real-time synthesis monitoring).^{77, 83, 84, 104, 118, 130, 134, 138, 179, 197, 199} Despite some ambiguities in the deconvolution of overlapping signals in the ^{29}Si NMR-MAS spectra into single components, this technique makes it possible to quantify the number Q^n of sites with specific coordination types, *i.e.*, $\text{Si}(\text{OSi})_n(\text{OH})_{4-n}$ ($n = 2-4$) in silicates (Fig. 7). The ratio between Q^n values depends on the degree of condensation of silicon in the silicate walls, which, in turn, is a function of the material preparation procedure. Using this technique, it was demonstrated that fluorides promote the polymerisation of silicon compounds; the addition of fluorides into the reaction mixture during the synthesis enables the preparation of materials with a higher degree of condensation. In particular, in the case of SBA-15, the ratios $Q^3:Q^4$ are 0.34–0.62 and 0.74–0.78 in the presence and in the absence of fluorides, respectively.¹⁹⁹ The solid-state ^{29}Si NMR-MAS was used to establish that the silicate M41S undergoes a structural change under the conditions of hydrothermal treatment such that the degree of polymerisation of siloxane links in the walls increases.¹³⁰ The ^{29}Si NMR-MAS technique is widely applied to quantify the degree of surface silylation of mesostructured materials after their hydrophobisation.^{134, 138, 186, 200}

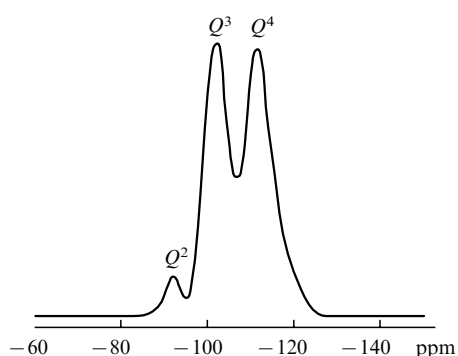


Figure 7. The ^{29}Si NMR-MAS spectrum of the titanium silicate Ti-MCM-41 (2.0% Ti).¹⁰⁴

Similar ratios of Q^n were found for mixed oxides with a low titanium content synthesised by the traditional method in an acidic medium with TEOS as a silicon source^{201, 202} and by the two-step method (see Section II) from ES-40.¹⁸¹ Meanwhile, smaller Q^4 and larger Q^2 and Q^3 were determined by ^{29}Si NMR-MAS for the $\text{TiO}_2\text{--SiO}_2$ samples prepared by the two-step method from TEOS.¹⁷⁹ Based on these results, it was concluded that the utilisation of ES-40 in the synthesis of mixed oxides $\text{TiO}_2\text{--SiO}_2$ increases the degree of silicon self-condensation (which correlates with the number of sites with the coordination type Q^4). It was found that the proportion of Q^4 relative to Q^3 in mixed oxides $\text{TiO}_2\text{--SiO}_2$ increases by approximately 20% (from 40% to 60%) with an increase in the titanium content, while the number of sites with the coordination type Q^2 remains virtually constant (<10%).¹⁸¹ A similar effect was observed by other authors,^{104, 200} which allowed them to conclude that the introduction of a small amount of titanium increases the degree of silicon condensation. However, if the titanium content exceeds a certain

critical value, the degree of silicon condensation decreases and the respective signals in the ^{29}Si NMR-MAS spectra become broader.²⁰⁰

5. Electron microscopy

Scanning electron microscopy (SEM), transmission electron microscopy (TEM) and high-resolution electron microscopy (HREM) are used for the elucidation of the texture and morphological properties of titanium silicates, including the size and shape of particles and pores. As has been established, the particles of Ti-HMS and Ti-MCM-41 are characterised by different morphologies. The former represent small spherical particles with a diameter of 0.2–0.3 μm .⁷⁴ Electron micrographs of Ti-MMM (Fig. 8a), Ti-HMS and Ti-MCM-41 (Ref. 73) samples clearly reveal a long-range-ordered porous structure with a hexagonal packing of identical mesopores. In contrast, a micrograph of Ti-MMM-2 (Fig. 8b)¹¹⁶ reveals domains of ordered mesopores, the degree of their ordering being substantially lower than that in Ti-MMM.

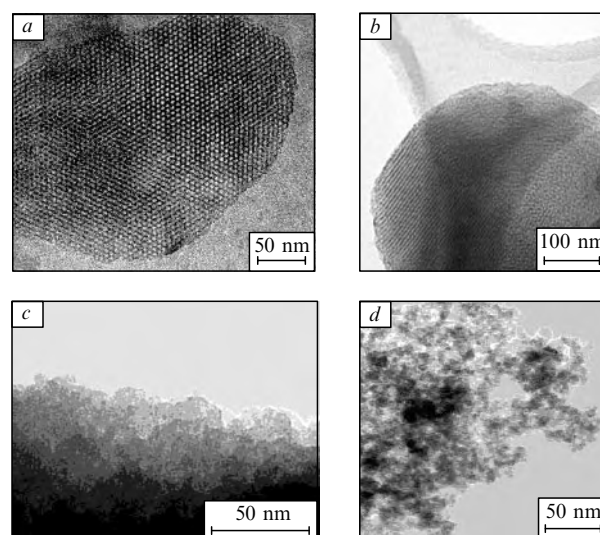


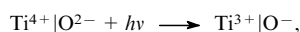
Figure 8. The electron micrographs of Ti-MMM (a), Ti-MMM-2 (b), xerogel $\text{TiO}_2\text{--SiO}_2$ (c) and aerogel $\text{TiO}_2\text{--SiO}_2$ (d).^{116, 181}

Microdomains of crystalline TiO_2 smaller than 1–2 nm in mixed titania–silica, which are invisible for X-ray diffraction, can be identified using HREM.^{81, 183, 203} According to TEM, samples of aerogels $\text{TiO}_2\text{--SiO}_2$ with the titanium content of 2 mass % – 17 mass % represent porous aggregates of interconnected amorphous particles (Fig. 8d).^{81, 181, 203} The size of primary aerogel particles is 3–5 nm and their shape is close to spherical. The size of primary SiO_2 particles in xerogels $\text{TiO}_2\text{--SiO}_2$ is virtually the same as in aerogels, but the xerogels are characterised by a significantly denser packing of the primary particles within the aggregates, which gives rise to a substantial contraction of the interparticle distance (Fig. 8c). Furthermore, the morphology of particles resemble a ‘crumbled glass’.^{81, 181, 203, 204} According to SEM, the use of a combined method for the preparation of mixed oxides $\text{TiO}_2\text{--SiO}_2$ involving suspending a mixed sol in an organic solvent (decanol or hexane) followed by its gelation affords spherical particles with a mean diameter of 50 μm .¹⁷¹

6. Diffuse reflectance optical spectroscopy

Diffuse reflectance ultraviolet (DRUV) spectroscopy is the simplest method for the determination of the electronic state of $\text{Ti}(\text{IV})$ ions in a solid silicate matrix. The charge transfer from a ligand X ($\text{X} = \text{HO}^-$, SiO^- or TiO^-) to a vacant d-orbital of the Ti^{4+} ions (ligand-to-metal charge transfer, LMCT) can be calculated from

the optical electronegativities (χ_{opt}) of the ligand X and the Ti^{4+} ion:



$$\nu = 30000 [\chi_{\text{opt}}(\text{X}) - \chi_{\text{opt}}(\text{Ti})].$$

With an increase in the coordination number of Ti(IV) from 4 to 6, the value of $\chi_{\text{opt}}(\text{Ti})$ increases from 1.85 to 2.05.⁸⁴ Therefore, in the case of Ti(IV) ions in the octahedral environment, the LMCT band should be red-shifted with respect to Ti(IV) ions in the tetrahedral environment.

According to numerous literature data,^{45, 68, 74, 77, 84, 87, 104, 197} the band position in the DRUV spectra of titanium silicates depends, in addition to the coordination number of Ti(IV), on the proximity of other titanium ions, *i.e.*, on the degree of dispersion of the titanium ions over the silicate matrix. The band at 205–208 nm observed in the spectrum of evacuated TS-1 is assigned to isolated titanium ions in the tetrahedral coordination environment.^{41, 45, 197, 205, 206} A treatment of TS-1 with water vapour or ammonia gives rise to an increase in the Ti coordination number, which is manifested in a reversible red-shift of the spectral maximum to 210–225 nm.^{68, 207, 208} The DRUV spectra of mesoporous titanium silicates with the titanium content below 2.5% typically reveal a main peak centred at 220–230 nm sometimes with a shoulder at 250–280 nm.^{74, 77, 84, 87} Table 3 summarises the literature data on the DRUV spectra of TS-1, Ti-MCM-41, Ti-MMM-2, mixed oxides $\text{TiO}_2\text{--SiO}_2$ and anatase (TiO_2). The band centred at 220–230 nm in the spectra of mesoporous titanium silicates is usually attributed to isolated Ti(IV) ions in the penta coordinated, octahedral (Refs 45, 72, 74, 77, 110, 116, 207, 208) or distorted tetrahedral coordination environment.^{104, 107, 209} This assignment is supported by the fact that there is no substantial blue-shift of the band upon the thermal dehydration of Ti-MCM-41 and Ti-HMS.¹⁰⁴ Since the bands corresponding to octahedral Ti(IV) in anatase and rutile are observed at 310–330 nm and 400 nm, respectively,^{45, 84, 197} the red-shift of the main band to this region or emergence of a shoulder in the spectra of titanium silicates is typically interpreted as clusterisation of octahedrally coordinated titanium ions due to the formation of the Ti–O–Ti bonds.^{41, 68, 77, 110, 167, 205, 209, 210} This interpretation agrees with the red-shift of the main band observed with an increase in the titanium content.^{87, 105, 106} Meanwhile, taking into account that the intensity of the band at 270 nm is reduced upon the thermal dehydration or evacuation of titanium silicates, it can be attributed to isolated titanium ions in a highly hydrated or distorted octahedral environment.^{68, 87, 104, 207, 211}

Table 3. Spectral parameters of selected titanium silicates.

Material	Parameter (method)			Ref.
	position of the maximum of the LMCT band /nm (DRUV)	pre-edge peak intensity (%) (XANES)	the average Ti–O bond length /Å (EXAFS)	
TS-1	205–208	75	1.80–1.81	45
$\text{TiO}_2\text{--SiO}_2$	220–240	58–75 ^a (32) ^b	1.81–1.82	84, 181
Ti-MCM-41	220–230	77 ^a (33) ^b	1.81	77
Ti-MMM-2	221	(30) ^b	—	116
Anatase	310–330	< 5	1.94	45

^a Data for evacuated samples. ^b Data for the samples in air.

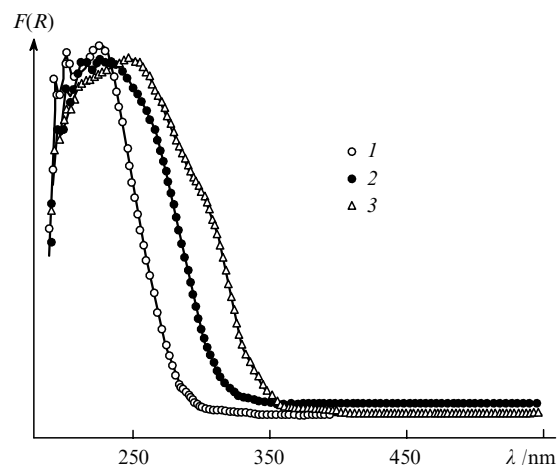


Figure 9. The DRUV spectra of mesoporous titanium silicates with similar titanium loadings.^{11, 125, 126} (1) Ti-MMM (1.89% Ti), (2) aerogel $\text{TiO}_2\text{--SiO}_2$ (1.68% Ti), (3) Ti-SBA-15 (2.05% Ti).

Figure 9 compares the DRUV spectra of Ti-MMM, aerogels $\text{TiO}_2\text{--SiO}_2$ and Ti-SBA-15 with similar titanium contents.[†] According to the spectral assignment described above, Ti-MMM and the aerogel contain isolated titanium ions with the coordination numbers of 4, 5 and/or 6. In the case of Ti-SBA-15, the band is red-shifted and broadened. Taking into account that the spectrum does not change after calcination of the sample, this indicates the presence of clusterised titanium ions.¹¹⁰

7. XANES and EXAFS

XANES spectroscopy (X-ray Absorption Near-Edge Structure) is substantially more expensive than DRUV, and thus it is utilised less frequently. Nevertheless, it gives important supplementary information on the coordination environment of titanium in titanium silicates. XANES spectra at the Ti K-edge of both ordered titanium silicates, such as TS-1,^{45, 197, 207} Ti-Beta,⁴⁵ Ti-MCM-41,^{72, 77, 92, 212, 213} Ti-HMS¹⁰⁴ and Ti-MMM-2,¹¹⁶ and amorphous mixed oxides $\text{TiO}_2\text{--SiO}_2$ ^{84, 181, 214, 215} containing only finely dispersed titanium ions reveal a distinct pre-edge peak (due to the electronic transition $1s \rightarrow 3d$) with the intensity strongly dependent on the degree of hydration of titanium ions (*i.e.*, on their coordination numbers). Dehydrated titanium ions in the tetrahedral coordination environment give rise to the pre-edge peak with an intensity of ~75%–80% of the X-ray absorption edge jump and the full width at half maximum of ~1.5 eV. Meanwhile, the pre-edge peak with the intensity of ~30% corresponds to penta(hexa) coordinated titanium ions, which are formed in the reaction of tetrahedral titanium ions with water.^{45, 77, 92, 104, 197, 200, 207} The XANES spectra of rutile and anatase manifest three weak pre-edge peaks, which thus correspond to clusterised octahedral titanium ions.^{45, 197, 214} Therefore, if a XANES spectrum of a mesoporous titanium silicate material manifests these three weak peaks, then it might be concluded that the sample contains clusterised octahedral titanium ions.^{110, 214, 216, 217} Figure 10 depicts the XANES spectra of mesoporous titanium silicates Ti-MMM-2 and Ti-SBA-15 and of aerogel $\text{TiO}_2\text{--SiO}_2$. The shape and intensity of the pre-edge peaks in the spectra of Ti-MMM-2 and aerogel indicate the presence of isolated penta(hexa) coordinated Ti(IV) ions in these samples, whereas Ti-SBA-15 undoubtedly contains oligomerised titanium ions. Therefore, the XANES results are fully consistent

[†]The DRUV spectra are given in the Kubelka–Munk units $F(R) = (1 - R)^2/2R$ (R is the reflectivity index).

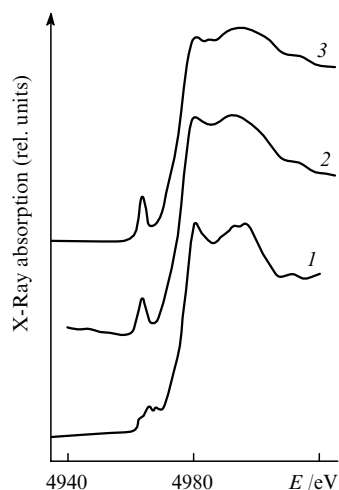


Figure 10. The XANES spectra of mesoporous titanium silicates measured in air.^{110, 116, 190}

(1) Ti-SBA-15 (2.05% Ti), (2) Ti-MMM-2 (1.68% Ti), (3) aerogel TiO₂–SiO₂ (3.68% Ti).

with the aforementioned DRUV spectral data.^{110, 116, 181} According to Table 3, the intensity of the pre-edge peak in the XANES spectra of Ti-MCM-41 and mixed oxides TiO₂–SiO₂ increases upon evacuation, which implies that the titanium ions are present in the samples dominantly in the isolated octahedral sites under atmospheric conditions but are converted into the tetrahedral state upon complete dehydration.^{77, 84, 104, 214}

The elucidation of titanium silicates by means of EXAFS spectroscopy (Extended X-Ray Absorption Fine Structure) reveals information on the number of oxygen atoms and Ti–O bond lengths in the first coordination sphere of the titanium ions and on distances between the titanium ions and second-coordination-shell neighbours. According to EXAFS results, the mean Ti–O bond lengths are 1.79–1.84 Å, 1.89–1.91 Å and 1.94–2.06 Å for tetra-, penta- and hexa-coordinated titanium ions, respectively.^{72, 84, 218}

8. X-Ray photoelectron spectroscopy

Using X-ray photoelectron spectroscopy (XPS), the electronic state of elements and chemical composition of the near-surface layer of catalysts with a thickness of up to 4–5 nm can be probed. The Ti(2p), Si(2p) and O(1s) core-level photoemission lines in titanium silicates have been studied by several authors.^{74, 84, 197} The absence of the Ti(2p) component at a binding energy of 457.4 eV typical of Ti³⁺ ions in the XPS spectra indicates that titanium is present exclusively as Ti⁴⁺ ions. The Ti(2p) core-level photoemission line shows up in the spectra as a spin–orbit doublet Ti(2p_{3/2})/Ti(2p_{1/2}) (Fig. 11). The exact position of the Ti(2p_{3/2}) photoemission line is indicative of the coordination environment of the titanium ions. The photoemission line in a binding energy range of $E_b = 458.4–458.6$ eV is commonly attributed to titanium in the octahedral coordination (as in TiO₂), whereas the line at 459.9–460.2 eV is assigned to isolated titanium ions with the tetrahedral coordination (Refs 45, 72, 74, 84, 197, 219, 220). The XPS spectra of Ti-MCM-41 and Ti-HMS reveal a photoemission line centred at $E_b = 459.9$ eV,⁷⁴ whereas the main component in the spectrum of TS-1 is located at $E_b = 460.2$ eV.⁴⁵ In the case of a catalyst Ti-SBA-15 (with 2.05–7.17 mass % of Ti), the Ti(2p_{3/2}) photoemission line is located at 458.3 eV, which is consistent with the octahedral environment of Ti(IV) ions similar to that in anatase (see Fig. 9).^{45, 74, 96} As a rule, XPS data fully agree with the DRUV spectral results.^{96, 110} A quantitative analysis of intensities of the

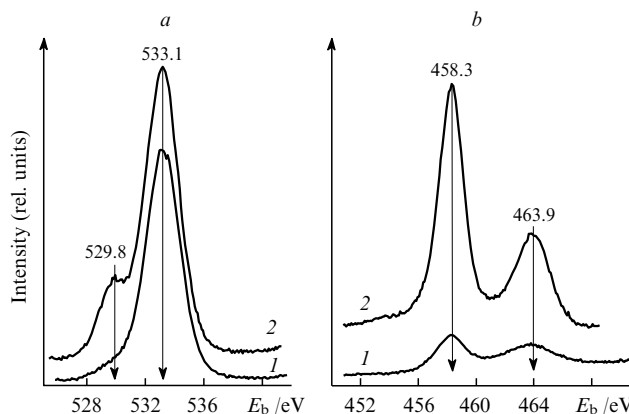


Figure 11. The XPS spectra of the mesoporous titanium silicate Ti-SBA-15 with the Ti loading of 2.05% (1) and 7.17% (2).¹¹⁰ (a) O(1s) core-level photoemission line, (b) Ti(2p) core-level photoemission line.

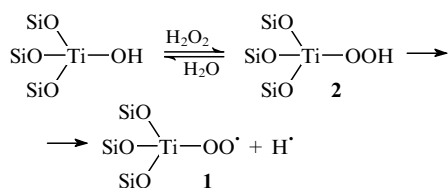
Ti(2p_{3/2}) and Si(2p) core-level photoemission lines yields the Ti:Si atomic ratio on the surface of titanium silicate catalysts.^{84, 110, 197, 219}

As for O(1s) core-level photoemission lines, the peak at $E_b = 532.9–533.3$ eV is attributed to the silicon-bound oxygen atoms, since the oxygen line of SiO₂ appears exactly at this position.^{221, 222} In TiO₂, the respective line is observed at $E_b = 529.8–530.0$ eV and thus this region is attributed to the titanium-bound oxygen atoms.^{45, 74, 221, 222} In the XPS spectra of mixed oxides TiO₂–SiO₂, in addition to the two above lines at $E_b = 530.6$ eV (which corresponds to the Ti–O–Ti bonds) and 532.7 eV (which corresponds to the Si–O–Si bonds), the third line at an intermediate binding energy (531.4 eV) is observed, which is thus assigned to the Ti–O–Si bonds.²¹⁹ The disappearance of this line upon calcination of the samples at 1000 °C is interpreted as a structural transformation of the sample giving rise to TiO₂ agglomerates.

9. Electron spin resonance spectroscopy

Electron spin resonance (ESR) spectroscopy is widely used for the detection and elucidation of properties of paramagnetic transition metal ions incorporated into molecular sieves. Capabilities of this method as regards titanium silicates are limited, since the titanium ions are characterised by the oxidation state 4+ and thus are diamagnetic. Structural information concerning Ti ions can be obtained after reduction of titanium silicate samples with CO, H₂, UV- or γ -radiation, *i.e.*, when the diamagnetic Ti(IV) ions are converted into the paramagnetic Ti(III) ions. This ESR-based approach was utilised to confirm the isomorphous substitution of Ti(IV) for Si(IV) in TS-1.^{223, 224} The ESR spectrum of TS-1 reduced by carbon monoxide manifests an axially symmetric signal with a split $g_{\parallel}$ -component [$(g_{\parallel})_1 = 1.98$, $(g_{\parallel})_2 = 1.97$] and $g = 1.913$ attributable to titanium(III) in the axially distorted tetrahedral coordination. This means that its precursor, *i.e.*, titanium(IV) ions, were also located in tetrahedral sites.²²³ So far, there have been only a few ESR studies on the state of titanium ions in mesoporous titanium silicates.^{225, 226} In particular, the ESR spectrum of γ -irradiated Ti-MCM-41 reveals, in addition to the aforementioned axial signal of tetrahedral titanium ions, an axial signal characterised by values of $g_{\parallel} = 1.898$ and $g_{\perp} = 1.967$ typical of Ti(III) in the distorted octahedral environment.²²⁵

The ESR technique is widely utilised in structural studies of catalytically active particles in particular, of Ti superoxide radicals **1**,^{207, 226–229} which are generated from titanium peroxo complexes **2**.²²⁷



In particular, titanium silicate TS-1 in the presence of H_2O_2 produces an intense anisotropic ESR signal with the following parameters of the g -tensor: $g_{xx} = 2.0030$, $g_{yy} = 2.0099$ and $g_{zz} = 2.0238$. This signal is attributed to superoxotitanium species $\text{Ti}(\text{O})_2$.²⁰⁷ The interaction of TS-1, Ti-Beta, Ti-MCM-41 and amorphous TiO_2 – SiO_2 with aqueous H_2O_2 yields two types of superoxotitanium species (*viz.*, **A** and **B**).^{228, 229} The superoxo particles **A** ($g_{xx} = 2.0023$, $g_{yy} = 2.0090$, $g_{zz} = 2.0266$) and **B** ($g_{xx} = 2.0023$, $g_{yy} = 2.0090$, $g_{zz} = 2.0238$) are characterised by rhombic g -tensors. It was suggested that the type **A** particles are produced from $(\text{SiO})_4\text{Ti}$ species localised inside the silicate walls, whereas the type **B** particles are formed from $(\text{SiO})_3\text{Ti}(\text{OH})$ species localised on the external surfaces of the walls. The fraction of the type **A** species decreases in the series TS-1 > Ti-Beta > amorphous TiO_2 – SiO_2 , whereas the fraction of the type **B** species decreases in the series Ti-MCM-41 > amorphous TiO_2 – SiO_2 > Ti-Beta > TS-1. It was proposed that the type **A** species are involved in the selective oxidation of styrene to the respective epoxide.

10. Raman spectroscopy

The Raman spectra of mesoporous silicate TS-1, which contains only isomorphously substituted isolated titanium ions within the silicate walls, reveal vibrational bands at 799 – 828 cm^{-1} , 467 cm^{-1} , 375 cm^{-1} and 290 cm^{-1} .¹⁹⁷ An increase in the titanium content gives rise to the appearance of four new bands at 140 – 145 cm^{-1} (it is the most intense band; its detection limit as regards TiO_2 is 0.05 mass %), 386 – 400 , 513 – 516 and 637 – 639 cm^{-1} . These bands are attributed to non-structural titanium; likely, they can be interpreted as the initial stage of anatase formation.^{45, 74, 84, 109, 197, 230, 231} Apparently, Raman spectroscopy is one of the most sensitive techniques that enables detection of early stages of the emergence of TiO_2 crystallites in mesoporous titanium silicates.^{110, 111} In particular, the Raman spectrum of Ti-SBA-15 with Ti contents 7.17 mass % manifests an intense peak at 145 cm^{-1} (Fig. 12). Meanwhile, neither X-ray diffraction nor electron microscopy give any evidence of the emergence of the TiO_2 phase in this sample.¹¹⁰

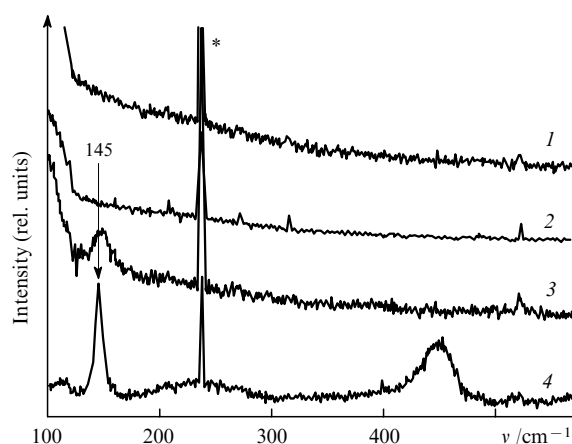


Figure 12. The Raman spectra of mesoporous titanium silicates.¹¹⁰ (1) Ti-MMM (1.89% Ti), (2) Ti-SBA-15 (2.05% Ti), (3) Ti-SBA-15 (7.17% Ti), (4) TiO_2 (anatase). The * mark corresponds to plasma excitation.

11. IR spectroscopy

There are two most informative regions in the IR spectra of titanium silicates: 3200 – 3800 cm^{-1} and 950 – 970 cm^{-1} . Two peaks at 3728 – 3748 cm^{-1} (narrow) and 3222 – 3540 cm^{-1} (broad) are observed in the region of stretching vibrations of the O–H groups.^{132, 197, 220} These bands are attributed to vibrations of the free and H-bonded silanol Si–OH groups, respectively.

The band at 960 cm^{-1} observed in titanium-containing zeolites is often assigned to the Ti–O–Ti bonds sites,^{45, 197, 206} an increase in its intensity with an increase in the titanium content in TS-1 is interpreted as a manifestation of titanium trapping in the silicate walls. However, in the case of mesoporous mesophase titanium silicates, the assignment of this band to the Ti–O–Ti bonds is not ambiguous, since spectra of metal-free mesoporous silicates reveal a band in the same region ascribed to Si–O vibrations of the Si–O–R groups.^{45, 72, 74, 77} Notwithstanding, the intensity ratios of the bands at 960 cm^{-1} and 800 cm^{-1} (the latter is attributed to symmetrical stretching vibrations of the SiO_4 groups) in the spectra of mesostructured titanium silicates is substantially larger than in their titanium-free analogues.⁷⁴

In the case of mixed oxides TiO_2 – SiO_2 , the relative degree of dispersion of titanium over a silicate matrix $D_{(\text{Ti}-\text{O}-\text{Si})}$ can be estimated on the semiquantitative level by analysing the intensity distributions of deconvoluted spectral components at 940 – 960 cm^{-1} (vibrations of the Ti–O–Si groups) and 1210 cm^{-1} (vibrations of the Si–O–Si groups).^{81, 164, 179, 181} Using this technique, it was demonstrated that the level of titanium dispersion decreases with an increase in its content in the mixed oxides.

12. IR spectroscopy of adsorbed CO molecules

The accessibility of active titanium sites for reagents is one of the most important parameter of mesoporous titanium silicate catalysts. Since the typical size of nanopores lies in the nanometre range, the diffusion hindrances to the transport of reagents towards the active sites can be quite decisively ruled out, however a part of the sites can appear trapped inside the silicate walls and thus become inaccessible for reagents. In this regards, the thickness of the silicate walls is an important characteristics of mesostructured titanium silicates. It is known that the wall thickness depends on the preparation procedure. For instance, the walls in Ti-MMM and Ti-MMM-2 are only 0.8 – 1.0 nm thick,^{87, 116, 125} which approximately corresponds to the size of two SiO_4 tetrahedra (the size of an SiO_4 tetrahedron is $\sim 0.4\text{ nm}$).¹⁷³ This means that all titanium sites in these materials should be accessible for reagents. Meanwhile, in the case of Ti-SBA-15, the wall thickness is already 1.5 – 2.0 nm ¹¹⁰ and thus a part of titanium sites can be located inside the walls and become inaccessible for reagents. Presently, there are no direct methods to strictly quantify the accessibility of titanium sites for reagents; however, this parameter can be estimated on a qualitative level using IR spectroscopy of adsorbed CO molecules.¹¹⁰ Three types of bands are observed in the IR spectra of adsorbed CO molecules, *viz.*, at 2135 cm^{-1} (attributed to physisorbed CO), 2153 cm^{-1} (CO forming complexes with the silanol groups)²³² and 2179 cm^{-1} (CO interacting with the Ti cations localised on the surface of the silicate matrix).^{233, 234}

This method was applied to a comparative analysis of Ti-MMM and Ti-SBA-15. It turned out that the band centred at 2179 cm^{-1} in the spectrum of Ti-SBA-15 is substantially less intense than that in Ti-MMM (Fig. 13), *i.e.*, the concentration of surface titanium ions accessible for reagents is lower in this sample.¹¹⁰ As has been established in a similar way, aerogels TiO_2 – SiO_2 are characterised by a larger amount of surface Ti ions than xerogels TiO_2 – SiO_2 .^{181, 204}

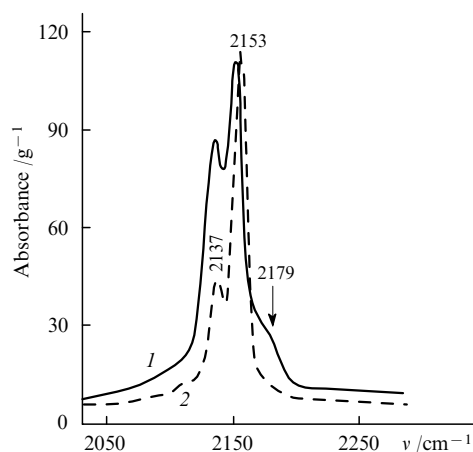


Figure 13. The IR spectra of CO adsorbed on mesoporous titanium silicates at 100 K (the region of C–O vibrations).¹¹⁰ (1) Ti-MMM (1.89% Ti), (2) Ti-SBA-15 (2.05% Ti).

IV. Catalytic properties

Numerous reports on the use of mesostructured titanium silicates and mixed oxides $\text{TiO}_2\text{--SiO}_2$ as catalysts for the selective liquid-phase oxidation of organic substrates have appeared over the last decade. Selected examples of such reactions are given in Table 4. The oxidation of non-functionalised and substituted alkenes, organic sulfides and alkylphenols has been studied most thoroughly. These reactions assisted by mesoporous titanium silicates are considered in more detail below. The problems concerning the efficiency of oxidant utilisation and the stability of catalysts under the reaction conditions, including the possibility of their recycling, are also discussed.

1. Oxidation of alkenes

Mesoporous titanium silicate Ti-MCM-41 has proven to be an efficient catalyst for the selective epoxidation of alkenes with aqueous hydrogen peroxide or alkyl hydroperoxides. Ti-MCM-41 is less active than TS-1 with respect to the oxidation of small molecules with hydrogen peroxide under similar conditions, which is explained by its higher hydrophilicity that prevents efficient adsorption of non-polar substrates.^{45, 69, 72, 77} Furthermore, some reactions easily realisable with TS-1 (in particular, propylene epoxidation, oxidation of linear alkanes and primary amines) are virtually impossible over Ti-MCM-41 and Ti-HMS.^{74, 254, 255} On the other hand, a clear advantage of Ti-MCM-41 and other mesoporous titanium silicates is that they are capable of catalysing the oxidation of bulky organic molecules, which cannot penetrate into the pores of microporous catalysts. In particular, only linear alkenes are efficiently oxidised over TS-1, whereas the majority of mesoporous titanium silicates actively catalyse the oxidation of cyclohexene (typically yielding the respective epoxides and/or diols as primary products).^{105–107, 122, 134, 137, 151, 166–168, 179, 182–185, 212, 235} The introduction of aluminium into the structure of SBA-15 with subsequent titanium deposition enables the deep oxidation of cyclohexene into adipic acid in a 88% yield at a 96% substrate conversion.¹¹⁴

Another advantage of Ti-MCM-41 and other mesoporous titanium silicates over microporous titanium silicates consists of the possible use of relatively large organic hydroperoxides as oxidants.^{41, 69, 72, 77, 78, 81, 166–168, 182–185, 200, 236, 238, 245–253} For instance, mesoporous titanium silicate Ti-MCM-41 manifested higher activity towards the oxidation of α -terpineol and norbornene with *tert*-butyl hydroperoxide as compared to zeolite Ti-Beta^{72, 236} (Table 5). If alkyl hydroperoxides are used as oxidants, titanium silicate catalysts provide higher selectivity of the epoxidation and manifest higher stability, although the oxidation rate is, as a rule, lower than in the case of the oxidation with H_2O_2 .¹²² In some cases, mesoporous titanium silicates

Table 4. Reactions of the liquid-phase selective oxidation of organic compounds with peroxides catalysed by mesoporous titanium silicates.

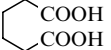
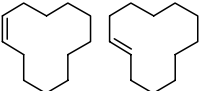
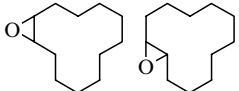
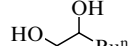
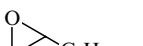
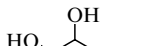
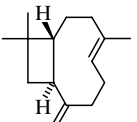
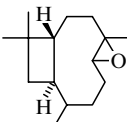
Substrate	Major products	Oxidant	Catalyst	Ref.
	   	H_2O_2 H_2O_2 , Bu^tOOH H_2O_2 H_2O_2 Bu^tOOH Bu^tOOH	Ti-HMS Ti-MCM-41 Ti-MCM-48 Ti-MMM Ti-TUD-1 $\text{TiO}_2\text{--SiO}_2$	235 72, 122 134 105, 106 107 166–168, 182–185 114
		Bu^tOOH	Ti,Al-SBA-15	114
		H_2O_2 , Bu^tOOH ROOH^a , H_2O_2	Ti-MCM-48, Ti-MCM-41 $\text{TiO}_2\text{--SiO}_2$	103, 121 166, 167
$\text{CH}_2=\text{CHBu}^n$	 	H_2O_2 , Bu^tOOH Bu^tOOH	Ti-MCM-41 $\text{TiO}_2\text{--SiO}_2$	69, 72 183, 200
$\text{CH}_2=\text{CHC}_6\text{H}_{13-n}$	 	Bu^tOOH	$\text{TiO}_2\text{--SiO}_2$	124, 200
	 	H_2O_2 , Bu^tOOH Bu^tOOH	Ti-MCM-41 $\text{TiO}_2\text{--SiO}_2$	72, 236 166, 167
		H_2O_2 Ti-MMM	Ti-MMM Ti-MMM-2	105 116

Table 4 (continued).

Substrate	Major products	Oxidant	Catalyst	Ref.
	 	H_2O_2 , Bu^tOOH	Ti-HMS, Ti-MCM-41	237
		Bu^tOOH Bu^tOOH	$\text{TiO}_2\text{--SiO}_2$ Ti-MCM-41	166, 203 238
	  	H_2O_2	Ti-MCM-41, Ti-HMS Ti-MCM-48	104 102
	   	H_2O_2 , Bu^tOOH	Ti-MCM-41, Ti-HMS Ti-SBA-15	235, 239 87
	 	H_2O_2	Ti-MCM-41 Ti-MMM Ti-MMM-2	240 105, 106 116
	 	H_2O_2	Ti-MCM-41	240
	 	H_2O_2	Ti-HMS	241
	 	H_2O_2	Ti-HMS	241
	 	H_2O_2	Ti-MCM-41, Ti-HMS	73, 104
	 	H_2O_2	Ti-HMA	242
	 	H_2O_2	Ti-MCM-41 Ti-MMM Ti-MMM-2 Ti-SBA-15 $\text{TiO}_2\text{--SiO}_2$	243 125, 126 116 99, 110 126, 181
	   	H_2O_2 , Bu^tOOH	Ti-MCM-41	244
		Bu^tOOH	$\text{TiO}_2\text{--SiO}_2$	183–185, 245–247
		Bu^tOOH	$\text{TiO}_2\text{--SiO}_2$	248

Table 4 (continued).

Substrate	Major products	Oxidant	Catalyst	Ref.
		Bu ^t OOH	Ti-MCM-41 TiO ₂ –SiO ₂	72, 236, 238 245, 249
		Bu ^t OOH	Ti-MCM-41	250
		H ₂ O ₂	Ti-MCM-41, Ti-MCM-48	134
		Bu ^t OOH	TiO ₂ –SiO ₂	185, 251
		Bu ^t OOH	TiO ₂ –SiO ₂	249, 252
		Bu ^t OOH	TiO ₂ –SiO ₂	168, 203
		Bu ^t OOH	Ti-MCM-41	253
		Bu ^t OOH	Ti-MCM-41	253
		H ₂ O ₂	Ti-MCM-41, Ti-HMS Ti-MCM-48	104 102

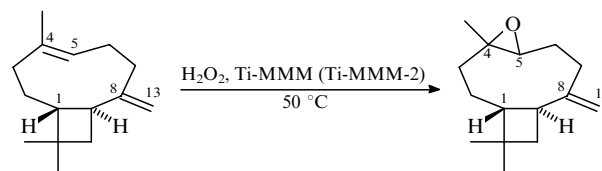
^a R is cumyl.

Table 5. The performance of titanium silicate catalysts in the oxidation of α -terpineol and norbornene with *tert*-butyl hydroperoxide.^{72, 236}

Catalyst				
	reaction time /h	yield (%) epox- ide other ide	reaction duration /h	yield (%) epox- ide alco- hol
Ti-MCM-41	8	32 9	11	42 6
Ti-Beta	8	8 6	11	18 13

prepared by the deposition of titanium onto a silicate matrix in the post-synthesis step demonstrated higher activities than Ti-MCM-41, which can be due to the higher accessibility of titanium sites in the supported catalysts.^{87, 107, 238}

A naturally occurring terpene, (–)-caryophyllene can be oxidised with hydrogen peroxide over Ti-MMM or Ti-MMM-2 to 4,5-monoepoxide derivative with a selectivity of 70%–80% at an alkene conversion of 70%–75% in 4 h.^{105, 116} It is of note that no reaction is observed in the presence of TS-1.¹¹⁶



The oxidation of α -pinene with *tert*-butyl hydroperoxide over Ti-HMS or Ti-MCM-41 yields the respective epoxide with 100% selectivity, although the substrate conversion does not exceed 11%.²³⁷ The epoxide ring can be opened to afford the respective diol using Ti-MCM-41 modified with acid sites (by doping with Al, Fe or B).²³⁷ The oxidation of styrene with hydrogen peroxide catalysed by titanium silicates, such as Ti-MCM-48, Ti-MCM-41 or Ti-HMS, proceeds with the cleavage of the C=C bond to yield benzaldehyde with a selectivity of 77%–85% at a substrate conversion of 10%–28%.^{102, 104} The catalyst Ti-MCM-48, which contains a three-dimensional framework of cylindrical mesopores, manifested higher activity than Ti-MCM-41 towards the oxidation of a number of higher alkenes with hydrogen peroxide.^{103, 134}

MCM-41 modified with titanium in the post-synthesis step is more active than Ti-MCM-41 towards the oxidation of unsaturated terpenic alcohols. The difference in their activities is smaller in the case of alcohols with the OH group located closer to the C=C double bond.²³⁸ Supported titanium catalysts MCM-41 manifest high activity and selectivity in the epoxidation of methyl esters of unsaturated fatty acids with *tert*-butyl hydroperoxide and, furthermore, the epoxidation proceeds stereospecifically.²⁵¹ In the case of Ti-MCM-41, the difference in the oxidation rates of *E*- and *Z*-isomers is substantially smaller than with Ti–SiO₂,

which is probably due to the higher accessibility of channels present in MCM-41 for the *E*-isomer (methyl elaidate) as compared to the *Z*-isomer (methyl oleate).

The catalytic properties of mixed oxides $\text{TiO}_2\text{--SiO}_2$ are best studied by the example of the epoxidation of olefins and oxidation of unsaturated alcohols and ketones with alkyl hydroperoxides (see Table 4). Aerogels synthesised by the low-temperature supercritical drying are more active than both xerogels and aerogels prepared by the high-temperature supercritical drying.¹⁶⁷ The use of aqueous H_2O_2 as an oxidant leads to the titanium leaching from the silicate matrix and the collapse of the porous structure. Therefore, organic hydroperoxide in non-aqueous solvents should preferably be used.¹⁶⁷

In a number of cases, it was possible to improve the selectivity of epoxidation by surface hydrophobisation of mixed oxides and mesostructured titanium silicates (Table 6). The hydrophobisation was accomplished by the surface silylation with hydrophobic reagents^{131–134} or by the introduction of hydrophobic modifiers directly into the silicate matrix during its synthesis.^{182–185} It was shown that the porous structure and activity of hydrophobised mesoporous titanium silicates is better sustained after several cycles of operation. Although hydrophobisation generally decreases the surface of mesopores and often decreases their diameter as well, hydrophobised catalysts exhibit improved activity and selectivity of the oxidation of alkenes and alkanes with respect to their non-hydrophobised precursors.^{131, 133, 134, 182, 184, 187} In addition, the efficiency of H_2O_2 (Refs 131, 134 and 182) and alkyl hydroperoxide utilisation is enhanced.¹³³

Table 6. The effects of the surface hydrophobisation on the performance of titanium silicate catalysts in the epoxidation of cyclohexene.

Catalyst	Reaction time /h	Oxidant	Cyclohexene conversion (%)	Epoxide selectivity ^a (%)	Ref.
Aerogel $\text{TiO}_2\text{--SiO}_2$	2	Bu^tOOH	18	80	184
Hydrophobised aerogel $\text{TiO}_2\text{--SiO}_2$ (see ^b)	2	Bu^tOOH	33	94	184
Ti-MCM-41	0.5	Bu^tOOH	63	91	133
Hydrophobised Ti-MCM-41 ^c	0.5	Bu^tOOH	87	99	133
Ti-MCM-41	3	H_2O_2	0.72	0	134
Hydrophobised Ti-MCM-41 ^d	3	H_2O_2	13	14	134

^a Based on the substrate. ^b The aerogel was modified with phenyl groups during the sol–gel synthesis. ^c The surface of Ti-MCM-41 was silylated with $(\text{CH}_3)_3\text{SiNHSi}(\text{CH}_3)_3$. ^d The surface of Ti-MCM-41 was silylated with $(\text{CH}_3)_3\text{SiCl}$.

The selectivity of epoxidation in the oxidation of unsaturated alcohols, in particular, cyclohexenol, with *tert*-butyl hydroperoxide in the presence of aerogel $\text{TiO}_2\text{--SiO}_2$ was substantially improved by the surface modification of the catalyst with amine and 3-acetoxypentyl groups either during the sol–gel synthesis^{245, 246} or by addition of an amine directly into the reaction mixture.²⁴⁸ The type of the modifier affects the ratio of *cis*- and *trans*-epoxides among the reaction products.

Numerous literature data indicate that the catalytic activity of mesoporous titanium silicates in the alkene oxidation reactions is mainly determined by the state and accessibility of titanium sites. However, it can also be affected by other factors, such as size and shape of crystallites (particles), concentration of surface defects, surface hydrophobicity/hydrophilicity and acid–base properties,

concentration of dopant ions, and so on.^{73, 84, 104, 179} As in the case of titanium-containing zeolites (TS-1, Ti-Beta, *etc.*),^{67, 256} the activity of mesoporous titanium silicates is likely to be strongly affected by the presence of sodium ions therein. The coordination number of titanium ions in the initial catalyst plays no decisive role in the catalytic properties of titanium silicates as regards oxidation with hydrogen peroxide, since tetra-coordinated titanium is unavoidably converted into penta- and hexa-coordinated species in the presence of water (see Sections III.6 and III.7).^{99, 116} Meanwhile, in the case of oxidation with alkyl hydroperoxides in non-polar solvents, titanium silicates originally containing tetra-coordinated titanium can manifest higher activity as compared to titanium silicates comprising titanium ions with the coordination numbers of 5 and 6.^{77, 84, 85} So far, no direct experimental evidence have been obtained that ordered titanium silicates are more active in the oxidation of alkenes and unsaturated alcohols than amorphous mesoporous titanium silicates with a similar titanium loading (provided that titanium is uniformly distributed over the matrix).^{98, 249, 257}

2. Oxidation of thioethers

Mesostructured titanium silicates Ti-MCM-41, Ti-HMS, Ti-MMM and Ti-MMM-2 are efficient catalysts of the oxidation of bulky organic sulfides to the respective sulfoxides and sulfones.^{70, 71, 77, 105, 106, 116, 240, 241} For the oxidation of methyl phenyl sulfide, the activity of titanium silicate catalysts decreases in the series $\text{Ti-MMM} \sim \text{Ti-MMM-2} \gg \text{Ti-SBA-15} > \text{TS-1}$,^{110, 116} the maximum selectivity of the sulfoxide formation is 76% at the 100% substrate conversion. The activity of TS-1 rapidly decreases in the following series of substrates: dimethyl sulfide $\gg$ diethyl sulfide $>$ methyl phenyl sulfide $>$ ethyl phenyl sulfide $\gg$ diphenyl sulfide (for the latter substrate, the conversion is nearly zero).²⁵⁸ Type Ti-Beta zeolites are more active than Ti-MCM-41 in the oxidation of methylphenyl sulfide, whereas the reversed series of activities is observed for bulkier sulfides, *e.g.*, for isopentyl phenyl sulfide.²⁴⁰

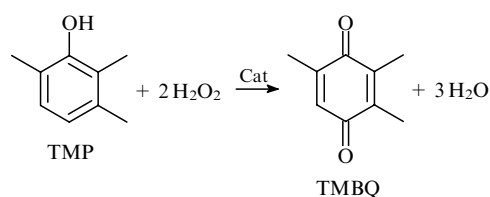
The catalyst Ti-HMS manifested a high activity in the oxidation of benzo- and dibenzothiophenes with hydrogen peroxide;²⁴¹ these reactions are considered as a prospective method for the removal of sulfur-containing compounds from motor fuels alternative to the hydrodesulfurisation.

3. Oxidation of substituted phenols

Mesoporous titanium silicates are efficient catalysts of the oxidation of sterically hindered phenols, such as 2,6-di-*tert*-butylphenol, 2,3,5-trimethylphenol, 2,3,6-trimethylphenol, *etc.*, with hydrogen peroxide to quinones and diquinones (Refs 73–75, 77, 99, 104, 116, 125, 126, 146, 148, 149). According to the experimental results, Ti-HMS is more catalytically active than Ti-MCM-41 towards the liquid-phase oxidation of methyl methacrylate, styrene and 2,6-di-*tert*-butylphenol.^{73, 104} It is of note that the difference in the activities of the catalysts becomes more distinct in the case of bulkier phenols. Probably, this is partly due to the higher texture mesoporosity of Ti-HMS, which facilitates the free transport of bulky substrates.^{73, 104}

According to the recently published results, the oxidation of 2,3,5-trimethylphenol with hydrogen peroxide over microporous Ti-APO-5²⁵⁹ and mesoporous Ti-HMA²⁴² affords 2,3,5-trimethyl-1,4-benzoquinone (which is an intermediate of the vitamin E synthesis) in yields of 85% and 58%, respectively. However, the authors gave no evidence of the heterogeneity of the process and the lack of titanium leaching. In general, the problem of titanium leaching from solid matrices and of structural degradation of the catalysts in the course of oxidation is not adequately addressed by many authors, although it represents the main factor restricting wide practical application of titanium-containing catalysts. The oxidation of 2,3,6-trimethylphenol (TMP) with hydrogen peroxide and *tert*-butyl hydroperoxide has been comprehensively studied^{110, 116, 125, 126} in the presence of diverse mesoporous titanium silicates, including mixed oxides

TiO₂–SiO₂ (both aerogels and xerogels), Ti-MMM, Ti-MMM-2 and Ti-SBA-15.



A new method for the synthesis of 2,3,6-trimethyl-1,4-benzoquinone (TMBQ) by the oxidation of TMP with hydrogen peroxide in the presence of mesoporous titanium-containing catalysts has been elaborated recently, which provided a selectivity as high as 98% at the 100% TMP conversion.¹⁸⁰ The main by-product of this reaction is 2,2',3,3',6,6'-hexamethyl-4,4'-biphenol; its yield increases with a decrease in temperature of the reaction mixture and an increase in the [TMP]:[Ti] ratio. No further substrate conversion occurs after withdrawal of the catalyst by the rapid filtration of the reaction mixture (Fig. 14). This, coupled with the results of the chemical analysis, gives strong evidence that the oxidation proceeds exclusively on the catalyst surface and that there is no noticeable leaching of Ti(IV) from the silicate matrix.^{125, 126}

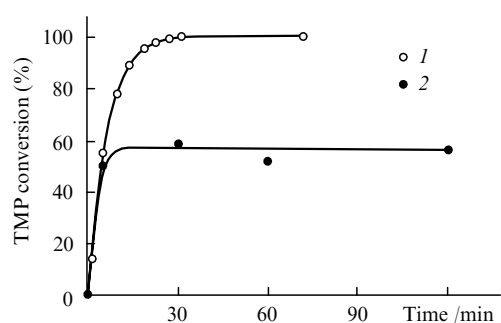


Figure 14. The kinetics of TMP oxidation with hydrogen peroxide in the presence of Ti-MMM.¹²⁵

Reaction conditions: 0.1 mol litre⁻¹ of TMP, 0.7 mol litre⁻¹ of H₂O₂, 1.3 × 10⁻² mmol of Ti, 3 ml of MeCN, 80 °C;

(1) without filtration, (2) the catalyst is removed by filtration in 5 min after the start of the reaction.

The activity of different types of mesoporous titanium silicates (aerogel TiO₂–SiO₂, xerogel TiO₂–SiO₂, Ti-MMM, Ti-MMM-2 and Ti-SBA-15) towards the oxidation of TMP per active catalytic site decreases with an increase in the titanium loading of the catalysts (Fig. 15a). This dependence can be rationalised taking into account that the level of dispersion of titanium over the silicate matrix decreases with an increase in the titanium loading, which gives rise to the formation of less reactive Ti–O–Ti bonds, as evidenced by the red-shift of the absorption band in the DRUV spectra. As has been already stated above, the degree of dispersion of titanium is one of the main parameters determining the catalytic activity of titanium silicates: the higher the degree of dispersion, the higher the activity (Refs 77, 84, 125, 126, 167, 168, 203).

The activity of catalysts with similar concentrations of titanium decrease in the following series: aerogel TiO₂–SiO₂ > Ti-MMM ~ Ti-MMM-2 > xerogel TiO₂–SiO₂ >> Ti-SBA-15 > TS-1. This activity series correlates well with the size of mesopores in the respective materials and also with the apparent activation energies of the reaction (*E*_a).^{125, 181, 260} In particular, the activation energies are 81 kJ mol⁻¹ and 60 kJ mol⁻¹ over the aerogel TiO₂–SiO₂ and Ti-MMM catalysts, respectively. Therefore, the oxidation of TMP with hydro-

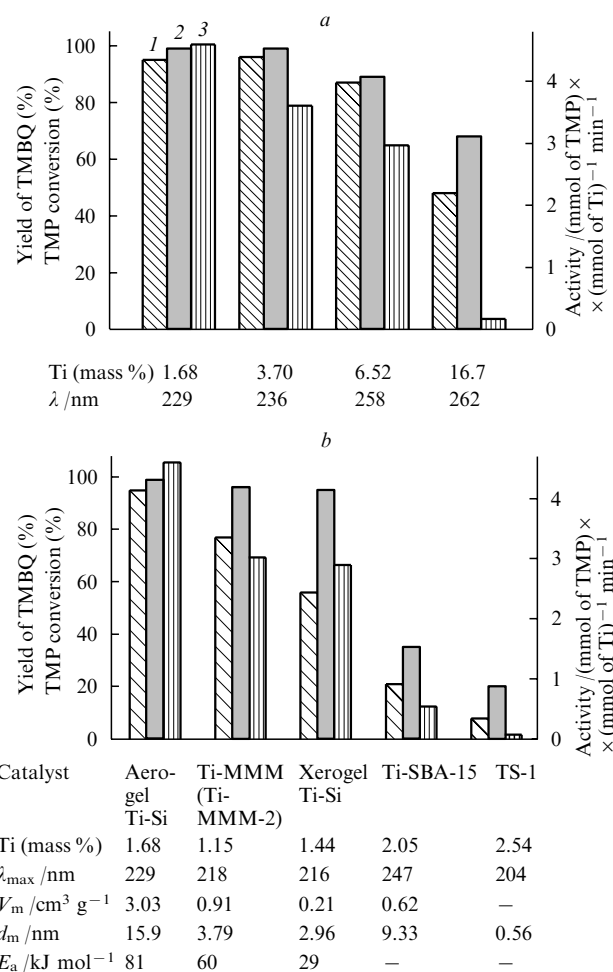


Figure 15. The performance of aerogels TiO₂–SiO₂ with various titanium loadings (a) and different mesoporous titanium silicates with similar titanium concentrations (b) in the catalytic oxidation of 2,3,6-trimethylphenol with hydrogen peroxide.^{110, 116, 125, 126, 181}

Reaction conditions: 0.1 mol litre⁻¹ of TMP, 0.013 mmol of Ti, 0.35 mol litre⁻¹ of H₂O₂, 3 ml of MeCN, 80 °C;

(1) the yield of TMBQ, (2) the conversion of TMP in 20 min after the start of the reaction, (3) the activity.

gen peroxide in the presence of these catalysts proceeds in the kinetic regime and is not limited by diffusion processes. In the case of the xerogel TiO₂–SiO₂, which is characterised by substantially smaller pores, the activation energy is *E*_a = 29 kJ mol⁻¹, which is rather typical of diffusion limited processes.²⁶⁰ Ti-SBA-15 represents an exception to this correlation, since its activity is substantially lower as compared to other mesoporous titanium silicates despite the large size of the mesopores therein. Probably, this is due to both the low degree of titanium dispersion and large thickness of the silicate walls in this material, which is in accord with the IR spectral analysis of adsorbed CO molecules (see Section III.12).¹¹⁰ It is important to note that the structural ordering of mesoporous titanium silicates does not correlate with their activities. For instance, Ti-HMS is more active than Ti-MCM-41,¹⁰⁴ whereas Ti-MMM-2 and Ti-MMM manifest similar activities,¹¹⁶ although Ti-MCM-41 and Ti-MMM are more structurally ordered than Ti-HMS and Ti-MMM-2, respectively.

4. The efficiency of H₂O₂ utilisation

The activity of mesoporous titanium silicate catalysts in the oxidation correlates with the rates of H₂O₂ decomposition in the absence of organic substrates: aerogel TiO₂–SiO₂ >

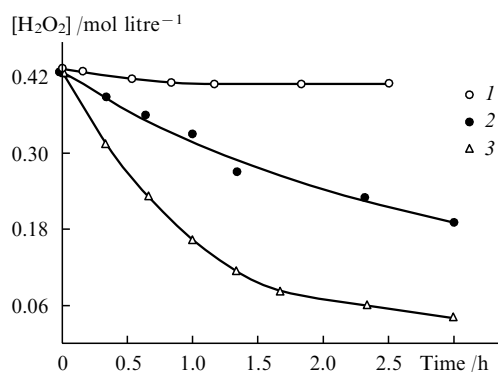


Figure 16. The kinetics of decomposition of H_2O_2 in the presence of Ti-SBA-15 (1), Ti-MMM (2) and aerogel $\text{TiO}_2\text{-SiO}_2$ (3).²⁰⁴ Reaction conditions: 1.29 mmol of H_2O_2 , 0.013 mmol of Ti, 3 ml of MeCN, 80 °C.

$\text{Ti-MMM} > \text{Ti-SBA-15}$ (Fig. 16).²⁰⁴ The efficiency of hydrogen peroxide utilisation (H_2O_2 selectivity) can be estimated as the ratio of the rates of H_2O_2 consumption by the target oxidation of an organic substrate and the concomitant non-productive decomposition of H_2O_2 over the catalyst. Since this ratio clearly depends on the substrate type and/or reaction conditions, the efficiency of H_2O_2 utilisation is also a function of these parameters (Fig. 17). The more active the substrate, the higher the efficiency of H_2O_2 utilisation. In particular, the efficiencies of H_2O_2 utilisation are 45% and 75% in the oxidation of cyclohexene and more nucleophilic caryophyllene, respectively.

The H_2O_2 selectivity is an important parameter of a catalytic process. In order to improve the efficiency of H_2O_2 utilisation, large-scale industrial oxidation processes of petrochemical synthesis are usually accomplished with a large excess of an organic substrate (which is typically less expensive than the oxidant). In contrast, substrates often appear more expensive than oxidants in fine chemical synthesis processes, such that it appears more cost-effective to use an excess of H_2O_2 (which partly decomposes non-productively) in order to enhance the substrate conversion and minimise the costs of product isolation and purification.^{26, 47} In certain cases, the efficiency of H_2O_2 utilisation can be improved by the surface hydrophobisation of mesoporous titanium silicates.^{131, 133, 134, 182}

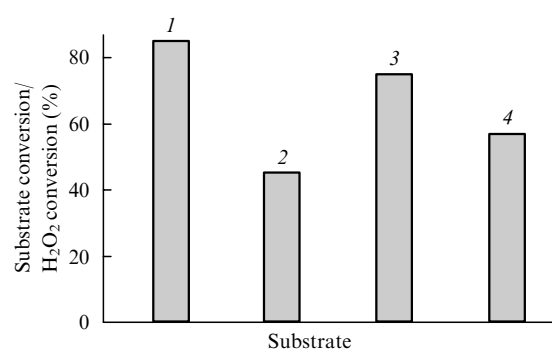


Figure 17. The efficiency of H_2O_2 utilisation in the oxidation of various organic substrates over Ti-MMM.²⁰⁴ Substrates: (1) methylphenylsulfide (20 °C), (2) cyclohexene (50 °C), (3) caryophyllene (50 °C), (4) 2,3,6-trimethylphenol (80 °C).

5. The problem of stability of titanium silicate catalysts

As has been mentioned above, the leaching of the active component and consequent loss of activity of catalysts is one of the most serious problems in the practical use of liquid-phase catalytic oxidation with aqueous H_2O_2 . The stability of titanium silicates against the titanium leaching depends both on the properties of the titanium silicate itself (the degree of dispersion of titanium over the silicate matrix, thickness of the silicate walls, surface hydrophobicity, etc.) and the reaction conditions (solvent type, H_2O_2 concentration, temperature, composition of the reaction products, etc.).¹²⁴ In particular, titanium is leached from Ti-MCM-41^{122, 250} and mixed oxides $\text{TiO}_2\text{-SiO}_2$,^{167, 203} if methanol is used as a solvent. Meanwhile, aerogels and xerogels $\text{TiO}_2\text{-SiO}_2$ and Ti-MMM proved stable against the titanium leaching in acetonitrile media.^{105, 106, 125, 126} Notwithstanding, the activity of the catalysts decreased substantially upon recycling, despite the lack of titanium leaching.

According to the systematic investigations into the factors affecting the stable functioning of mesoporous titanium silicate catalysts upon repetitive use, the main reason for the loss of activity of Ti-MMM catalysts and mixed oxides $\text{TiO}_2\text{-SiO}_2$ is the negative impact of water (or aqueous hydrogen peroxide) on the hydrophilic surface of the catalysts.^{106, 110, 125, 126} As has been established by small-angle X-ray diffraction and N_2 adsorption, the structure of Ti-MMM degrades as a result of treatment with water (Fig. 18). The structural decomposition of Ti-MCM-41 in

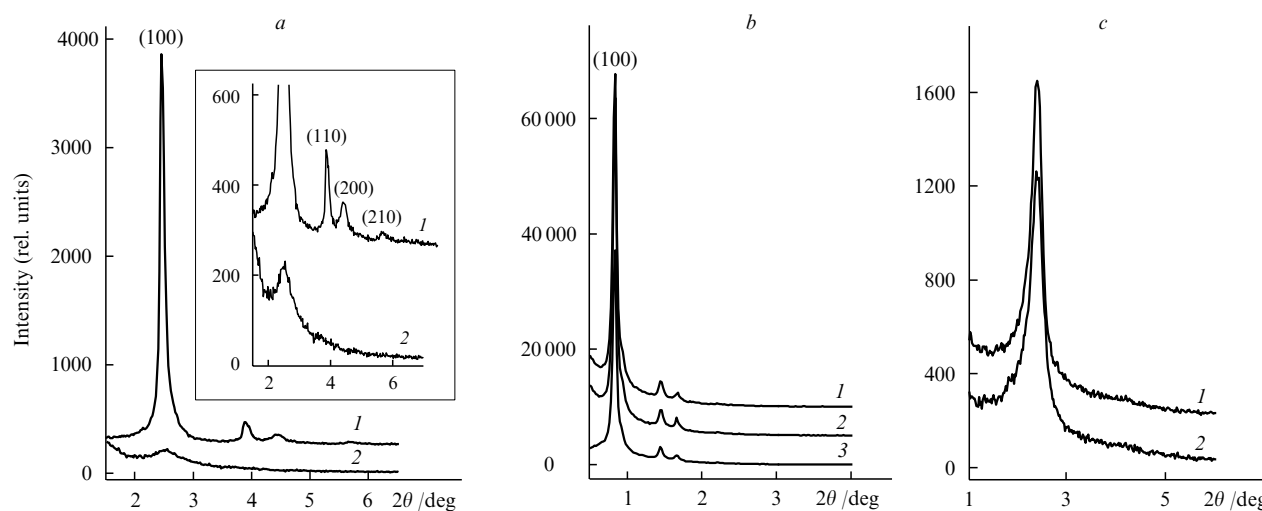


Figure 18. X-Ray diffraction patterns of Ti-MMM (a), Ti-SBA-15 (b) and Ti-MMM-2 (c) before (1) and after their treatment with H_2O (2) or with 30% aqueous H_2O_2 in MeCN (3).^{110, 116, 125}

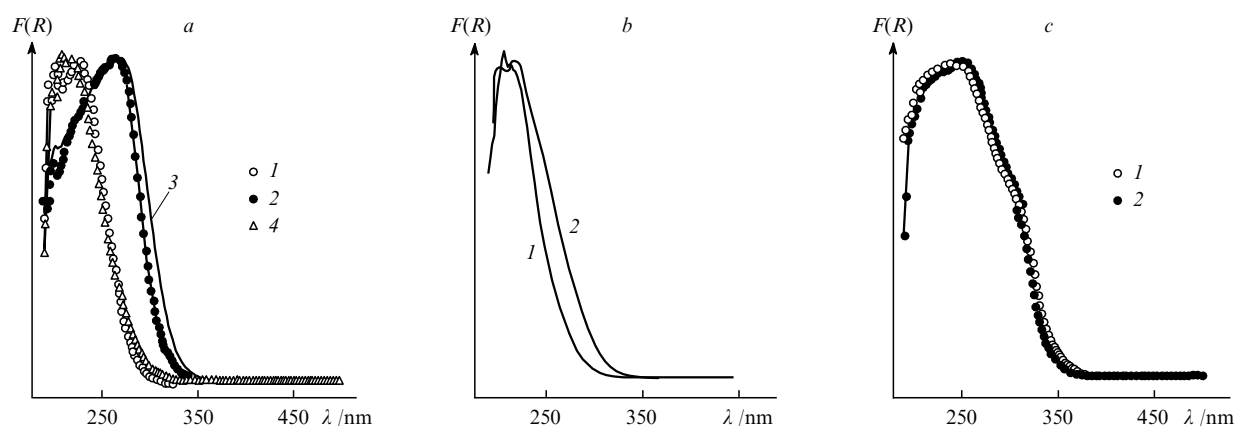


Figure 19. The DRUV spectra of Ti-MMM (1.89% Ti) (a),¹²⁵ Ti-MMM-2 (1.67% Ti) (b)¹¹⁶ and Ti-SBA-15 (2.05% Ti) (c).¹¹⁰ (1) Prior to treatment, (2) after the treatment with 30% aqueous H_2O_2 in MeCN, (3) after the second treatment with the same solution, (4) after the treatment with a 74% solution of H_2O_2 in MeCN. Treatment conditions: 1.3×10^{-2} mmol of Ti, $0.35 \text{ mol litre}^{-1}$ of H_2O_2 , 3 ml of MeCN, 80°C , 1 h.

the course of phenol hydroxylation¹²³ and upon its treatment with water vapour was revealed by X-ray diffraction.¹²¹ In the case of mixed oxides TiO_2-SiO_2 , a decrease in the specific surface area and volume of the mesopores was detected following their treatment with a 30% solution of H_2O_2 in MeCN.¹²⁶ The collapse of the porous structure gives rise to 'oligomerised' forms of titanium, which are inert in the oxidation, as evidenced by the irreversible red-shift of the band in the DRUV spectra of Ti-MMM and mixed oxides TiO_2-SiO_2 after their treatment with H_2O_2 in MeCN (Fig. 19). The emergence of 'oligomerised' forms of titanium was also registered by DRUV spectroscopy in zeolites Ti-Beta and Ti-MWW after several catalytic cycles,^{53, 68} although Ti-MWW exhibited slightly higher stability against the hydrogen peroxide action than Ti-Beta. A similar conclusion on the conversion of isolated titanium ions into 'oligomeric' agglomerates in the course of the oxidation with H_2O_2 was derived from the comparative analysis of the XANES spectra of Ti-MCM-41 before and after the reaction.^{123, 212}

A decrease in the water concentration in the oxidation of TMP increases the catalyst stability but gives rise to an overall loss of its activity (Fig. 20). The surface hydrophobisation of titanium silicate catalysts gives rise to similar effects.²⁰⁴ Although a decrease in water concentration in the reaction mixture has a positive effect on the oxidation of non-polar substrates (e.g., alkenes), the efficient oxidation of polar substrates requires a certain amount of H_2O . Water is involved in the formation of the Ti-OH bonds manifesting high reactivity towards H_2O_2 ,^{261, 262} thus promoting the generation of active oxidising species, viz., titanium hydroperoxo complexes.^{43, 45, 263} As has been established recently,²⁶⁴ water also promotes the adsorption of H_2O_2 on titanium sites in TS-1.

In contrast to Ti-MMM, Ti-MMM-2 and Ti-SBA-15 synthesised in weakly acidic media can be considered as hydrothermostable materials. According to the X-ray diffraction data, no structural changes with Ti-MMM-2 and Ti-SBA-15 are observed after their boiling in water for several hours (see Fig. 18). The DRUV spectrum of Ti-SBA-15 does not change at all after treatment with 30% aqueous of H_2O_2 in acetonitrile at 80°C . In the case of Ti-MMM-2, the DRUV band is only insignificantly broadened, although its position remains constant (see Fig. 19). Furthermore, the DRUV spectrum of Ti-MMM-2 reveals no changes, if hydrogen peroxide treatment is performed at a lower temperature (e.g., at 20°C), which implies that the initial state of the titanium ions in the samples is not affected. The state of the titanium ions in Ti-MMM-2 also remains unaffected after treatment with boiling water, in contrast to, for example, Ti-MMM¹²⁵

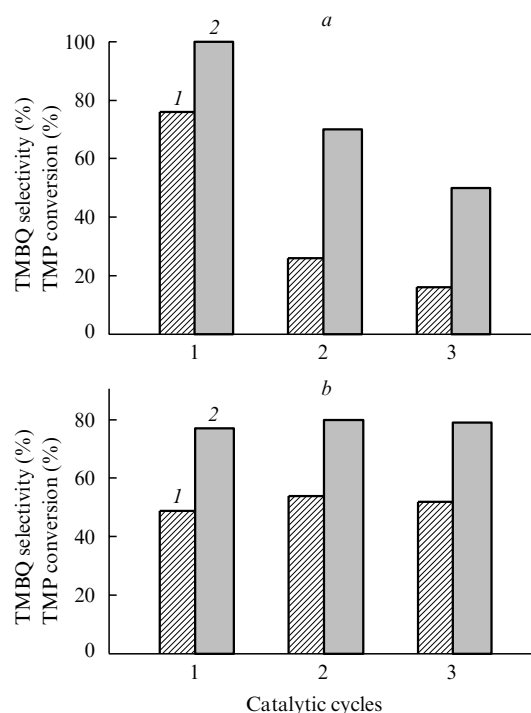


Figure 20. The performance of Ti-MMM (1.89% Ti) in the oxidation of 2,3,6-trimethylphenol with 30% (a) and 84% (b) aqueous solutions of H_2O_2 .¹²⁵

For the reaction conditions, see caption to Fig. 15.

(1) TMBQ selectivity, (2) TMP conversion in 30 min (a) and in 100 min (b) after the start of the reaction.

and Ti-TUD-1,¹⁰⁷ which exhibit red-shifts of the respective bands in the DRUV spectra. In contrast to Ti-SBA-15, the silicate walls in Ti-MMM-2 are sufficiently thin and titanium is smoothly dispersed over the matrix. These factors are responsible for the high catalytic activity of this material, which is comparable to that of hydrolytically unstable Ti-MMM in the first catalytic cycle. The structural stability provides the steadiness of the catalytic properties of the material. In contrast to Ti-MMM, Ti-MMM-2 can be repeatedly used in the reaction without significant losses of activity (Fig. 21), which makes it a promising catalyst for the oxidation of large organic molecules.

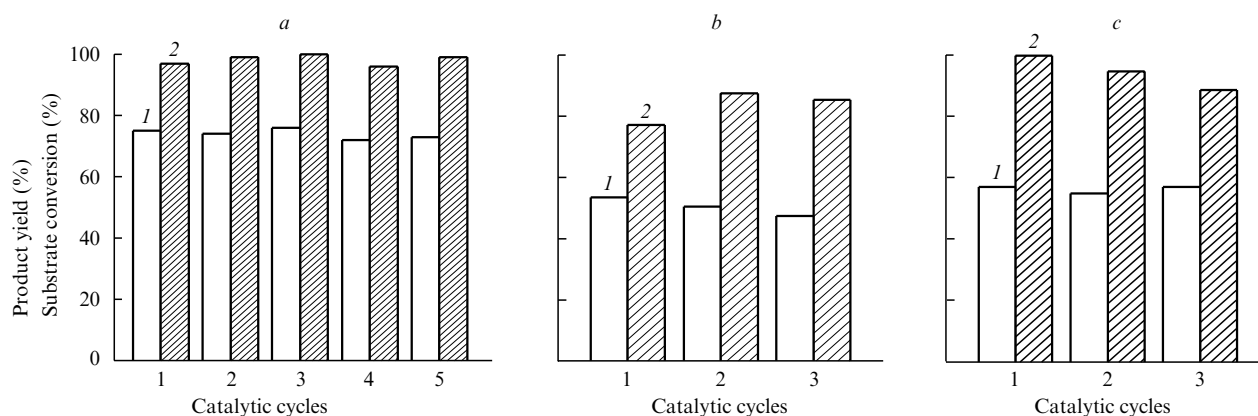


Figure 21. The performance of Ti-MMM-2 (1.67% Ti) in the oxidation reactions of methyl phenyl sulfide to the respective sulfoxide (a), of caryophyllene to the respective epoxide (b) and of 2,3,6-trimethylphenol to 2,3,6-trimethyl-1,4-benzoquinone (c) with hydrogen peroxide.¹¹⁶ Reaction conditions: (a) 0.1 mol litre⁻¹ of MeSPH, 0.12 mol litre⁻¹ of H₂O₂, 6 × 10⁻³ mmol of Ti, MeCN, 20 °C; (b) 0.1 mol litre⁻¹ of caryophyllene, 0.11 mol litre⁻¹ of H₂O₂, 6 × 10⁻³ mmol of Ti, MeCN, 50 °C; (c) see caption to Fig. 15. (1) The product yield, (2) substrate conversion in 35 min (a), 4 h (b) and 30 min (c) after the start of the reaction.

V. Conclusion

A large number of mesoporous titanium silicates, both ordered and amorphous, have been synthesised over the last decade and reliable procedures of their detail structural characterisation using a combination of physicochemical instrumental methods have been elaborated. The use of small-angle X-ray diffraction, electron microscopy and low-temperature nitrogen adsorption gives valuable insights into the real structure of these materials (including such parameters as the size, shape and packing type of the mesopores, degree of ordering, thickness of the silicate walls, particle size, and so on). The degree of surface hydrophobicity/hydrophilicity of titanium silicate materials can be assessed using the gravimetric analysis of water adsorption/desorption or ²⁹Si NMR-MAS spectroscopy. The combined application of spectroscopic techniques (DRUV, XANES, IR, Raman, XPS, ESR, and some others) sheds light upon the structure of active titanium sites in the catalysts (*i.e.*, the coordination environment and degree of their dispersion over the silicate matrix). IR spectroscopy of adsorbed CO molecules gives qualitative comparative information on the accessibility of titanium ions in various materials, however methods for the quantitative analysis of this parameter are yet to be developed.

Mesoporous titanium silicates are promising catalysts for the oxidation of large organic molecules with peroxides owing to the suitable pore size and high specific surface area. Using such catalysts, the selective oxidation of different classes of organic substrates has been successfully implemented, in particular, the oxidation of alkenes to epoxides and diols, of unsaturated alcohols, ketones and esters to epoxides, of organic sulfides to sulfoxides and sulfones, of alkylphenols to quinones and dibenzoquinones, *etc.* It has to be stressed that both the characteristics of specific catalysts (titanium loading, concentration of dopant ions, thickness of the silicate walls, specific surface area, diameter and specific volume of mesopores, *etc.*) and the reaction conditions have to be taken into account in the comparative analysis of the literature data on the catalytic activities of different types of mesoporous titanium silicates in the oxidation reactions. All available information obtained by the set of physicochemical instrumental techniques should be consistently analysed in order to understand the differences in the activities of specific catalysts.

Systematic investigations into the mutual relationships between the structural, texture and catalytic properties of mesoporous mixed oxides TiO₂–SiO₂ and mesostructured titanium silicates established that it is the degree of dispersion (isolation) of titanium ions over the silicate matrix and the accessibility of the active titanium sites for reagents, which is in turn determined by

the size of pores and the thickness of the silicate walls, that are the key factors governing their activity as catalysts. In contrast, the coordination number of titanium ions is apparently of low importance in the case of the oxidation with aqueous hydrogen peroxide, since tetrahedral titanium ions are effectively converted into penta- and hexa-coordinated species in the presence of water. So far, there have been no direct experimental evidence that ordered mesoporous titanium silicates are any superior to amorphous titanium silicates with similar titanium loadings in terms of the catalytic activity. The surface acid–base properties of titanium silicates strongly affect their activity and selectivity towards certain reactions. The systematic investigations into this phenomenon can shed light upon the origin of the selectivity manifested by mesoporous titanium silicates in the oxidation of various classes of organic substrates.

For the majority of presently known mesoporous titanium silicates, the problem of their stability against hydrolysis is a very urgent question, which restricts wide practical applications of these materials to the liquid-phase oxidation of different substrates with aqueous hydrogen peroxide. The surface hydrophobisation is a promising means to improve upon the structural stability of the catalysts. Hydrophobised catalysts manifest higher activity towards the oxidation of non-polar and weakly polar compounds (*e.g.*, alkanes and alkenes) than their non-hydrophobised precursors. The reverse trend is observed for the oxidation of polar substrates (*e.g.*, alkylphenol or naphthols). A substantial progress in solving the problem of the hydrolytic instability of mesoporous titanium silicates has been made with the synthesis of a thermohydrostable catalyst Ti-MMM-2, which compares well with Ti-MCM-41 and Ti-MMM in terms of activity but is, unlike them, stable against the action of water.

The authors are grateful to Professor V B Fenelonov and PhD M S Melgunov for valuable comments and to PhD M P Vanina for the help in the manuscript preparation.

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Molecular assemblies of polymethine dyes

B I Shapiro

Contents

I. Introduction	433
II. Polymethine state of dyes	434
III. Dye aggregation in solution	434
IV. Dye aggregation on silver halide microcrystals	440
V. Conclusion	453

Abstract. Aggregation processes of polymethine dyes in solutions and a heterogeneous system of AgHal microcrystals are considered. The mechanism of formation of nanoaggregates is discussed. The relationship between the aggregation and the structure of dye molecules is demonstrated. The aggregation is shown to depend on the composition and habit of AgHal microcrystals and the emulsion factors of real photographic systems. The structures and energy levels of aggregates are surveyed. The mechanism of photographic action of aggregates and ways of increasing their photochemical activity are discussed. The bibliography includes 272 references.

I. Introduction

Polymethine (cyanine) dyes became of practical interest after they have been used extremely successfully as spectral sensitizers of silver halide photographic materials. Spectral sensitisation was discovered by H Vogel more than 130 years ago.¹ It should be noted that Vogel was the first to demonstrate the uniqueness of polymethine dyes as spectral sensitizers. In spite of numerous attempts to employ other classes of dyes, only cyanines have found use in photographic technology.

In the course of development of spectral sensitisation, optimal polymethine dyes (Dy) were selected. Initially, dyes have been used primarily in the molecular (M) form. More recently, these dyes began to be used in the aggregated state. As demonstrated in numerous publications (see, for example, the reviews^{2–6}), polymethine dyes capable of forming supramolecular structures, the so-called J-aggregates, have the highest photographic efficiency. Nowadays, most black-and-white and colour photographic materials are spectrally sensitised in the visible spectral region with J-aggregates of polymethine dyes.

The J-aggregation of polymethine dyes is a bright example of self-organisation of organic matter, which is somewhat similar to biological processes. Drawing the analogy between the dye aggregation and self-organisation in living matter, it should be

noted that helical structures can also appear in the former case.⁷ It should be emphasised that J-aggregation is a simpler phenomenon than self-organisation in living organisms, at least because molecules of the same (or related) compounds interact with each other, unlike genes or protein molecules whose helices contain different nucleotides or amino acids, respectively. Hence, the dye aggregation has attracted attention of researchers attempting both to understand general features of aggregation and to find application of the resulting self-organised systems. As mentioned above, some of these systems have long been in use in photographic processes.

Complicated organised structures of organic molecules (molecular assemblies) are of considerable interest primarily because such structures hold promise for processing and storage of large data sets. This phenomenon is used by nature. Reliable information libraries, such as DNA molecules in living organisms, are bright examples. It should be noted that biological self-organisation processes occur in aqueous solutions containing dissolved salts. Life originated from a salt solution of the primeval ocean. The present review shows that salts play an exceptionally important role also in the polymethine dye aggregation.

In the period of extensive development of optical methods for data recording and storage, molecular assemblies consisting of organic dyes have attracted considerable interest. Of all classes of organic dyes, polymethine dyes are distinguished by a high intensity of light absorption and tendency to aggregation.

It is commonly accepted that J-aggregation of cyanine dyes in solutions was virtually simultaneously discovered by Jelly⁸ and Scheibe.⁹ However, Sheppard has observed this phenomenon much earlier.^{10,11} He revealed systematic changes in the absorption curves of cyanine dyes in various solvents and found substantial changes in absorption in aqueous solutions. Jelly and Scheibe also found that absorption maxima are either shifted to shorter wavelengths (H-aggregation) or sharply shifted to longer wavelengths (J-aggregation) relative to the absorption maximum of the molecular form with increasing concentration of dye solutions.

The J-aggregation process is most typical of polymethine dyes. Hence, before proceeding to problems of aggregation, it is worthwhile to consider the specific features of polymethine dyes, which distinguish these compounds from other classes of dyes both by the optical properties and tendency to self-organisation as highly ordered aggregates. The case in point is the so-called polymethine state associated with the specific structural features of polymethine dyes.

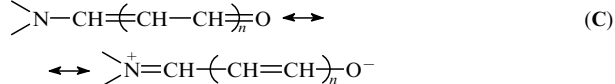
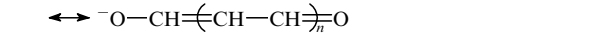
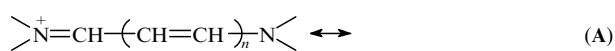
B I Shapiro Scientific Centre 'NIIKHMIFOTOPROEKT', Leningradsky prosp. 47, 125167 Moscow, Russian Federation. Fax (7-495) 258 75 98, tel. (7-495) 157 04 26, e-mail: bishapiro@mail.ru

Received 15 April 2005

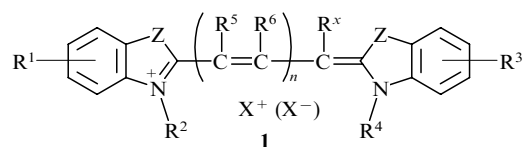
Uspekhi Khimii 75 (5) 484–510 (2006); translated by T N Safonova

II. Polymethine state of dyes

Polymethine dyes (PMD) contain either of the following three main chromophoric systems: the amidinium ion (A), the carboxyl ion (B) and the bipolar amidic system (C)



Schemes A–C show the limiting (resonance) structures of the chromophores. These π -conjugated systems are characterised by the presence of an odd number of methine groups between the charged polar atoms or groups.^{2,3} Positively charged quaternary nitrogen atoms serve as such polar structural elements in amidinium-ion systems; negatively charged oxygen atoms, in carboxylion systems. In formally neutral amidic systems, heteroatoms at the ends of the chromophoric system have opposite charges, *viz.*, the positive charge on the quaternary nitrogen atom and the negative charge on the oxygen atom. Generally, the terminal nitrogen and oxygen atoms are involved in heterocyclic fragments, such as benzothiazole, benzoxazole, benzimidazole, quinoline, indolenine, rhodanine, thiohydantoin, *etc.* The formula of dyes of the amidinium-ion type can be represented as



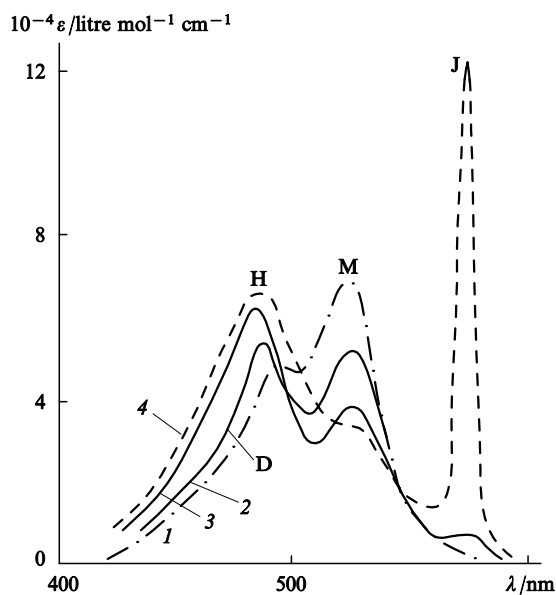


Figure 2. Absorption spectra of aqueous solutions of 1,1'-diethyl-2,2'-cyanine chloride.² The concentrations of the solution at 25 °C /mol litre⁻¹: (1) 1.3×10^{-5} , (2) 1.3×10^{-3} , (3) 7.1×10^{-3} , (4) 1.4×10^{-2} .

common π -electron system is present, which is manifested in a bathochromic shift of the absorption band, a decrease in its width and, consequently, an increase in intensity. Absorption in the J-band region is due to the cooperative action of all molecules involved in the aggregate, and the absorbed energy is distributed throughout the aggregate. This process is typical of the exciton motion, *i.e.*, the transfer of the excited state, which is formed upon light absorption by one molecule in the close-packed aggregate, from one molecule to another in a time shorter than the oscillation period of the dye. The aggregation of cyanines in solution was reviewed in detail by Herz.^{16, 17}

It is worthwhile to consider the spectroscopic manifestation of interactions between molecules in aggregates in terms of McRae–Kasha's model^{18, 19} for a dimer as the simplest case. The probability of the electron transition from the ground state (*G*) to the excited state (*E*) split due to an intermolecular interaction depends on the angle α between the direction of the transition dipole moments and the axis of the aggregate (the axis through the centres of the molecules in the aggregate, see Fig. 3). For $\alpha = 90^\circ$, the spectral transition to the higher split excited state is most probable. This corresponds to sandwich-type dimers of cyanine dyes characterised by an absorption band hypsochromically shifted relative to the M-band. The transition to the lower split

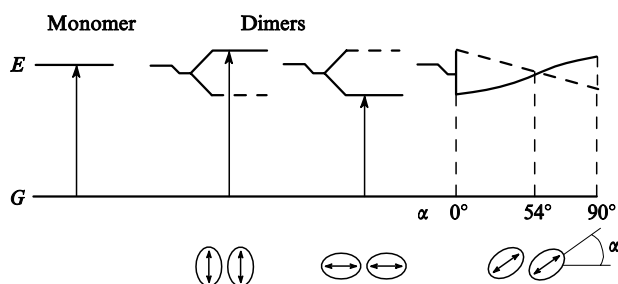


Figure 3. Diagram of the energy levels of the monomer of the dye and its dimers depending on the angle between the direction of transition dipole moments and the axis of the aggregate;^{18, 19} *G* is the ground state, *E* is the excited state.

state is forbidden. If $\alpha = 0^\circ$, the transition to the lower split excited state is preferable, which corresponds to a bathochromic shift of the absorption band of the dimer. In the general case, for example, at $\alpha > 54^\circ$, the transition to the higher split state with a hypsochromic shift of the absorption band is more probable. For $\alpha < 54^\circ$, the transition to the lower split state with a bathochromic shift is preferable.

This model was extended to larger aggregates (H- and J-aggregates). Based on X-ray diffraction data and results of calculations for aggregates of cyanine dyes, it was concluded that the structural parameter, *viz.*, the packing angle in the aggregate, is of most importance for the spectral properties of such aggregates.^{3, 20, 21}

The structure of an aggregate can be pictorially represented as a deck of cards (Fig. 4). The shift angle in a slipped deck of cards is the above-mentioned packing angle determining the spectral absorption of the aggregate. Calculations demonstrated that $\alpha = 60^\circ$ corresponds to H-aggregates, whereas $\alpha = 30^\circ$ and 19° correspond to J-aggregates. The smaller the angle α , the larger the bathochromic shift of the absorption band of J-aggregates.

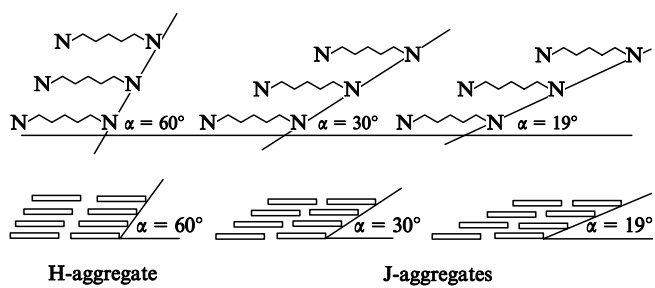


Figure 4. Schematic representation of the structures of H- and J-aggregates of cyanine dyes;⁶ α is the packing angle of the aggregate.

The two-dimensional structure of J-aggregates considered by Kuhn, the so-called brickwork structure with the packing angle $\alpha = 19^\circ$ (Fig. 5a), is substantiated the most.^{21–24} Calculations by the molecular orbital (MO) method demonstrated that 3–5 cyanine molecules are sufficient for the appearance of the J-band in the absorption spectrum of a brickwork structure.^{20, 25, 26}

It should be noted that the aggregation of some dyes, for example, of *meso*-methyl-substituted thiacyanines, (particularly, on silver halides) is characterised by double absorption bands. One peak is hypsochromically shifted relative to the M-band, whereas another peak of approximately equal intensity is shifted bathochromically. For such aggregates, a herringbone structure is considered (Fig. 5b).²⁷ In the latter, dimers of the dye serve as the main structural units, which are repeated (translated)

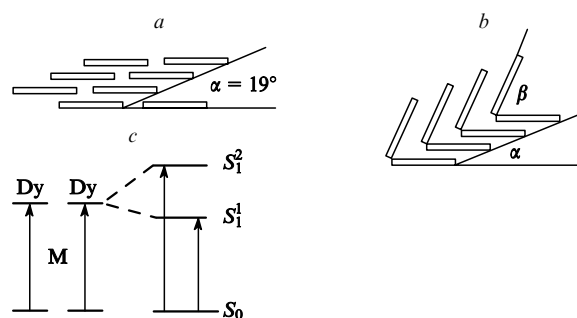


Figure 5. Brickwork (a) and herringbone structures (b) of J-aggregates and the scheme of energy level splitting in dimeric fragments of the aggregates (c).²⁷

many times. Due to splitting of the energy levels of the dye in the dimer (according to Davydov), two spectral transitions occur (Fig. 5c). The intensity ratio of these transitions is determined by the angles α and β .²⁷ For $\beta = 90^\circ$, two transitions have equal intensities.

A dimer is the simplest dye aggregate. The formation of dimers was described in early publications (see, for example, the review¹⁶). Dimers are formed by cyanines containing polymethine chains with different lengths (dyes **1**, $n = 0-3$). The formation of dimers from anionic monomethinecyanines has also been documented.²⁸⁻³⁰ The M- and D-forms are in thermodynamic equilibrium. This is exemplified by thiacyanine ($n = 0$) in Fig. 6. The intensity of the M-band increases, whereas the intensity of the D-band decreases with decreasing dye concentration and increasing temperature, the curves passing through an isosbestic point.

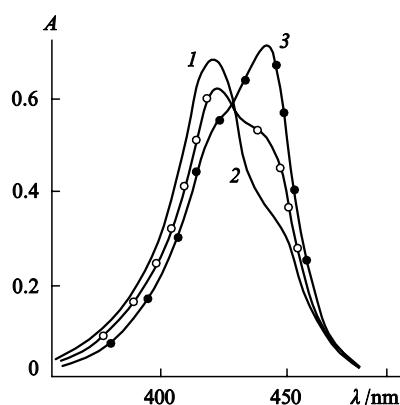


Figure 6. Absorption spectra of aqueous solutions of the triethylammonium salt of 5,5'-dichloro-3,3'-di(γ -sulfopropyl)thiacyanine;²⁸ A is the optical density; the concentration of the solution/mol litre⁻¹: (1) 1×10^{-5} , (2) 1×10^{-6} , (3) 1×10^{-7} ; the cell length/cm: (1) 0.1, (2) 1.0, (3) 10.

Van der Waals forces and dispersion interactions of π -conjugated systems play the major role in the formation of dimers.¹⁶ Dimerisation of cyanines was studied in detail by West and Pears.³¹ It was found^{17,31} that dimerisation in aqueous solutions increases with increasing length of the polymethine chain and with increasing hydrophobicity due to elongation of N -alkyl substituents and, on the contrary, dimerisation decreases with increasing degree of non-planarity of dye molecules, in particular, due to bulky substituents. The free energy of dimerisation of cationic cyanines changes only slightly (by 5–7 kcal mol⁻¹).³¹ For anionic dyes containing sulfoalkyl groups at the nitrogen atoms in heterocyclic moieties, the changes in the free energy of dimerisation are larger.²⁸ Apparently, stability of dimers of anionic cyanine dyes is determined by a strong intermolecular Coulombic interaction between the sulfo group of one molecule and the positive charge on the chromophore of another molecule. The possibility of formation of mixed dimers containing cationic thiacyano- and dicarbocyanines in aqueous solutions was discussed.³¹

It should be noted that the formation of dimers in aqueous solutions leads to fluorescence quenching with a simultaneous increase in the role of triplet states.¹⁶ The only exception is dimers of oxacyanine, which exhibit stronger fluorescence in solutions compared to its monomers.³² Apparently, this is associated with the difference in the structure of two isomers of cyanines involved in the dimers.

Larger aggregates, *viz.*, trimers, tetramers and n -mers, including H-aggregates (Fig. 7), are formed as the dye concentration of in solution increases and the temperature decreases,³³ the hypsochromic shift of the absorption band of aggregates being increased. As a rule, H-aggregates, like dimers, show no lumines-

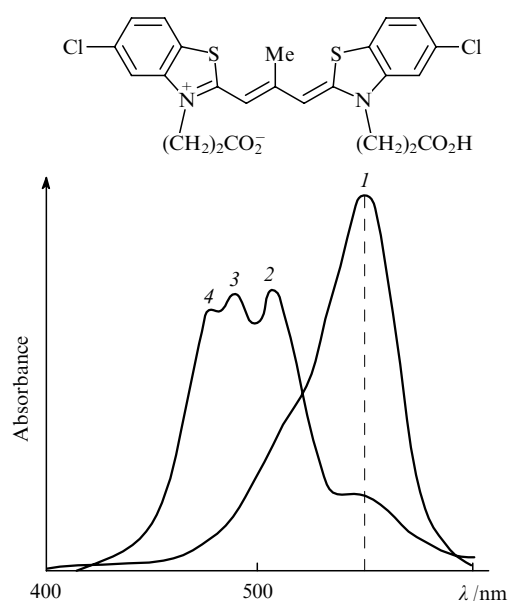


Figure 7. Absorption spectra of different forms of thiacyanine in aqueous solutions at different concentrations and temperatures;³³ (1) a monomer, (2) a dimer, (3) a trimer, (4) a tetramer. The concentration of the solution/mol litre⁻¹: (1) 2×10^{-6} , (2–4) 2×10^{-4} ; the temperature /°C: (1) 60, (2–4) 5.

cence. However, the appearance of narrow H-bands (H^*) was observed.³⁴ Colloidal particles can be H^* -aggregates exhibiting strong luminescence.^{33,34}

The J-aggregation of cyanine dyes is of particular interest. Most earlier studies investigated cationic dyes. The formation of J-aggregates from individual molecules occurred. This process was poorly controlled and led to the uncontrolled growth of J-aggregates up to the formation of colloidal particles.^{16,17} The results of investigation of J-aggregation of imidacarbocyanine molecules performed by Herz^{16,17} are presented in Fig. 8 as an example.

Equilibria between the monomeric and aggregated forms of dyes can be studied by analysing absorption spectra at different dye concentrations. According to the law of mass action, the equilibrium between the monomeric and J-aggregated forms can be written as follows:¹⁶

$$n c_M \rightleftharpoons c_J, \quad (1)$$

$$K = \frac{c_J}{c_M^n},$$

$$\log(nc_J) = \log(nK) + n \log c_M, \quad (2)$$

where n is the number of monomers in the J-aggregate and K is the equilibrium constant. The plot of $\log(nc_J)$ vs. $\log c_M$ should be linear with a slope of n . The change in the free energy of aggregation is determined from the temperature dependence of K .

For imidacarbocyanine in an aqueous electrolyte solution, $n = 4$.^{16,17} Herz hypothesised¹⁶ that, under experimental conditions, colloidal particles can be formed, and $n = 4$ corresponds to the single spectroscopic unit rather than to the size of J-aggregates. The same value of n was obtained for the J-state of cationic naphthothiacyanine²⁵ in an aqueous solution and for 1,1'-diethyl-2,2'-cyanine.³⁵ Small values of n were determined from spectroscopic data in some other studies.¹⁶ It should be noted that irreversibility of the equilibrium in a monomer–J-aggregate system is the main problem in determining the number of molecules in J-aggregates and the thermodynamic parameters of aggregation. Generally, small J-aggregates (consisting of a few molecules) grow into colloidal particles. The identification of

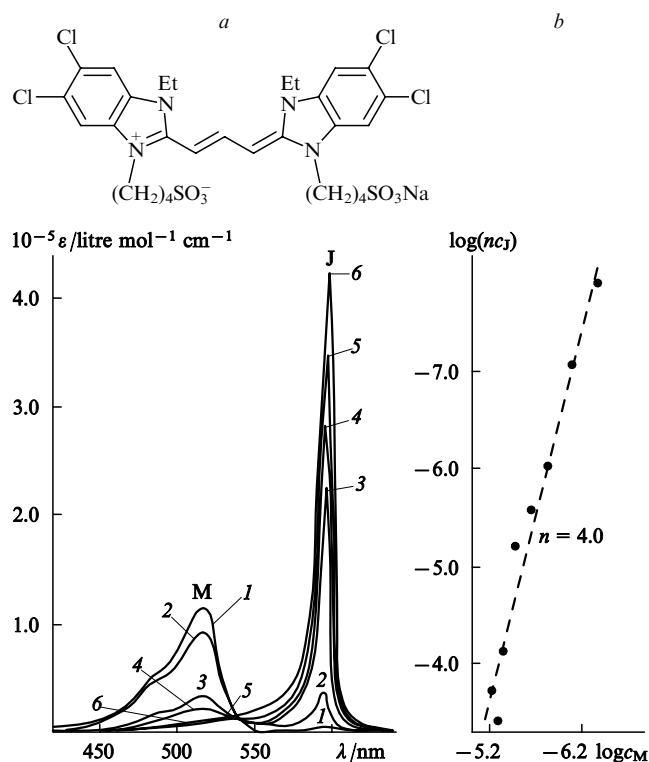


Figure 8. Dependence of absorption of benzimidacarbocyanine at 25 °C on its concentration in a 10^{-3} M NaOH aqueous solution.¹⁶ The concentration of the solution /mol litre $^{-1}$: (1) 0.5×10^{-6} , (2) 1.0×10^{-6} , (3) 5.0×10^{-6} , (4) 1.0×10^{-5} , (5) 1.0×10^{-4} , (6) 4.0×10^{-4} ; c_M and c_J are the concentrations of the monomeric and aggregated forms of the dye, respectively.

states by spectroscopic methods is complicated by the fact that particles of different sizes give similar absorption maxima. Hence, reversibility of the equilibrium and colloidal stability of solutions in time are the main criteria in the determination of the state of dyes.

A new method of J-aggregation (from dimers rather than from individual molecules) was examined in the studies.^{36,37} This method typical of anionic cyanine dyes is referred to as the block construction of aggregates.³⁷ The equilibrium between dimers and J-aggregates of the pyridinium salt of 3,3'-di(γ -sulfopropyl)-4,5,4',5'-dibenzo-9-ethylthiacarbocyaninebetaine is illustrated in Fig. 9. It can be seen that the equilibrium is thermodynamically reversible because the spectral curves pass through an isosbestic point. The tendency of dyes to aggregation is enhanced with decreasing temperature and increasing concentration. These results are consistent with the characteristic features of aggregation of thiacyanines.^{28,36}

To determine the sizes of J-aggregates, the plot of $\log(nc_J)$ vs. $\log c_D$ was constructed (Fig. 10). The slope of the line [corresponding to the number (m) of dimers in the J-aggregate] is 2, *i.e.*, the J-aggregate consists of two dimers or four monomers. Probable structures of J-aggregates formed from two dimers are shown in Fig. 11.^{21–23} In all cases, the formation of J-aggregates from dimers is associated with the shift of the molecules in dimers with respect to each other. It was hypothesised that a brickwork structure is most preferable. It was demonstrated that J-aggregates of thiacyanine [triethylammonium salt of 5-chloro-3,3'-di(γ -sulfopropyl)-4',5'-benzothiacyaninebetaine] also consist of two dimers, *i.e.*, of four dye molecules.³⁶

In studies of the equilibria between different forms of anionic thiacyanine dyes in aqueous solutions the following, at first glance, paradoxical conclusion was reached: the block construction of J-aggregates from dimers is the most preferable method for

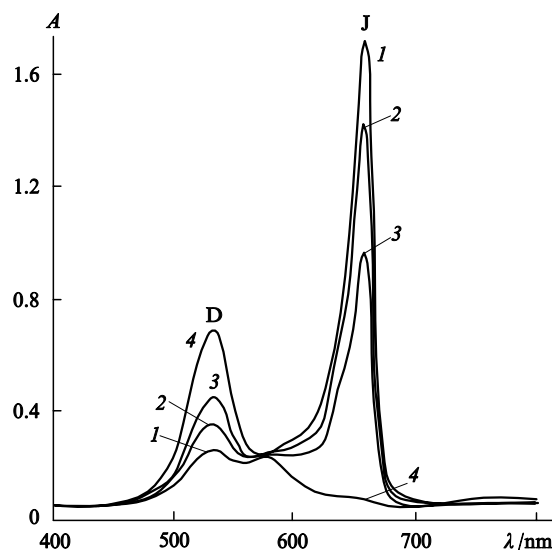


Figure 9. Absorption spectra of thiacarboaniline in aqueous solutions. The concentration of the solution /mol litre $^{-1}$: (1) 10^{-4} , (2) 3.3×10^{-5} , (3) 1×10^{-5} , (4) 0.5×10^{-5} ; the cell length /cm: (1) 0.1, (2) 0.3, (3) 1.0, (4) 2.0.

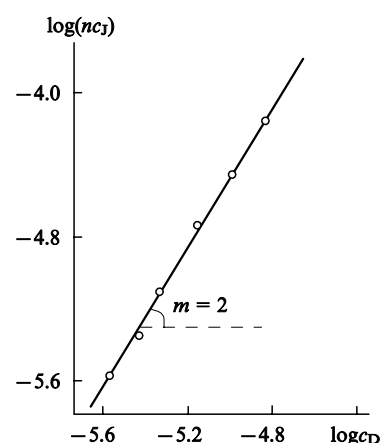


Figure 10. Plot of $\log(nc_J)$ vs. $\log c_D$ for thiacarboaniline.

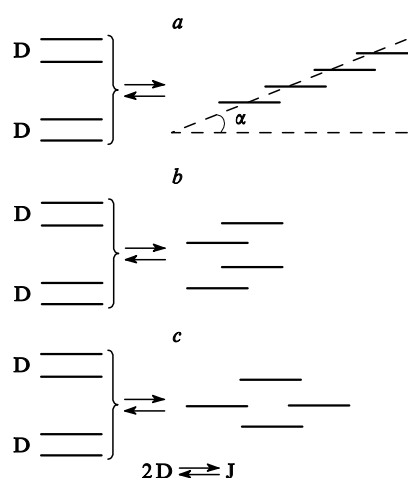


Figure 11. Schemes of formation of J-aggregates of the slipped-deck-of-cards (a), ladder (b) and brickwork (c) types from dimers.

the construction of 'ideal' J-aggregates of the same size (monostructural J-aggregates). This new approach to the construction of J-aggregates was used for the preparation of mixed J-aggregates from dyes containing polymethine chains of different lengths.^{37, 38} To our knowledge, Scheibe *et al.*³⁹ observed for the first time the appearance of new bands in the absorption spectrum of a system consisting of two dyes, *viz.*, 1,1'-diethyl-2,2'-cyanine and its 2-benzoselenazole analogue. In the spectrum of a complex mixture of solvents, benzene–amyl alcohol–water, an additional absorption band was found between the bands of J-aggregates of individual dyes. The appearance of new bands for analogous dyes containing long alkyl groups in the spectra of Langmuir–Blodgett films was described by Penner and Mobius.⁴⁰ Mixed amalgam-type aggregates were obtained⁴¹ in Langmuir–Blodgett films for 3,3'-diethyl-9-phenylthiacarbocyanine dyes substituted in heterocycles. It should be noted that J-aggregates composed of two types of dyes were formed in heterogeneous systems at the water–organic solvent interface.

The main scheme of the block construction of J-aggregates from molecules of different dyes in water involves the preliminary formation of dimers of these dyes due to a shift of the J-aggregate $\rightleftharpoons$ dimers equilibrium toward the dimers (upon heating of their solution) followed by the formation of complex aggregates (upon cooling of the systems).^{37, 38} The absorption spectrum of a mixture consisting of solutions of thiocarbocyanine and thiadicarbocyanine is a summary curve of the bands of the starting dyes (Fig. 12, curve 1). Heating of the solutions to 50–80 °C leads to destruction of J-aggregates of individual dyes and the appearance of bands corresponding to absorption of dimers of dyes (see Fig. 12, curve 2). After subsequent cooling of the solutions, the dimers form new J-aggregates including different molecules (see Fig. 12, curve 3). The absorption band of mixed J-aggregates appears at longer wavelengths compared to the band of J-aggregates of thiocarbocyanine and is hypsochromically shifted relative to the absorption band of J-aggregates of thiadicarbocyanine. This phenomenon is common to thiacyanines, which can form J-aggregates in aqueous solutions and contain an extensive π -conjugated system in the heterocycles. Therefore, mixed aggregates with desired spectral properties can be prepared by choosing appropriate pairs of dyes.

Apparently, the resulting mixed J-aggregates are homogeneous structures analogous to solid solutions of dyes, which is confirmed by the character of their fluorescence spectra. Intrinsic luminescence bands (Fig. 13 *b*) correspond to individual absorp-

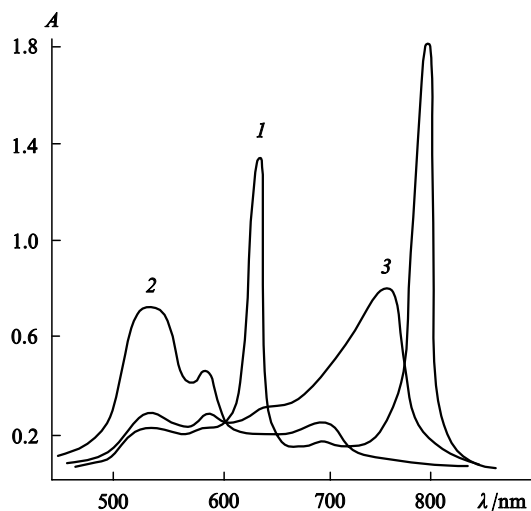


Figure 12. Absorption spectra of a 1 : 1 mixture of aqueous solutions of thiocarbocyanine and thiadicarbocyanine ($c = 1 \times 10^{-4}$ mol litre $^{-1}$) after mixing at 20 °C (1), upon heating to 50 °C (2) and after cooling to room temperature (3).^{37, 38}

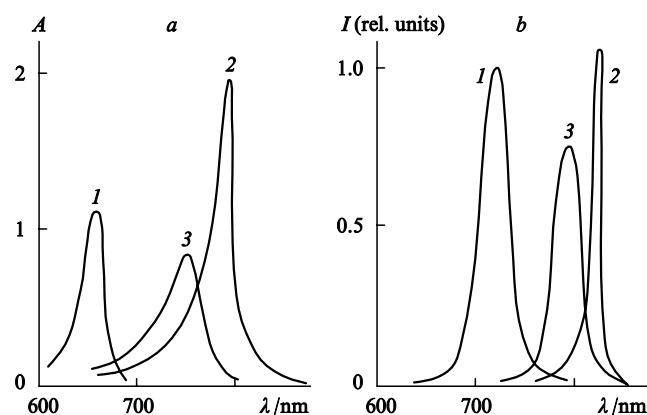


Figure 13. Absorption spectra (*a*) and fluorescence spectra (*b*) of J-aggregates of thiocarbocyanine (1) and thiadicarbocyanine (2) and their mixture (3) in aqueous solutions.^{37, 38}

tion bands of J-aggregates of the starting dyes and their mixture (Fig. 13 *a*). Therefore, the block construction of J-aggregates in solution is an efficient method for the preparation of J-aggregates of cyanine dyes containing polymethine chains with different lengths and mixed J-aggregates. Hence, this method can be considered as a promising approach to the formation of complex organised structures, *viz.*, molecular assemblies with new optical properties.

A different type of aggregates composed of dimers was obtained in studies of cyanine dyes, which substantially differ in the length of the polymethine chains, *viz.*, thiacyanines and thiadicarbocyanines.⁴² In this case, mixed J-aggregates are not formed, absorption bands of dimers of thiadicarbocyanines disappear and the absorption spectra show new absorption bands. This is illustrated in Fig. 14, which shows the absorption spectra

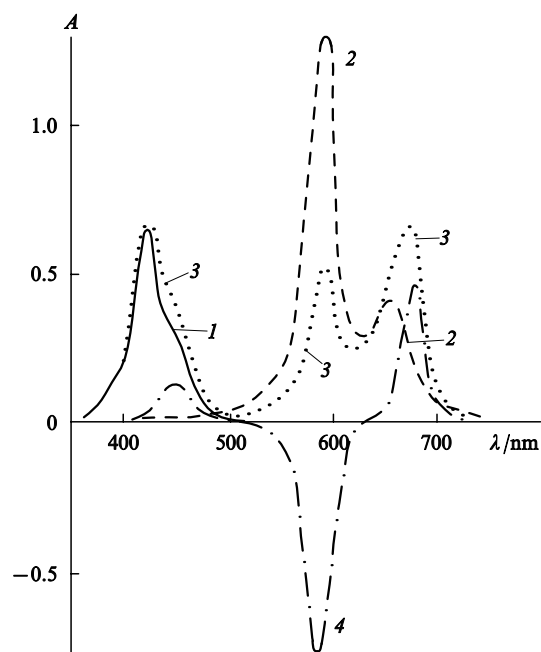


Figure 14. Absorption spectra of aqueous solutions of triethylammonium salts of 5'-chloro-3,3'-di(γ -sulfopropyl)-4,5-benzothiacyanine (1) and 3,3'-di(γ -sulfopropyl)-9,11-(β , β -dimethyltrimethylene)-10-methylthiadicarbocyanine (2) and their mixture (3) at room temperature.⁴² The concentration of the dyes $c = 1.0 \times 10^{-5}$ mol litre $^{-1}$; (4) the difference spectrum of the starting dyes and their mixed solutions.

of aqueous solutions of triethylammonium salts of 3,3'-di(γ -sulfo-*propyl*)-4,5-benzo-5'-chlorothiacyanine and 3,3'-di(γ -sulfo-*propyl*)-9,11-(β,β -dimethyltrimethylene)-10-methylthiadibenzocyanine. The thiacyanine existed in the dimeric ($\lambda_{\text{max}} = 421 \text{ nm}$) and monomeric ($\lambda_{\text{max}} = 442 \text{ nm}$) forms (curve 1). The thiadibenzocyanine also existed in the dimeric ($\lambda_{\text{max}} = 588 \text{ nm}$) and monomeric ($\lambda_{\text{max}} = 655 \text{ nm}$) forms (curve 2). Curve 3 represents the absorption spectrum of mixed equimolar solutions of the dyes. After mixing of solutions of the dyes, the intensity of the dimer band of the thiadibenzocyanine substantially decreases and new absorption bands appear at $\lambda_{\text{max}} = 444$ and 678 nm , which is shown by curve 4 (obtained by subtracting curves 1 and 2 from curve 3). This interaction between thiacyanines and thiadibenzocyanines has a general character regardless of the nature of substituents in the heterocyclic moieties of the dyes.⁴² Therefore, interaction between dimers of two dyes is pronounced. It was hypothesised that this is associated with the presence of dimer(1)–dimer(2) interactions involving different dyes. Apparently, splitting of the dimer band of the dicarbocyanine dye is due to splitting of the electron levels of the dimer in a 'heterocontact dimer' due to the perturbing action of the dimer of the thiacyanine dye. It was concluded that the formation of 'heterocontact' aggregates is energetically more favourable than the formation of dimers and J-aggregates of individual dyes. Therefore, in this case, as in the case of formation of mixed J-aggregates, dimers are the main building blocks of organised polymolecular structures. However, the formation of mixed J-aggregates is, apparently, hindered due to a substantial difference in the geometry of the interacting molecules and, consequently, the so-called suprastructures with incommensurate elements are formed.⁴³

The influence of electrolytes and surfactants on aggregation of cyanines was examined in several studies (see, for example, Refs 16, 20 and 44). It is evident that the aggregation of charged cyanine dye molecules is influenced by electrolytes. Generally, the introduction of inorganic electrolytes stimulates aggregation.¹⁶ This is related to the salting out of the dye from a solution under the action of an electrolyte. The charge of the ion opposite to the charge of the dye molecule plays a great role. In aqueous solutions of anionic dyes,⁴⁵ the electrolyte concentration stimulating aggregation decreases and the J-aggregation rate increases with increasing charge of the cation.[†] It was hypothesised that the self-aggregation becomes more probable in the presence of framework-forming auxiliary partners (for example, ions). Figuratively speaking, ions can serve as 'nails' facilitating the building of J-aggregates. In addition, ions involved in J-aggregates can promote their stabilisation.

Organic surfactants (unlike inorganic electrolytes) hinder the self-association of dyes in water.⁴⁶ This influence is characteristic also of micelle-forming non-ionic surfactants.¹⁶ This property lies at the basis of the spectroscopic method for the determination of the critical micelle concentration. It should be emphasised that dye aggregation can, on the contrary, occur in the pre-micellar region of surfactant concentrations.

The influence of surfactants on aggregation was examined.^{7, 47–50} The presence of long hydrocarbon fragments at the nitrogen atoms in the imidazobenzocyanine molecule is found to favour the formation of helical structures of J-aggregates, in which the hydrocarbon tails serve as a framework at which a helical packing of the dye molecules is assembled as a nanotube. An example of such structures characterised by a two-band spectrum of the J-aggregate is shown in Fig. 15.⁵⁰

Unlike the deaggregating action of micelle-forming surfactants, polymeric surfactant ions (polyelectrolytes) stimulate aggregation. The spectral shifts caused by interactions of polyelectrolytes with both anionic and cationic dyes were studied in detail (see references in the review¹⁶).

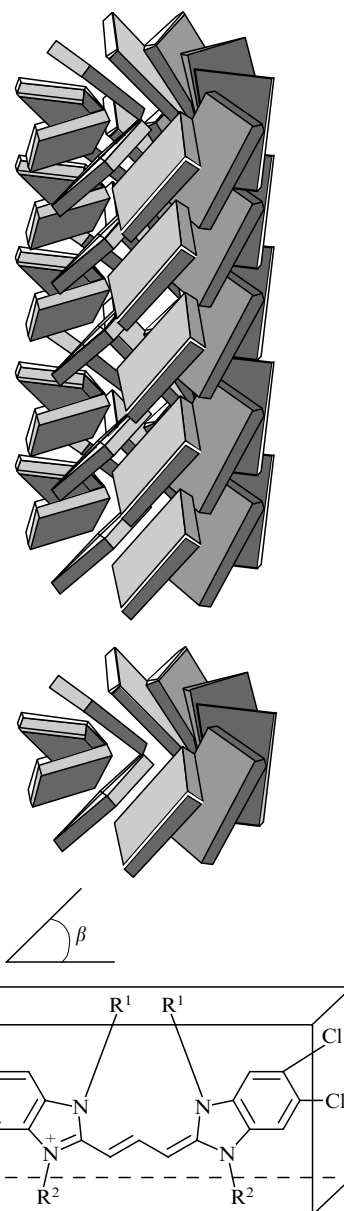


Figure 15. Cylindrical model of the helical structure of imidazobenzocyanine.⁵⁰

The influence of gelatine on aggregation of cyanine dyes in solutions was studied in depth. The appearance of a new band at longer wavelengths after the addition of traces of gelatine to aqueous solutions of carbocyanines was observed for the first time by Sheppard⁵¹ and Solov'ev.⁵² More recently, Dickinson,⁵³ Borin⁵⁴ and Boyer *et al.*⁵⁵ performed systematic studies of the influence of the gelatine concentration, the temperature and pH on aggregation of cationic dyes in aqueous gelatine solutions. It was found that J-aggregation of dyes is initiated in the presence of a small amount of gelatine ($\sim 0.01\%$), and a further increase in the gelatine concentration in solution leads to destruction of J-aggregates to give monomers. In a 1% gelatine solution, J-aggregates are absent. In addition, pH of an aqueous gelatine solution should be higher than pH of the isoelectric point of gelatine. It should be noted that the solutions contained not only J-aggregates but also other 'short-wavelength' aggregates of dyes. More recently, Hermel and Seeboth⁵⁶ studied the influence of the molecular mass distribution of gelatine and the effect of liquid-crystalline *N*-substituted butylaniline on aggregation of oxacar-

[†] See also the publication by T D Slavnova, A K Chibisov, H Gorner *J. Phys. Chem. A* **109** 4758 (2005).

bocyanine. Krasovskii *et al.*⁵⁷ investigated the properties of the anionic analogue of this dye containing sulfopropyl groups at the nitrogen atoms in aqueous solutions near the gel-formation threshold of gelatine. It was found that J-aggregates are more readily formed in low-molecular-weight gelatines. However, mixtures of monomeric and several aggregated forms (dimers, H- and J-aggregates) were obtained in these systems as well. It was demonstrated^{51,52} that traces of gelatine act as aggregation centres because adsorption of dyes occurs on particular groups of gelatine.

Gelatine was demonstrated⁵⁸ to promote J-aggregation of anionic dyes from dimers according to the mechanism of block construction. In this case, gelatine serves as the third component facilitating aggregation.

A study of the dependence of J-aggregation on the type of gelatine showed⁵⁹ that the aggregation is substantially influenced by the positively and negatively charged groups. In acidic gelatines, J-aggregation occurs much more readily than in alkaline gelatines. In acidic gelatines containing positively charged quaternary nitrogen atoms at a pH under study, J-aggregation starts at higher temperatures and lower gelatine concentrations. J-Aggregation is slowed down as the number of acidic groups in the gelatine molecule increases. It was concluded that the quaternary nitrogen atoms in acidic gelatines serve as J-aggregation centres of anionic dyes. The ability of gelatine to catalyse J-aggregation was exploited for the preparation of gelatine layers containing nanoparticles of J-aggregates consisting of several dye molecules.

In recent studies, considerable attention was given to the formation of J-aggregates in films of various polymers, including electroconducting polymers. Composites containing J-aggregates are promising materials for the construction of electroluminescent displays and the preparation of electrorefractive layers, nonlinear optical systems and other systems used in nanoelectronics. Mal'tsev *et al.*^{60–62} investigated J-aggregates as a light-emitting medium in electroconducting polymers. The authors observed electroluminescence of J-aggregates of mono-, tri-, penta- and heptamethinecyanines in the visible and IR spectral regions. The photoelectrical, nonlinear optical and photorefractive properties of J-aggregates in polyimide films were investigated.^{63,64} The nonlinear optical properties of J-aggregates of thiocarbocyanine dyes in multilayer polymer films were studied.⁶⁵ Films containing J-aggregates of cyanine dyes were used for generation of ultra-short laser pulses and nonlinear optical transformations.^{66–70} The J-aggregation of thiocarbocyanine dyes in polymer films was investigated.⁷¹ Data on J-aggregation in polymeric matrices were obtained primarily for pseudoisocyanine in polyvinyl alcohol,^{72,73} polystyrene sulfonate and polyacrylic acid.^{74–76}

IV. Dye aggregation on silver halide microcrystals

The most detailed information on aggregation of cyanine dyes was obtained in long-term studies of spectral sensitisation of AgHal-based photographic materials. It is known that J-aggregation more readily occurs at the AgHal/solution interface.^{2,16} The use of cyanine dyes for spectral sensitisation of photographic silver halide emulsions provides a substantial increase in additional light sensitivity in the region, where AgHal microcrystals do not absorb light. Dyes capable of forming supramolecular structures, *viz.*, J-aggregates, are characterised by the highest photographic efficiency.^{2–6,77}

The J-aggregation process is determined primarily by the molecular structure of the dye (the lengths of the polymethine chain, the structure of heterocyclic rings and the presence of substituents in these moieties and in the chain), the nature of the halogen atom, the habit and size of emulsion microcrystals, the presence of ions and compounds adsorbed on AgHal (stabilisers, surfactants, colour-forming components, *etc.*), pBr and pH.^{2,3,16,17,20,77,78}

The J-aggregation by itself is not a sufficient condition for high efficiency of spectral sensitisation. Many J-aggregating dyes

are inefficient under particular conditions. The photographic efficiency of J-aggregates cannot be attributed only to a change in the position of the energy levels of dye molecules upon J-aggregation. The experience showed that the surface state of AgHal microcrystals and the topography of impurity centres play a decisive role. The surface defects and impurity centres are of importance in J-aggregation and location of photogenerated electrons and holes. Interactions between J-aggregates of a dye and impurity sites can lead to a decrease in the photographic activity of the dye. Generally, this is attributed to desensitisation and self-desensitisation of dyes.^{79,80} Desensitisation causes a decrease in the intrinsic (blue) light sensitivity of AgHal. Self-desensitisation leads to a decrease in the light sensitivity in the absorption zone of dyes. The efficiency of spectral sensitisation can substantially be increased by introducing supersensitisers (compounds, which inhibit or completely exclude self-desensitisation of dyes).

1. Relationship between aggregation and the structure of dyes

The relationship between the structure of dyes and their tendency to form aggregates in solutions and on the surface of AgHal were studied in depth (see references in the publications^{2–6,77–80}). The available data are rather contradictory due to complexity of a photographic system.

Among cyanine dyes unsubstituted in heterocyclic fragments and the outer polymethine chain, mono- and trimethinecyanines are most prone to aggregation on the surface of AgBr(I) emulsion grains.^{2,3,77} Generally (with rare exception^{81–83}), di- and tri-carbocyanines (penta- and heptamethinecyanines) form H-aggregates rather than J-aggregates on AgHal substrates.^{17,77} This may be related to the requirements of a highly ordered arrangement of molecules in J-aggregates, whereas the uniformity of the states of the molecules is less probable due to an increase in the number of *cis-trans* isomers with increasing length of the polymethylene chain of dyes.⁸⁴ As a result, any deviation from the uniformity of structural elements, in particular, due to *cis-trans* isomerism, hinders aggregation. For example, only rigid fixation of the chain by polymethylene bridges in thiadi- and -tricarbo-cyanine molecules preventing *cis-trans* isomerism results in J-aggregation of dyes containing such a long polymethine chain in solutions and on AgHal.^{37,38,83,85}

Derivatives of partially hydrogenated rings (thiazoline and pyrrolidine) show almost no tendency to form J-aggregates. Analogous dyes containing conjugated heterocyclic fragments (thiazole and 1,3,4-thiadiazole) have a weak tendency to form aggregates, whereas this tendency is substantially stronger in the case of compounds containing fused heterocyclic systems with a high degree of π -electron delocalisation (such as benzoxazole, benzoselenazole, benzothiazole, quinoline, *etc.*). J-Aggregation in AgHal emulsions accompanied by a shift of absorption bands to longer wavelengths increases in the thiazoline < thiazole < benzothiazole < naphthothiazole series. This indicates that interactions of π -electrons in heterocyclic systems play a considerable role in the formation of polymolecular states. The phenyl groups in the thiazole or thiadiazole moieties have an analogous effect on J-aggregation.⁷⁷ Indo- (see Ref. 78) and imidacarbocyanines,⁸⁶ as well as indo- and thiadiazolo-1,3,4-dicarbocyanines,⁷⁷ also show a tendency to form J-aggregates.

Merocyanines rarely form J-aggregates on AgHal, although dimethinemerocyanines containing indolenine and pyrazolone moieties and malonodinitrile derivatives⁸⁴ give J-bands in emulsions. Sensitisation and absorption spectra of a number of dimethinemerocyanines, derivatives of unsymmetrical cyclic compounds (in particular, 3-alkylrhodanine and 1,3-dialkylthiohydantoin), show J-bands whose intensity increases with increasing duration of storage of melted sensitised emulsions.⁷⁷

The introduction of substituents into different classes of dye molecules has a similar effect on their aggregation. For example, J-aggregation is substantially enhanced in the presence of chlorine atoms in heterocyclic fragments of various carbocyanines or the

methyl and ethyl groups in the *meso* positions of thia-, oxa- and selenacarboxyanines.^{2, 77, 78} Taking into account considerable differences in the tendency of structurally similar dyes to form J-aggregates, small modifications would be expected to change the mutual orientation of the molecules responsible for their interactions. The specificity of the influence of an increase in the bulkiness of substituents was observed even in a single series of dyes. For example, the ability of 9-ethyl-6,6'-dimethoxycarboxyanines to form J-states is substantially higher than that of the corresponding 6,6'-diethoxy and, particularly, 6,6'-dipropoxy derivatives, whereas the tendency to form H-states substantially increases in this series.⁷⁷

It is commonly accepted that the ability to form aggregates is enhanced in the presence of halogen (except for iodine) atoms and COOR, CN and some other electron-withdrawing groups in the heterocyclic rings of indo-, imida, quino(2,2')- and oxacarboxyanines containing unsubstituted chains due to a strengthening of π - π -electron interactions between the molecules.⁸⁷ The influence of other substituents is very specific.

In the quino-(2,2')-cyanine series, *N,N'*-dimethoxides are much less prone to J-aggregation than ethoxides.⁷⁸ Sheppard *et al.*⁸⁸ demonstrated that this property is inherent also in methoxides of cyanines prepared from other bases, in particular, from benzothiazole and benzoxazole. *N,N'*-Dimethoxides of quino-, oxa-, thia- and selenacarboxyanines are less efficient due to their high ability to form photochemically inactive H-polymers.⁷⁷ If methoxides and ethoxides of thia-, imida- and indocarboxyanines are characterised by a similar tendency to undergo polymerisation, they are similar in the sensitising action. The intensity of the J-band sharply decreases with increasing number of carbon atoms in the alkyl groups at the nitrogen atoms (C_2H_5 – n - C_4H_9) in the series of 5,5'-disubstituted 9-ethylthiacarboxyanines,⁷⁸ whereas the intensity of this band remains virtually unchanged in the case of imidacarboxyanines.⁷⁷ In the series of dimethinemercocyanines, *viz.*, rhodanine and thiohydantoin derivatives,⁷⁸ the ability to form J-aggregates, on the contrary, either appears or is enhanced.

Among carboxyanines containing alkyl and sulfoalkyl substituents, dyes containing sulfoalkyl groups at the nitrogen atoms are more prone to aggregation, the photographic activity of J-states being much higher than that of dyes containing alkyl substituents with different structures.³

As mentioned above, the ability of dyes to form various polymolecular states is enhanced in the presence of methyl and ethyl groups at the *meso* position of the polymethine chain of thia-, oxa- and selenacarboxyanines. A comparison of the sensitisation and absorption spectra of dyes and the experimental relative quantum yields of sensitisation for several groups of dyes demonstrated that the introduction of methyl and ethyl groups at the *meso* position of carboxyanines leads to the formation of the photochemically active H_1 - and J_1 -states of 9-methylcarboxyanine and the J_2 - or J_3 -states of 5,5'-disubstituted 9-ethylthiacarboxyanines in the adsorption layer.^{77, 78} More recently, it was found that the common polymolecular herringbone structure characterised by two spectral transitions rather than two different states (H_1 and J_1) are formed for 9-methyl-substituted thiacarboxyanines.^{80, 89} In these studies, as well as in other investigations (see references in the publication²⁰), the introduction of alkyl groups at the *meso* position was demonstrated to have a substantial effect on the enhancement of J-aggregation, the replacement by the ethyl group being more favourable for the *cis* configuration, whereas the presence of structurally identical dye molecules facilitates their self-assembly as J-aggregates.

The dependence of the ability to form aggregates not only on the number of isomers, but also on such factors as the planarity of cyanine molecules and the absence of internal rotational motion was examined^{84, 86, 90} and the contribution of these factors to the colour and the ability to undergo polymerisation and be sensitised was investigated. The compactness of molecules and a small deviation from planarity are particularly favourable for aggrega-

tion because planar molecules more readily form close-packed relatively rigid structures, which are less susceptible to thermal decomposition. Brooker *et al.*⁸⁶ classified dyes into free, compact and overcrowded. The first two groups involve planar molecules and the third group includes nonplanar molecules. The fact that substituents violating the planarity of molecules hinder aggregation is well illustrated by 1,1'-diethyl-2,2'-cyanine derivatives. The tendency of this compact dye to form aggregates is weakened by 3,3'-alkyl substituents, which push the heterocyclic rings out of the plane of the molecule. In some cases, the required compactness and the related ability to form aggregates can be achieved by fixing the heterocyclic moieties by bridging groups, thus forming a rigid cyclic structure of the molecule. This is typical of *N,N'*-ethylenebenzimidazolocyanine, which readily forms J-aggregates on the surface of AgHal. By contrast, the sterically hindered and nonplanar *N,N'*-diethyl-substituted analogue cannot undergo aggregation.^{17, 91}

Carboxyanine derivatives of *N,N'*-dialkylbenzimidazoles were studied in detail.^{77, 78} The introduction of alkyl substituents at position 9 of these dyes causes a substantial deviation from coplanarity and decreases the ability to form J-aggregates. Likewise, the introduction of bulky substituents, such as NO_2 , SO_2CF_3 or SCF_3 , at position 5 of the heterocycle suppresses the formation of J-aggregates of compact *N,N'*-dialkylbenzimidazole molecules on the surface of AgHal.

The introduction of the CH_3O and C_6H_5 groups at the *meso* position of the chain and of aryloxy groups at positions 8 and 10 can assist aggregation of oxa- or thiacarboxyanines, which are aggregated poorly, if at all, because it becomes possible to form compact structures from all-*trans* or mono-*cis* configurations.^{25, 26} Taking into account the role of substituents in the chain and at the nitrogen atoms of the ring, it was hypothesised that small deviations from the plane of the dye molecule due to the presence of ethyl and other groups, can facilitate the formation of J-states with a brickwork structure from compact planar dye molecules.^{92, 93}

Therefore, the factors favourable for the planarity of a molecule, an elongation of the π -conjugated system of the dye and the uniformity of the isomeric composition of the molecule are responsible for the ability to form J-aggregates. However, these are necessary but not sufficient conditions for J-aggregation. Since J-aggregates are particular three-dimensional packings of dye molecules, J-aggregation depends on the volume of the substituents both in the rings and the chain, which can cause steric hindrance to interactions of the π -conjugated systems of dyes in aggregates.

2. Influence of emulsion factors on aggregation of spectral sensitisers

The nature of the halogen atoms in AgHal microcrystals of photographic emulsions is one of the most important factors influencing J-aggregation. It is known^{2, 3} that the adsorption strength of cyanine dyes on AgHal powders decreases in the series $AgI > AgBr > AgCl$. For many dyes, J- and H-aggregation decreases in the following series: $AgBr(I) > AgBr > AgBr(Cl) > AgCl$.^{77, 78} Meyer⁹⁴ was the first to find that the introduction of 3 mol.% of silver iodide into crystals of a silver bromide emulsion substantially enhances J-aggregation of 9-ethyl-3,3',5,5'-tetramethylthiacarboxyanines accompanied by an increase in the light sensitivity of photolayers.

The influence of the nature of halide ions in monodisperse emulsions containing cubic and octahedral crystals was investigated⁹⁵ and J-aggregation of microcrystals of the same habit of silver chloride bromide and silver bromide iodide emulsions was demonstrated to be better compared to silver chloride emulsions.

Aggregation of dyes upon adsorption on AgHal microcrystals of different habits was studied in depth.^{77, 95–106} It was noted^{100, 101} that absorption spectra of some dyes in emulsions prepared by the ammonia method differ from those prepared by the ammonia-free method. In neutral emulsions, the conditions

for aggregation of dyes are more favourable than those in ammonia emulsions. This may be associated not with the presence or absence of ammonia in the emulsion but with the different habits of microcrystals (a spherical habit in ammonia emulsions and a tabular habit in neutral emulsions).

Dye aggregation on cubic and octahedral AgHal microcrystals has been studied in sufficient detail. It was found that aggregation of cyanines on the (100) faces differs from that on the (111) faces. Experimental data and a theoretical justification for the predominant J-aggregation on the surface of octahedral crystals were reported.^{95–99, 102, 105} 9-Methylthiacarbocyanines, which form J₂-aggregates on the (111) faces giving a band at $\lambda_{\text{max}} = 625$ nm and aggregates on the (100) faces characterised by two absorption bands at $\lambda_{\text{max}} = 590$ and 520 nm, were primarily used as model compounds.

It was found^{97, 102} that readily aggregating dyes (imida- and 5,5'-dichloro-9-ethylcarbocyanines) form, at low concentrations, J-aggregates predominantly on octahedra. Adsorption of cyanines is determined by Coulombic interactions between the negatively charged (111) surface and the positively charged terminal nitrogen atoms of a polymethine chromophore. The fact that the distances between the molecules in the aggregate are similar to those between the ions on the surface of octahedral AgBr microcrystals satisfies the requirement for a closer packing, which is also favourable for J-aggregation. In spite of steric and electrostatic hindrance, readily aggregating dyes whose aggregation is facilitated by water molecules are primarily adsorbed in the J-state on the (100) faces. Tani¹⁰² found that not only J-aggregation but also H-aggregation of cyanines is stronger on the (111) faces than on the (100) faces.

It was noted⁹⁹ that J-aggregation of dyes, in particular, of 9-methylthiacarbocyanines, occurs predominantly on the (100) faces of AgCl analogous to that observed on the (111) faces of AgBr. It was hypothesised that J-aggregates are additionally stabilised by denser solvate shells. This is due to the difference in the influence of Cl[−] and Br[−] ions on the structure of water on the surface. In the presence of chloride ions, the solvation effect is enhanced,⁹⁶ and, consequently, hydrophobic binding of dye molecules with each other is possible.

On the contrary, experimental data on the enhancement of J-aggregation of dyes on cubic microcrystals were reported.^{103–107} A small amount of a dye is sufficient for J-aggregation because the (100) faces contain a small number of crystal lattice defects.¹⁰⁴ Octahedral microcrystals contain a larger number of surface defects. Hence, H-aggregation occurs at low concentrations, whereas higher concentrations of dyes are necessary for J-aggregation. Kazmierczak and Markocki¹⁰⁶ studied the photographic action of thia-, oxa- and selenacarbocyanines at different pAg and pH of emulsions. It was found that particular elements of the dye molecules can facilitate J-aggregation on either (100) or (111) faces. Carbocyanines containing methoxy or phenyl groups at position 5 of heterocyclic fragments show a tendency to form J-aggregates on the (100) faces. Unsubstituted dyes are more prone to J-aggregation on the (111) faces. 5,5'-Dichloro- or 5,5'-dimethyl-substituted carbocyanines behave analogously. Some dyes form J- or H-aggregates regardless of the habit of AgHal microcrystals.

Grishina¹⁰⁸ found that the influence of different structural elements of anionic and cationic thiacyanines on J-aggregation has a general character and is independent of the habit and homogeneity of AgHal microcrystals. More stable J-aggregates are formed on the (100) faces compared to those on the (111) faces.

The size of emulsion microcrystals is yet another important factor determining J-aggregation of spectral sensitizers. However, the available published data do not allow one to reveal general features of dye aggregation depending on the dispersion of silver halide microcrystals in photographic emulsions.

Of all sensitisation bands, the J-band is most dependent on the additives. The concentration of Ag⁺ ions in emulsions and pH of the medium have a considerable effect on J-aggregation. In an

aqueous medium under ambient conditions, the surface of AgBr is stoichiometric to the lattice ions at pAg 5.3. The surface of AgBr acquires a negative charge as the concentration of Br[−] ions increases. The limiting surface area, which can be occupied by adsorbed bromide ions, is ~20% of the surface area of the microcrystals, a particular concentration of Br[−] ions corresponding to each habit.³ Adsorption of dyes leads to a shift of the equilibrium between the bromide ions in solution and on the surface and an increase in pAg. The amount of the adsorbed dye and the strength of adsorption on the surface of AgBr depend on the structure of the dye. For example, merocyanines and cationic dyes, which bind silver ions, are adsorbed in larger amounts at lower pAg. Adsorption of cyanines binding bromide ions is favoured by an increase in pAg.³ However, it was demonstrated⁹⁹ that adsorption of certain cationic carbocyanines depends only slightly on the change in pAg in a rather wide range and substantially decreases only at rather high silver ion concentrations (pAg < 4).

The influence of pAg on adsorption of cyanines having different structures is often determined by the influence of this factor on J-aggregation in the adsorption layer. An enhancement of the tendency to form J-aggregates upon adsorption of dyes on an AgBr powder from ethanol was observed in the presence of an excess of both Br[−] and Ag⁺ ions.^{109, 110}

In investigations of spectral sensitisation of photographic emulsions,^{5, 110} the degree of dye aggregation not necessarily changes with decreasing concentration of bromide ions (during washing of sensitised layers with water with the aim of increasing the light sensitivity). More recent studies demonstrated¹¹¹ that J-aggregation of many cyanines is suppressed in the presence of an excess of silver ions, a considerable amount of dyes being displaced to gelatine. The addition of an AgNO₃ solution (to pAg 3–4) to a monodisperse emulsion before the addition of a spectral sensitizer led to suppression of J-aggregation of quino-2-cyanines compared to J-aggregation in the starting emulsion. This was not observed in the case of other mono- and trimethine-cyanines.¹¹² Therefore, J-aggregation of cyanine dyes depends not only on pAg but also on the way of changing this parameter.

Cyanine dyes are bases whose protonation constants differ by 14 orders of magnitude¹⁷ depending on the structure of the dye and, as a consequence, the influence of pH on aggregation is substantially different for dyes having different structures. Generally, an increase in pH leads to a particularly substantial weakening of the J-band of basic cyanines as pH is lowered. The following factors cause a decrease in the effect of pH on J-aggregation: the cubic habit of microcrystals, high concentrations of I[−] ions in the substrate, an excess of Hal[−] ions in the solution, a high molar absorption coefficient of the dye and the absence of competitive adsorbents.^{113, 114} It should be taken into account that pAg and pH can substantially depend on the presence of sensitizers and other additives in emulsions. For example, the addition of a sensitizer to an acidic emulsion followed by an increase in pH does not lead to a weakening of J-bands of thiacyanines.

For dye aggregation, not only pAg, pH and the nature of the adsorbent but also the nature of gelatine, which is used in photographic emulsions as a dispersion medium, are of considerable importance. The influence of gelatine was examined in a number of studies (see, for example, Ref. 20). The absorption spectra of dyes substantially depend on the gelatine concentration. Small amounts of gelatine serve as aggregation sites, while the carboxy groups of gelatine can serve as adsorption sites for dyes in solution. The influence of gelatine on J-aggregation, in particular, the dependence of J-aggregation on the concentration of gelatine and its type, was studied.²⁰ Dye aggregation starts on particular sites of gelatine molecules. The concentrations of these sites in different types of gelatines are different.

The influence of gelatine on J-aggregation of cyanine dyes is associated with pH,²⁰ because gelatine is a polyelectrolyte, different types of gelatine having somewhat different isoelectric points.

The influence of the main stabiliser of photographic emulsions of 4-hydroxy-6-methyl-1,3,3a,7-tetraazaindene (sta-salt) on aggregation of different dyes was studied in detail by Shapiro *et al.*^{79,80,115–118} The action of the sta-salt on quino-2,2'-cyanine was examined. In the study of an emulsion containing cubic AgBr microcrystals with dimensions $0.17\ \mu\text{m}$ subjected to gold and sulfur sensitisation, the sta-salt was demonstrated to cause a transformation of the J-band ($\lambda_{\text{max}} = 575\ \text{nm}$). At low concentrations of the sta-salt, this band is shifted to shorter wavelengths; an increase in the concentration of the sta-salt to $(2-5) \times 10^{-3}$ mol per mole of AgBr gives rise to two distinct absorption bands at $\lambda_{\text{max}_1} = 570\ \text{nm}$ and $\lambda_{\text{max}_2} = 580\ \text{nm}$; at the sta-salt concentration of $\geq (8-10) \times 10^{-3}$ mol per mole of AgBr, one J₂-band appears at longer wavelengths. However, the character of aggregation and the efficiency of supersensitisation substantially depend on the order of addition of the sta-salt and a dye. The action of the sta-salt was related^{115–118} to adsorption on surface defects, on which J-aggregation starts. Aggregation is suppressed by stabilisers belonging to heterocyclic thio derivatives (benzothiazole-2-thiol and 1-phenyltetrazole-5-thiol).¹¹⁹

The addition of various surfactants to emulsions causes changes in the absorption spectra of J-aggregating sensitizers.^{120,121} It was concluded that J-aggregates of anionic cyanine dyes are more stable against surfactants, which are used as precipitants of the solid phase, than those of cationic dyes.

The addition of colour-forming non-diffusing components (CNC) to an emulsion medium impairs J-aggregation of cationic cyanine dyes.^{77,78} This is attributed to desorption of the sensitizer from the surface of emulsion microcrystals. J-Aggregates of betaine dyes are even more stable against the desorption action of CNC; for these dyes, spectral sensitisation in the J-band is retained in the presence of CNC.⁷⁷ This fact was also noted by Lifshits and co-workers (see references in the publications^{77,78}), who demonstrated the stability of cyanine dyes against CNC to increase upon fusion of benzene and thiophene rings. The sensitising action of J-bands of benzimidacarbocyanines in the presence of CNC is enhanced by the Hal, CF₃, CN and CO₂R substituents in heterocyclic fragments. This may be associated with an increase in the strength of bonds in J-aggregates on AgHal microcrystals.

Bis-quaternary salts, in particular, benzimidazole derivatives,^{122–124} contrary to CNC, facilitate J-aggregation. In the presence of bis-quaternary salts, the J-band is shifted to longer wavelengths and its intensity slightly increases. Such changes were observed, for example, in the spectra of 3,3'-di(γ -sulfopropyl)-9-ethyl-4,5,4',5'-dibenzothiacarbocyanine betaine. An increase in the intensity of J-bands, including the appearance of J₂- and J₃-bands, was observed also for other carbocyanines, which show a weak tendency to form long-wavelength aggregates characterised by the highest photographic efficiency. According to the results of the study,¹²⁴ co-adsorption of dyes and bis-quaternary salts results in an increase in the strength of adsorption of polymethine dyes against the desorption action of CNC. The influence of bis-quaternary salts of α -picoline on J-aggregation of cyanine dyes was examined.^{125,126} The addition of a bis-quaternary salt of α -picoline at concentrations similar to the concentrations of the dye was demonstrated to enhance J-aggregation. This phenomenon is arbitrarily called catalysis of aggregation.

J-Aggregation is enhanced in the presence of inorganic I[−], CN[−] and SCN[−] anions.^{2,77,78} These anions form poorly soluble salts with Ag⁺ ions and, being located in the adsorption layer, provide prerequisites for a close packing of dyes, resulting in a substantial increase in aggregation adsorption. The influence of these anions on J-aggregation and photographic efficiency of thiamonomethinecyanines adsorbed on cubic AgCl microcrystals and planar AgBr(I) microcrystals was examined.¹²⁷ It was found that J-aggregates of thiamonomethinecyanines are formed in the presence of the I[−], CN[−] or SCN[−] ions and the efficiency of spectral sensitisation substantially increases. The most pronounced effect was observed in the presence of SCN[−].

In the presence of SCN[−], adsorption is increased and J-aggregation of thiamonomethinecyanines and oxa-, imida- and thiocarbocyanines on cubic AgCl microcrystals is enhanced.^{128–131} The factors responsible for the observed changes were revealed.¹²⁸ Electronic photographs of microcrystals of the starting emulsion and the emulsion treated with a KSCN solution were published. Surface etching occurs on microcrystals treated with rhodanide ions, and pronounced outgrowths are observed at the vertices and edges of AgCl cubes. An increase in the structure imperfection due to formation of a new phase (apparently, of AgSCN) is favourable for nucleation and growth of J-aggregates. This is accompanied by a substantial increase in the spectral sensitivity at the maximum of the J-band. The introduction of SCN[−] ions into an AgCl emulsion before the addition of a dye solution⁸³ is favourable also for J-aggregation of thiadicarbocyanine dyes, which serve as spectral sensitizers for the IR spectral region, thus substantially shifting the spectral sensitivity range to the IR region.

J-Aggregates consisting of two different dyes are of particular interest. It should be noted that data on such J-aggregates are scarce. The formation of mixed J-aggregates from two thiadicarbocyanine dyes having different structures was documented.¹³² Absorption spectra of photographic layers sensitised by individual thiadicarbocyanines and their composites are shown in Fig. 16*a*. Each dye forms its own J-aggregate. The simultaneous

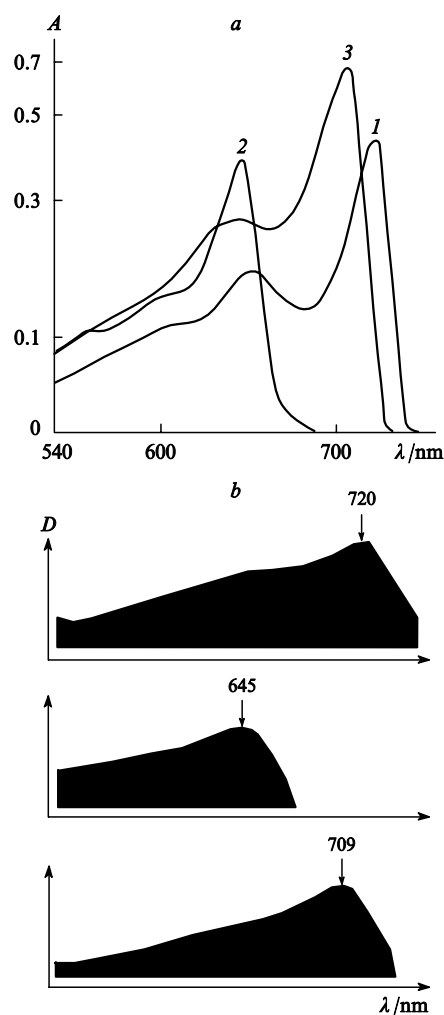


Figure 16. Absorption spectra of photographic layers sensitised by 3,3'-diethyl-5,5'-dimethoxy-8,10-dimethylenethiacarbocyanine tosylate (1), the pyridinium salt of 3,3'-di(γ -sulfopropyl)-5,5'-dimethoxy-9-ethylthiacarbocyanine (2) and their composite (3) (a) and the spectrograms of the corresponding layers (b);¹³² D is the blackening density.

addition of equimolar concentrations of dyes to an emulsion gives rise to a new J-band (curve 3 in Fig. 16a), the intensities of the J-bands of individual dyes being decreased. The spectrograms obtained on the corresponding photographic layers (Fig. 16b) are clear evidence of the formation of a new photochemically active J-band, whose maximum is between the sensitisation maxima of the individual J-bands of two dyes. The principal conclusion¹³² was that the position of the sensitisation maximum can be varied over a wide range by changing the concentrations of dyes involved in mixed J-aggregates.

Mixed J-aggregates of thiocarbo- and thiadicarbocyanines were examined in the study.¹³³ The results are presented in Fig. 17. The method of formation of mixed J-aggregates allows the selection of J-aggregates. In this case, a new J-aggregate inherits the properties of the parent dyes. For example, mixed J-aggregates containing carbo- and dicarbocyanines combine the efficiency of carbocyanines with the spectral sensitisation zone in the IR spectral region characteristic of dicarbocyanines.¹³⁴ The formation of mixed J-aggregates from oxacarbocyanines having different structures was observed for the first time in the study.¹³⁵ The problem of supersensitisation in mixed J-aggregates of thiadicarbocyanine dyes was discussed.¹³⁶

In the studies,^{137,138} the possibility of the formation of mixed and heterocontact J-aggregates from thiadicarbocyanine and monomethinecyanine dyes both in an aqueous gelatine solution and on the surface of AgBr(I) crystals with (S + Au)-chemical sensitisation was examined. The structures and properties of

mixed J-aggregates formed on the surface of AgHal were studied.¹³⁹

From the aforesaid, the following conclusion can be drawn. Since J-aggregation of dyes occurs on the surface of AgHal microcrystals, the J-aggregation process often more substantially depends on the surface state than on changes in the structure of the dye. The surface state of microcrystals in an emulsion is determined primarily by their habit. It is known¹¹¹ that the (111) surface has a larger number of jogs and kink-sites, *i.e.*, it is more imperfect than the (100) surface. Hence, the (111) surface contains a larger number of sites with an excessive energy at which nucleation of J-aggregates can occur. Therefore, the nucleation of aggregates should occur more easily on the (111) surface. However, J-aggregation, like crystallisation, includes two steps, *viz.*, nucleation and crystal growth (growth of J-aggregates). Presumably, the subsequent growth of J-aggregates, which determines the position of the absorption maximum of the J-band, occurs more readily on the less imperfect (100) surface on which the smaller number of J-aggregates are nucleated. It is the contribution of these two steps that determines J-aggregation of a particular dye. If a dye is not prone to J-aggregation, nucleation more readily occurs on the (111) surface. However, an increase in the size of aggregates on this surface is unlikely. On the contrary, if a dye is prone to aggregation, nucleation does not limit the process and ordered J-structures more readily grow on the (100) surface of the crystal. Apparently, the different contributions of these processes to the formation of J-aggregates account for the seemingly contradictory published data on the ease of aggregation on the (111) and (100) surfaces.

Evidently, the charge state of the surface of AgHal microcrystals is determined by the concentrations of the Ag^+ and Hal^- ions in an emulsion. In the presence of an excess of Ag^+ , adsorption of molecules of certain dyes (particularly those containing sulfur atoms) on the surface is facilitated, which hinders J-aggregation. Compounds adsorbed on the surface of AgHal (surfactants, thio derivatives and various heterocyclic bases), particularly those which are capable of forming poorly soluble complexes and salts with silver ions, should play a great role. Apparently, stabilising and antifogging compounds and inorganic ions belong to this class.

Therefore, J-aggregation is determined not only by the molecular structure of dyes but also by parameters combined under the general name 'emulsion factors'.

3. Structures of dye aggregates adsorbed on AgHal microcrystals

The aggregate structures both in solution¹⁴⁰ and in crystals¹⁵ were studied in depth. It was noted that J-aggregation in solution is similar to crystallisation. In particular, two steps are distinguished: nucleation and aggregate growth.¹⁴¹

As mentioned above, dye molecules differ in the ability to form aggregates depending on their structure. In the general case, J-aggregation more readily occurs on the surface of solid phases than in solution. The numbers of monomeric fragments involved in J-aggregates of dyes in aqueous solutions were determined by different methods.^{3,16-18,20,142} The degree of polymerisation of aggregates can vary from 2 to 10^6 depending on the molecular structure of the dye and the method used for the determination. The main methods for the determination of the number of molecules in J-aggregates in solution were described in the publications.^{3,16,24}

In early studies, a knowledge of the structures of J-aggregates was based on X-ray diffraction data obtained by Hoppe¹⁴³ for aggregates of 2,2'-cyanine dyes. These results are as follows:

- individual dye molecules are extended parallel to each other;
- short axes of dye molecules are inclined to the axis of the aggregate; the deviation from the normal is 35° ;
- the normal distance between the molecules along the axis of the aggregate is $\sim 3.6 \text{ \AA}$.

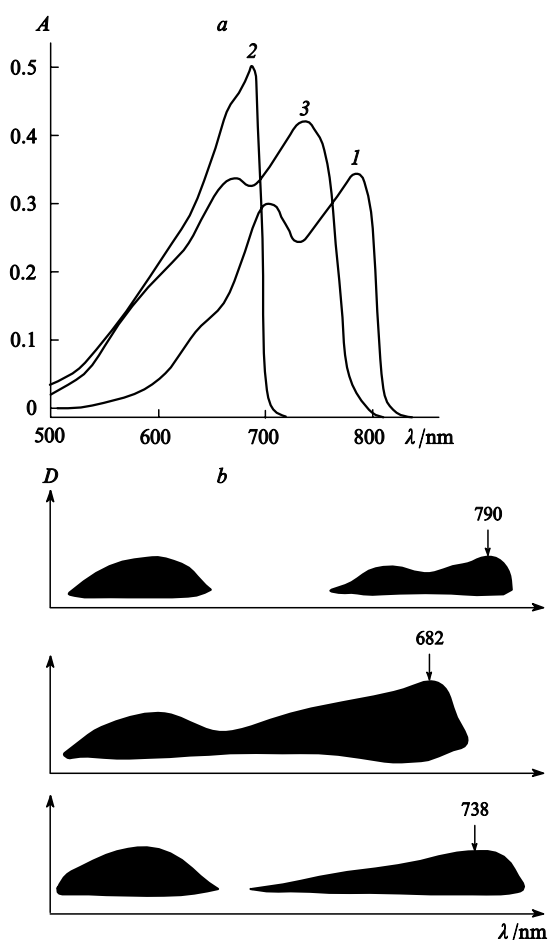


Figure 17. Absorption spectra of photographic layers sensitised by the triethylammonium salt of 5,5'-dichloro-3,3'-di(γ -sulfopropyl)-9,11-(β , β -dimethyltrimethylene)-10-methylthiadicarbocyanine (1), the pyridinium salt of 3,3'-di(γ -sulfopropyl)-4,5,4',5'-dibenzo-9-ethylthiadicarbocyanine (2) and their composite (3) (a) and the spectrograms of the corresponding layers.¹³³

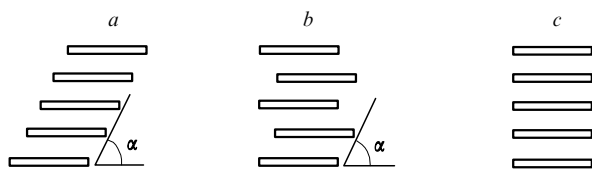


Figure 18. Models of structures of J- (*a*, *b*) and H-aggregates (*c*) of cyanine dyes.^{144, 145}

A slipped-deck-of-cards structure: a staircase structure (*a*) and a ladder structure (*b*).

In early studies, Scheibe *et al.*^{144, 145} proposed models for structures of J-aggregates as a slipped deck of cards, *viz.*, a staircase and a ladder, with consideration for the results obtained by Hoppe (Fig. 18 *a, b*). The authors reached a conclusion that dye cations are adsorbed on edges of AgHal in close-packed monolayers. Based on the degree of light polarisation in absorption bands of quino-2,2'-monomethinecyanine aggregates on freshly cleaved mica crystals, the angle α between the plane of the molecules and the axis of the aggregate was estimated as $\sim 55^\circ$. At the same time, the plane of the molecule in the structure of H-aggregates (a hypsochromic shift) is perpendicular (in the authors' opinion) to the axis of the aggregate (Fig. 18 *c*).

The above-considered structures of J-aggregates were generally accepted until the late 1960s. Bird and co-workers³³ refined the basic staircase structure proposed by Scheibe with the use of the point-dipole theory. These results contribute to the development of an idea, according to which the main structures of H- and J-aggregates are, in principle, identical. However, $\alpha < 54^\circ 44'$ in J-aggregates and $\alpha > 54^\circ 44'$ in H-aggregates. The initial version of the point-dipole theory was inapplicable to precise quantitative calculations of J-aggregates. Hence, this theory was improved based on the quantum-chemical model of interactions between molecules in aggregates taking into account electron cloud overlap (an electron gas model). This theory was applied to large aggregates of various dyes, and, although the results of calculations were inaccurate, they allowed one to obtain correct orders of the angles.

Presumably, aggregates of cyanine dyes in solution differ from those adsorbed on a substrate in that the structure of adsorbed aggregate is related to the crystal lattice structure of the adsorbent and molecules in adsorbed aggregates are packed less closely than in solution. This is evidenced by the results of spectroscopic studies. J-Aggregates of the same dye give a narrower J-band in solution compared to that in the adsorbed state. Apparently, this is associated with the affinity of particular fragments of cyanine dye molecules for local regions of the surface of AgHal.⁹³

Bird and co-workers^{146–148} applied an improved point-dipole model to a specific case of benzothiazole dyes on an AgBr substrate. Circular dichroism measurements of adsorbed J-aggregates demonstrated that dye molecules are oriented in a particular fashion on different faces of AgBr microcrystals.¹⁴⁷ It was postulated^{146, 147} that the long axis of the dye molecules in aggregates is oriented predominantly on the surface of microcrystals along the [110] direction. In this case, rows of Ag^+ ions on the surface of a cube are at a distance of 4.08 Å, whereas rows on the surface of an octahedron are at a distance of 3.54 Å, *i.e.*, at a distance similar to the standard intermolecular distance in the graphite lattice (3.4 Å) found²⁰ for the packing of planar aromatic molecules. Bird suggested that chemisorption of dyes is accompanied by the formation of bonds between the Ag^+ ions of the AgBr lattice and the sulfur atoms of the benzothiazole moieties of the molecules, which form a structure of a slipped-deck-of-cards type and are adsorbed so that the sulfur atoms are oriented toward the surface of microcrystals and the NR groups border the solution. As a consequence, the formation of particular aggregate structures of dye molecules with a lateral shift by 3, 2, 1 or 0 ionic

radii can be formed on the octahedral surface. An application of this chemisorption model to cubic microcrystals presents certain difficulties.

The slip angles of dye molecules along the aggregate axis (z) in the structures formed on the octahedral surface are 19, 30, 60 and 90° . According to Bird's theory, the slip angles of 90 and 60° corresponding to Scheibe's staircase structures are assigned to H-aggregates; the slip angles of 30 and 19° , to J-aggregates. These angles are well consistent with the spectral shifts of absorption bands of aggregates.²⁰ The results of calculations performed within the framework of the molecular-exciton theory¹⁴⁹ confirmed the aggregate structures for thiocarbocyanine and its homologue. The largest bathochromic shift for linear J-aggregates corresponds to the angle of 19° between the long molecular axis of the dye and the axis of a J-aggregate.

The same slip angles ($90, 60, 30$ and 19°) were expected along the [110] direction on the (111) surface of AgCl. However, in this case the dye molecules should be located closer to each other than along the [110] direction on the octahedral surface of AgBr, because the rows of ions along the [110] direction on AgCl are located at a distance of 3.4 Å.

The researchers encountered obstacles when generalising Bird's model to the (100) surface of cubic AgBr, because the distance between the rows of silver ions along the [110] direction is larger (4.08 Å) than the graphite-like distance for aromatic structures. Bird proposed a model,¹⁵⁰ in which the assumed $\text{Ag}^+ \cdots \text{S}$ bond is deformed and, hence, the angle between the long axis of the dye molecules and the [110] direction is 24.4° . Smith demonstrated¹⁵¹ that a rotation of the molecule by only 5° is necessary for the aggregate structure to be identical to that present on the (111) surface; however, the angle α is equal to 21.7° .

A study of the aggregate structures of some sensitising dyes adsorbed on AgI, AgBr or AgCl by electron diffraction demonstrated²⁰ that the 1,1'-diethyl-2,2'-cyanine and 3,3',9-trimethylthiocarbocyanine molecules are inclined to the surface of AgHal, and the inclination angle depends on the nature of Hal^- . It was concluded²⁰ that the molecules are arranged in a regular fashion corresponding to strong adsorption forces. If adsorption forces are weak, the aggregate structure is disordered.

Based on the data on aggregation of thia- and oxacarbocyanines and taking into account the steric factors, it was concluded^{20, 152, 153} that the formation of the epitaxial $\text{Ag}^+ \cdots \text{S}$ bond proposed by Bird is highly improbable and this bond is of secondary importance in adsorption. The sizes of dye molecules do not necessarily correspond to the crystal lattice parameters of silver halide. The distances between the rows of molecules and the slip angles in the aggregates are determined by the molecular geometry and intermolecular interaction forces rather than by chemisorption forces, which, in turn, depend on the structure of dyes (the nature of heterocycles and substituents both in the chain and heterocycles and the length of the polymethine chain).

A model of physical adsorption of dyes on the surface of silver halide was proposed.¹⁵⁴ The adsorption is considered as a function of the crystallographic lattice parameters of AgHal. In the studies,^{147, 154} the adsorption of dyes was considered taking into account that the ideal (111) and (100) surfaces do not exist because of Coulombic restrictions. It is known that such surfaces contain a large number of steps parallel to the [110] direction. The orientation of the molecules of aggregated cyanine dyes formed upon adsorption is determined by the presence of steps on the surface of AgBr microcrystals. The rate of J-aggregation of pseudocyanine was higher on a larger number of defect sites of the (111) surface. The average size of J-aggregates is smaller and absorption occurs at shorter wavelengths compared to those on the (100) surface and other surfaces. The dichroism was studied as a function of the deviation of the growth direction of a dye aggregate *vs.* the [110] direction and as a function of the deviation of the real crystal surface from the perfect surface. The orientation of J-aggregates of pseudocyanine along the [110] direction was preferable. However, this tendency was not revealed for other eleven known thia-

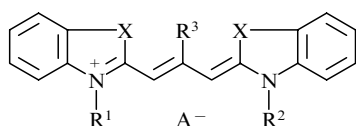
oxa- and imidacarbocyanines. Presumably, a complex variation of the arrangement of the dye molecules on the surface steps with different *hkl* indices vs. the dye structure and the absence of a pronounced orientation along the [110] direction are evidence that chemisorption plays an insignificant role.

Maskasky¹⁵⁵ also cast doubt on the occurrence of chemisorption in the case of aggregation of oxa- and imidacarbocyanines on cubic and planar AgCl and AgBr microcrystals. The orientation of J-aggregates on AgCl along the [110] and [100] directions studied by low-temperature luminescence microscopy remained unexplained within the framework of the theory of chemisorption. It was hypothesised that J-aggregates are located along surface defects of microcrystals (surface steps).

It was established that chemical bonding and Coulombic attraction make a particular contribution to aggregation of most dyes. However, van der Waals forces between a polarisable substrate and delocalised π -electrons of dyes contribute the most to adsorption.³ This accounts for the fact that the heats of adsorption of cyanines on more polarisable AgBr and AgI are higher than that on AgCl.^{156, 157} However, the model of chemisorption appeared to be useful in considering certain problems of spectral sensitisation, such as the dependence of absorption spectra of adsorbed dyes on the habit and halide composition of microcrystals,^{98, 147, 148, 158} the mechanism of supersensitisation,⁶ the influence of substituents in the chromophore chain on the spectral shifts and the relationship between the structure of aggregates and their adsorption.^{90, 146–148, 159–161}

Taking into account the model of chemisorption, Reich²⁷ explained the observed two-band spectrum in the case of adsorption of 3,3'-bis(β -carboxyethyl)-5,5'-dichlorothiarcobocyanine on AgBr and AgCl microcrystals. He proposed a model of J-aggregates consisting of two non-parallel stacks of dye molecules, in which one stack is adsorbed along the [110] direction of AgHal microcrystals, whereas another stack is adsorbed along the [101] direction to form a herringbone structure (see Fig. 5*b*). The results of calculations of the energy splitting in electronic spectra of aggregates are consistent with the experimental data for a herringbone structure with $\alpha = 30^\circ$ within each stack for an octahedral surface and with $\alpha = 35^\circ 5'$ for a cubic surface (the spectra contain broad bands in the visible spectral region).

Adsorption isotherms were used in early studies of aggregation. However, it is known that these isotherms do not allow one to establish unambiguously whether dyes are adsorbed as individual molecules or aggregates. This problem can be solved only by comparing adsorption isotherms and reflection spectra.^{3, 20, 159} The initial weak rise of adsorption isotherms up to an inflection point for carbocyanines of the type



X = S, Se, NR, CH=CH, O; A[−] — counterion;
R¹–R³ — substituents.

is accounted for by the fact that the molecules are initially adsorbed on the microcrystal surface by their planes. Further adsorption results in that the dye molecules take edgewise orientation and form a monomolecular layer of a close-packed aggregate, which is accompanied by the appearance of an inflection point in the isotherm.¹⁰³ Another explanation is that the dye molecules are adsorbed on the long edge of the molecule perpendicular to the microcrystal surface even at low concentrations, but the molecules are disordered. An increase in the dye concentration gives rise to larger ordered aggregates.

Based on the results of investigation of the shifts of spectral absorption bands and their comparison with the shifts calculated by a quantum chemical method, Kuhn and co-workers^{22, 162, 163} proposed a generalised two-dimensional model of a brickwork

arrangement of dye monomers (see Fig. 5*a*). In the case of a two-dimensional aggregate structure and the appropriate angle α , one type of aggregates can be transformed into another type (H-aggregates are transformed into J-aggregates with decreasing α and *vice versa*). A quantitative examination of X-ray spectra¹⁶⁴ of *meso*-alkyl-substituted thiarcobocyanines revealed the existence of J-aggregates formed in a brickwork fashion from sandwich dimers, which consist of monomers with the oppositely directed *meso*-alkyl groups.

It is rather difficult to determine the degree of polymerisation in the case of formation of adsorbed J-aggregates. It is hardly correct to extrapolate large self-association numbers for dyes in solution (an order of 10²) to adsorbed J-aggregates, because the properties of aggregates depend only slightly on the number of molecules in the aggregates if the self-association number is rather large. A reasonable conclusion is that the number of molecules in aggregates is small and the lower limit for the size of J-aggregates corresponds to the ratio of the sensitizer concentration to the supersensitizer concentration in mixed aggregates, at which the J-band of a supersensitizer disappears. According to estimates, J-aggregates of a pseudocyanine should contain at least three molecules. It is known that adsorbed dyes form several aggregates, which substantially differ in absorption and position of the energy levels.^{115–118}

Tani *et al.*^{165–168} made an attempt to determine the number of molecules in J-aggregates of *meso*-ethyl-substituted thiarcobocyanine by a spectroscopic method from the ratio of the half-widths of absorption bands of the monomer to those of an adsorbed J-aggregate of the dye. The calculated numbers of the molecules vary from 5 to 15. Studies by the desorption method demonstrated¹⁶⁹ that J-aggregates of thiarcobocyanine on the (111) surface included 10–37 molecules; on the (100) surface, 34–53 molecules.

In the studies,^{129–131} the sizes of J-aggregates of thiamonomethinecyanines¹²⁹ and oxa-, imida- (see Ref. 130) and thiarcobocyanines¹³¹ in an AgCl emulsion containing cubic microcrystals were estimated from the ratio of the half-widths of absorption bands of the monomers to those of adsorbed J-aggregates of the dyes. The calculated numbers of the molecules were 2–7, 3–4, 6–27 and 6–12 for thiarcocyanines, oxacarbocyanines, imidacarbocyanines and thiarcobocyanines, respectively.

Recently, due to an improvement of experimental technique, it has become possible to study the sizes of J-aggregates by direct observation using atomic force microscopy (AFM). It was found¹⁷⁰ that molecules of triethylammonium salt of 3,3'-di(γ -sulfopropyl)-5,6,5',6'-dibenzo-9-ethylloxacarbocyanine and sodium salt of 5,5'-dichloro-3,3'-di(γ -sulfopropyl)-9-ethylthiarcobocyanine form linear rows along the [210] direction on the surface of cubic AgBr microcrystals. These rows of J-aggregates form larger structures, *viz.*, columns with sizes from 20 × 60 to 30 × 60 nm,² the macrostructures of J-aggregates of oxacarbocyanine being longer than those of J-aggregates of thiarcobocyanine.

The structure of J-aggregates of quino-2,2'-cyanine on the surface of cubic AgBr microcrystals was also studied by this method.¹⁷¹ The dye molecules in a two-dimensional packing of J-aggregates are inclined at an angle of 10° to the [010] direction. The supramolecular structure of thiarcobocyanines on AgBr was studied by AFM.^{172–174} The differences in the molecular packing of H- and J-aggregates were clearly seen depending on the dye structure. Brickwork- and herringbone-type structures of aggregates were observed for the first time. The brickwork and herringbone structures of H-aggregates are shown in Fig. 19. This figure also shows a model reconstruction of thiarcobocyanine aggregates. Therefore, different aggregate structures, which have been considered earlier in the literature, were confirmed by experimental methods for the first time.

The sizes of columns of J-aggregates determined by AFM agree well with the results of investigation of these aggregates by analytical colour fluorescence electron microscopy (ACFEM).

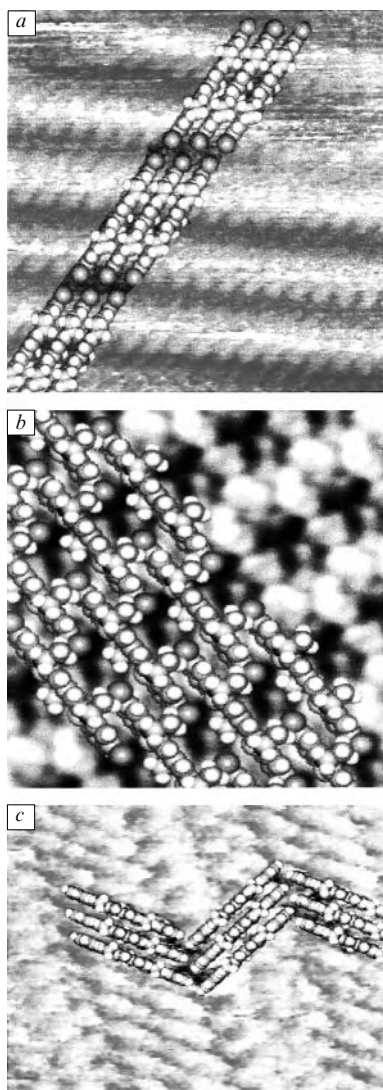


Figure 19. Structures of aggregates of thiocarbocyanine dyes determined by the AFM method;¹⁷³

(a) an H-aggregate of 5,5'-dichloro-3,3'-diethyl-9-methylthiocarbocyanine tosylate, an image area is $5.6 \times 5.6 \text{ nm}^2$; (b) a brickwork structure of 5,5'-dichloro-3,3'-diethyl-9-ethylthiocarbocyanine tosylate, an image area is $3.6 \times 4.2 \text{ nm}^2$; (c) a herringbone structure of 3,3'-dimethyl-4,5,4',5'-dibenzo-9-methylthiocarbocyanine tosylate, an image area is $4.1 \times 4.5 \text{ nm}^2$.

Studies by ACFEM demonstrated¹⁷⁵ that the dimensions of columns depend on the nature of the dye. The size distribution of J-aggregates of oxa- and thiocarbocyanines depending on the location of J-aggregates on the (100) face of AgBr was also studied by ACFEM.¹⁷⁶ It was found that large J-aggregates are predominantly formed in zones bordering the vertices of microcrystals; large and small J-aggregates, in zones bordering the edges; small J-aggregates, in the middle region of the face. The sizes of aggregates were determined in pixels (1 pixel = $3.3 \times 4.1 \text{ nm}^2$). The sizes of large, medium and small aggregates were 5–6, 3–4 and 1–2 pixels, respectively. J-Aggregates of cyanine dyes on AgBr microcrystals were also studied by ACFEM.¹⁷⁷ The surface area of J-aggregates was $\sim 30 \times 70 \text{ nm}^2$. The size of J-aggregates increased without change in their number with increasing amount of the adsorbed dye. It was demonstrated that aggregates on the surface of cubic AgBr are extended along the [110] or [210] direction.

The ACFEM method was used to study J-aggregation and the orientation of quino-2,2'-cyanine and oxacarbocyanine on the

(100) and (111) surfaces of cuboctahedral AgBr microcrystals.¹⁷⁸ It was found that the luminescence colour of J-aggregates changes under the action of the electron flux during measurements. No differences in luminescence on the (100) and (111) surfaces were revealed. The formation of J-aggregates on different faces of AgHal was revealed from luminescence studies.^{178, 179} J-Aggregation of thia- and indocarbocyanine dyes on cubic and planar AgBr microcrystals was investigated by ACFEM.¹⁸⁰ Based on the results of this investigation, it was concluded that the sizes of J-aggregates of 5-substituted thiocarbocyanines on cubic microcrystals are larger than those of unsubstituted dyes. It was noted that an increase in the sizes of J-aggregates of dyes with time occurs according to the mechanism of Ostwald ripening.

Thus, the structures of J-aggregates in solution and the structures of aggregates adsorbed on the surface of AgHal were studied in depth. The main structures of J-aggregates of cyanine dyes were calculated and determined experimentally. J-Aggregates were demonstrated to be highly organised and their structures are determined by the geometry of the dye molecules, the surface of AgHal microcrystals and the surface concentration of the dye. However, due to a complexity of photographic systems, the aggregate structures formed in a particular photographic emulsion cannot always be determined with high precision. Nowadays, it is impossible to take into account, in full measure, all various interrelating factors in real emulsion systems, the role of the dye structure, the method of the addition of the dye to photographic emulsions, the role of supersensitisers and aggregating additives and the surface state of microcrystals. Nevertheless, the main factors responsible for J-aggregation, which can be used to initiate the formation and control the growth of J-aggregates, were revealed. It is impossible to control these processes without knowledge of the surface state of AgHal emulsion microcrystals.

4. Energy levels of aggregated forms of dyes

The positions of the energy levels of aggregates responsible for their physicochemical properties depend primarily on the electronic structures of individual dye molecules and the mutual geometric arrangement of the molecules in aggregates.

Two π -electrons are located in the highest occupied molecular orbital (HOMO) of a monomeric dye in the ground state. Absorption of a light quantum by a dye without a change in the spin leads to excitation of one π -electron from HOMO to the lowest unoccupied molecular orbital (LUMO) and the molecule is converted into the first excited singlet state (Dy^*). The energy of transition from the ground state to the first excited singlet state is equal to the energy difference between LUMO and HOMO. The positions of the energy levels of LUMO (ϵ_{LUMO}) and HOMO (ϵ_{HOMO}) relative to the electron bands of AgHal determine the efficiency of spectral sensitisation by a dye.^{2, 3}

The positions of the energy levels of organic dyes can be found experimentally and calculated by quantum chemical methods. Since it is difficult to determine the energy levels of dyes adsorbed on AgHal by experimental methods,³ quantum chemical methods have gained wide acceptance.

First attempts to relate the energy levels (calculated by the Hückel method) of the simplest cyanines to their photographic efficiency were made in the studies.^{181, 182} More recently, systematic studies by Tani and Kikuchi^{183, 184} and Sturmer and Gaugh^{185, 186} were published. The charge distributions in molecules were calculated by semiempirical all-valence-electron methods at the CNDO/2 level and by the Pariser–Parr–Pople method.^{187, 188} These methods give satisfactory estimates for the energies of spectral transitions, charge distributions, dipole moments, redox potentials and $\text{p}K_{\text{a}}$ of dyes. When studying the excited state, Forster¹⁸⁹ provided a qualitative verification of the spectra of cyanine dyes based on the selection rules for electron transitions. The calculated data were summarised by Kachkovskii.^{14, 190}

According to experimental data, the ionisation energies are 4.4–5.9 eV,^{191, 192} and the electron affinities are 3.0–3.3 eV.¹⁹³

Experimental methods for the determination of ionisation potentials and electron affinities, which characterise the ground and excited states of adsorbed dyes, are very complicated and give ambiguous results. Electrochemical methods for the determination of reduction and oxidation potentials have gained wide acceptance. These potentials correlate with $\varepsilon_{\text{LUMO}}$ and $\varepsilon_{\text{HOMO}}$, respectively.^{3, 6, 20} The polarographic half-wave reduction ($E_{1/2}^{\text{red}}$) and oxidation ($E_{1/2}^{\text{ox}}$) potentials of dyes in solution are generally measured. These potentials correlate with $\varepsilon_{\text{LUMO}}$ and $\varepsilon_{\text{HOMO}}$, respectively. The polarographic potentials for different types of dyes vary in the following ranges: $E_{1/2}^{\text{red}}$ from -0.6 to -2.2 V and $E_{1/2}^{\text{ox}}$ from 0.2 to 1.3 V (relative to a saturated silver chloride electrode).^{186, 192}

Adsorption of individual dye molecules on AgHal leads to changes in the positions of $\varepsilon_{\text{LUMO}}$ and $\varepsilon_{\text{HOMO}}$ because the energy levels of dyes are subjected to the perturbing action of surface defects of the substrate and impurity centres. Sets of values rather than one value are typical of $\varepsilon_{\text{LUMO}}$ and $\varepsilon_{\text{HOMO}}$ of adsorbed dyes.^{194, 195} Consequently, the mean potentials are dealt with. Therefore, the use of polarographic potentials, which are thermodynamic (*i.e.*, mean) values, is quite justified.

Taking into account aggregation, which also leads to changes in the positions of the energy levels, the situation is complicated. Evidently, the positions of the levels $\varepsilon_{\text{LUMO}}$ and $\varepsilon_{\text{HOMO}}$ of an aggregated dye relative to the conduction and valence bands of AgHal are of most importance for spectral sensitisation. Calculations of $\varepsilon_{\text{LUMO}}$ and $\varepsilon_{\text{HOMO}}$ of aggregates present considerable difficulties because it is necessary to take into account a combination of molecules characterised by a particular electron density distribution, the mutual orientation of the molecules and the influence of the substrate. Hence, the results of all calculations are approximate.

The molecular-exciton theory in the point-dipole approximation gives qualitative estimates of the shifts of the maxima in absorption spectra of J-aggregates with respect to the position of the maximum in the spectrum of the monomer depending on the intermolecular distance in the aggregate, the number of monomers in the aggregate and the packing angle.^{33, 93} When studying the spectroscopic characteristics of J-aggregates, Kuhn and co-workers^{22, 162, 163} developed a perturbation method based on the Schrödinger equation in the π -electron approximation. The calculations adequately reproduce the bathochromic shifts of absorption bands for one- and two-dimensional brickwork arrangements of molecules.

The energy change in an aggregate depending on the angle α was estimated by the Pariser–Parr–Pople method.^{196–198} It was demonstrated that there is a complex correlation between the energy change and the spectral shift. The plot of the energy of the spectral transition has a pronounced minimum at acute angles α for all dyes (Fig. 20). The angle α at the minimum energy of the spectral transition is $\sim 29^\circ$, $\sim 24^\circ$ and $\sim 21^\circ$ for tri-, penta- and heptamethinecyanines, respectively. For thia-, oxa- and imidacar-

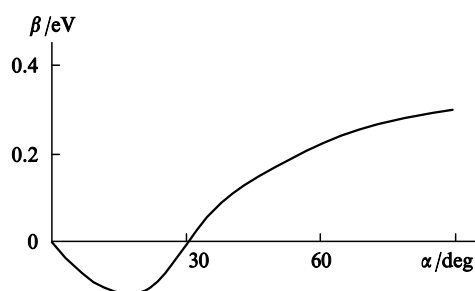


Figure 20. Plot of the energy of the spectral transition *vs.* the packing angle of molecules in J-aggregates for thia-, oxa- and imidacarbocyanines and quino-2,2'-carbocyanine.¹⁹⁸

The angle α at the minimum energy is $19 \pm 2^\circ$.

bocyanines and pinacyanol, the angle α is $19 \pm 2^\circ$; for pyridocarbocyanine, $22 \pm 2^\circ$.¹⁹⁸

Calculations for narrow J-bands are generally performed with the use of a statistical exciton model,^{199–208} according to which the random disorder in the environment is averaged by a moving Frenkel exciton in a J-aggregate. In terms of this model, the electronic structure of isolated polymethine dye molecules involved in J-aggregates is ignored. Egorov^{209–212} reduced the problem of electronic excitation of an aggregate to the problem of an elementary electron transfer, which provided an insight into the nature of the J-band.

The determination of the energy levels of J-aggregates by experimental methods presents considerable difficulties. In the review by Dietz,²¹³ the results of investigations of the energy levels in dye aggregates and the methods for their determination were generalised and analysed. The ionisation potentials, electron affinities and basicities were considered. The difficulties in measuring the redox potentials of dyes adsorbed on silver halide microcrystals were mentioned. It was concluded that the validity of the extrapolation of the polarographic half-wave potentials, which were measured in solution, to adsorbed dyes is not evident.

Nelson^{214–216} determined the ionisation energy of pinacyanol adsorbed on CdS as an aggregate. This energy is ~ 4.5 eV, which is comparable with the ionisation potential of the monomeric form. For some cyanine dyes, the ionisation potentials remain virtually constant ($5 \text{ eV} \pm 4\%$). Dyes differ in the length of the polymethine chain and the nature of heterocyclic groups. Taking into account a small difference in the experimental values, it was concluded that the level $\varepsilon_{\text{HOMO}}$ changes only slightly upon J-aggregation.

In the review by Dietz,²¹³ considerable attention was given to investigations of the luminescent properties of adsorbed polymethine dye J-aggregates, which are important for the determination of the energy levels of aggregated dyes. It is commonly accepted that luminescence of aggregates on a substrate is due to bimolecular electron–hole recombination. Usual resonance fluorescence excited in the J-band is observed for adsorbed J-aggregates. Luminescence of J-aggregates and dimers can be explained in terms of the exciton theory of splitting of the excited states due to aggregation.²⁰ Fluorescence quenching is caused by poly- and monophenols and OH^- ions. The degree of polymerisation of dyes in J-aggregates can be estimated by mathematical processing of fluorescence data.

Cooper demonstrated^{217, 218} that two bands appear in low-temperature fluorescence spectra of quino-2,2'-cyanines in solution and emulsions. These bands correspond to allowed bands of J-aggregates in the absorption spectrum with maxima at $\lambda_{\text{max}1} = 570.5$ nm and $\lambda_{\text{max}2} = 575$ nm. Based on a comparison of the intensities of resonance fluorescence of two aggregates adsorbed on a chemically sensitised AgBr emulsion, Cooper concluded that the electron transition to the conduction band of AgBr from photoexcited J₂-aggregates is more efficient than from J₁-aggregates because the latter have a more intense fluorescence band, while the intensity of the adsorption band is lower. Measurements of the microwave photoconductivity of photographic layers performed by Kellogg *et al.*²¹⁹ confirmed this fact. It was demonstrated that the low efficiency of fluorescence of J₂-aggregates corresponds to the higher efficiency of the formation of electrons in the conduction band in an AgBr emulsion. Due to the presence of impurities, the intensities of two bands change in a different way. The intensity at shorter wavelengths decreases more substantially than that at longer wavelengths. It is assumed that the difference in the photographic activity of these aggregates is associated primarily with the difference in the arrangement of molecules in J-aggregates rather than with the change in the number of molecules in the aggregates.

Based on a comparison of the results obtained in photographic studies of supersensitisation of quino-2,2'-cyanine J₁- and J₂-aggregates upon the addition of oxathiocarbocyanines with different $E_{1/2}^{\text{ox}}$ (from 0.54 to 0.98 V *vs.* SCE) and upon fluorescence

quenching in supersensitised aggregates, it was concluded^{115–118,220} that the difference in ϵ_{HOMO} for J₁- and J₂-aggregates and the positions of ϵ_{LUMO} in these aggregates relative to each other and relative to the conduction band of AgBr can be rather precisely estimated by combining these methods. An analysis of the dependence of the supersensitisation coefficient on $E_{1/2}^{\text{ox}}$ of the supersensitiser demonstrated that the position of ϵ_{HOMO} for J₂-aggregates can be estimated on the electrochemical potential scale at 0.8 V (vs. SCE), whereas the level of ϵ_{HOMO} of J₁-aggregates is lower. Fluorescence of J₁- and J₂-aggregates at 77 K is excited both in the absorption region of the dye (500–530 nm) and in the main absorption region of AgBr (337 nm). This implies that the levels of S_1 (ϵ_{LUMO}) of aggregates are lower than the conduction band bottom of AgBr. The triplet states of dyes change only slightly upon aggregation,²¹³ and the splitting of the triplet levels upon dimerisation and polymerisation is small.³⁴

In studies by Sviridov and co-workers,^{221–223} the changes in the positions of the energy levels of dyes upon J-aggregation were estimated by photochemical oxidation of poly- and monomolecular forms of carbocyanine dyes on the surface of WO₃ films. It was demonstrated that aggregates act as reducing agents for the monomeric form in oxidation of thiocarbocyanine dyes, whereas nonaggregated dyes serve as a reducing agent in the case of imidacarbocyanines. Therefore, the level ϵ_{HOMO} of thiocarbocyanines increases upon aggregation, whereas the level ϵ_{HOMO} of imidacarbocyanines decreases. For oxacarbocyanines, the levels ϵ_{HOMO} of J-aggregates also increase. An increase in the energy levels ϵ_{HOMO} of thiocarbocyanine J-aggregates compared to the energies of the occupied electronic levels of monomers was observed by Kawasaki *et al.*,^{224–226} who used electrochemical oxidation. In the case of J-aggregation, the oxidation potential becomes more negative (by ~ 0.2 V).

Cramp *et al.*,^{227,228} and Ehrlich²²⁹ were the first to study cyanine dye aggregates by flash photolysis. Chibisov *et al.*,^{230,231} employed flash photolysis to study the positions of the energy levels of dyes in J-aggregates. It was demonstrated that excitation of dyes to the J-band is accompanied by ‘whitening’ of this band and the formation of induced short-wavelengths absorption bands belonging to radical dications of dyes followed by band relaxation of J-aggregates. The relaxation rate correlates with $E_{1/2}^{\text{ox}}$ of dyes. Therefore, ϵ_{HOMO} for J-aggregates of different dyes can be related to $E_{1/2}^{\text{ox}}$.

Lenhard and Hein^{232,233} performed experimental studies on the changes in the positions of the energy levels (the redox potentials) for J-aggregation of thiadicarbocyanine containing a bridging substituent in the chain. The aggregation state of the dye was varied by introducing a deaggregating agent. An energy level diagram was constructed. According to this diagram, aggregation of thiadicarbocyanine leads to only a weak change in ϵ_{HOMO} , and the level ϵ_{LUMO} decreases by 0.32 eV.

In conclusion, let us note that substantial changes in the positions of the levels ϵ_{HOMO} and ϵ_{LUMO} upon aggregated adsorption (by about 0.2–0.3 eV) explain to a large extent the behaviour of cyanine dye J-aggregates as either sensitisers or desensitisers of silver halides. Hence, to predict and verify the methods for intensification of spectral sensitisation, it is important to know the positions of the energy levels of J-aggregates.

5. Mechanism of the photographic action of dye aggregates

In the pioneering studies performed by Spence and Carroll²³⁴ as well as by West and Carroll,²³⁵ the photochemical activity of dyes was quantitatively estimated and the molecular state was demonstrated to be photochemically active. More recently, Natanson and Klimzo^{4,5} found that the photochemical activity of J-aggregates generally increases as the corresponding band is shifted to longer wavelengths, and the activity of H-bands decreases as the band is shifted to shorter wavelengths. It should be noted that the photochemical activity of J-aggregates of well-aggregating dyes is higher than the activity of the molecular state. As a rule, the

sensitising ability of J-aggregates characterised by a narrow band is higher than that of J-aggregates with a broad band.⁴

If J-aggregates are formed on the surface of AgHal microcrystals only at rather high dye concentrations, these aggregates were demonstrated^{4,5} to be photographically less active than monomers. The lower photochemical activity of J-aggregates of some sensitising dyes compared to that of dyes in the M-state is attributed to a higher probability of secondary dye desensitisation and self-desensitisation competing with the formation of a latent photographic image.^{6,80}

Processes responsible for desensitisation lead to a decrease in the intrinsic light sensitivity of photographic emulsion layers. Photoexcitation of dyes also causes desensitisation. This process is referred to as dye self-desensitisation.^{3,6} The difference between dye desensitisation and self-desensitisation is related to the differences in the photoprocesses upon photoexcitation of AgHal and dyes.^{6,236} As a rule, a decrease in the light sensitivity due to self-desensitisation is more pronounced in the region of additional light sensitivity compared to the intrinsic light sensitivity.^{6,236}

Aggregated forms of dyes are characterised by self-desensitisation according to the hole mechanism (type II dye self-desensitisation):⁶ recombination of dye holes and photoelectrons trapped on the surface of AgHal microcrystals. These processes are most typical of dye J-aggregates, in which holes are translated to considerable distances. The type II desensitisation process, unlike type II self-desensitisation, involves a larger number of steps (Fig. 21).⁶ Photoexcitation of AgHal can result in that some holes are trapped on the surface of AgHal microcrystals by the dye to form dye holes and some holes can be trapped by hole-acceptor impurity centres (see Fig. 21a). The type II self-desensitisation process is, apparently, simpler because dye holes inevitably appear upon spectral sensitisation, *i.e.*, in the case of electron transfer from Dy* to AgHal (see Fig. 21b). Therefore, the number of dye holes can be larger. Hence, the probability of self-desensitisation can be higher than the probability of desensitisation and, as a consequence, its influence on spectral sensitivity can be larger than the influence of desensitisation on intrinsic light sensitivity. It should be noted that if the level ϵ_{HOMO} of a dye is lower than or

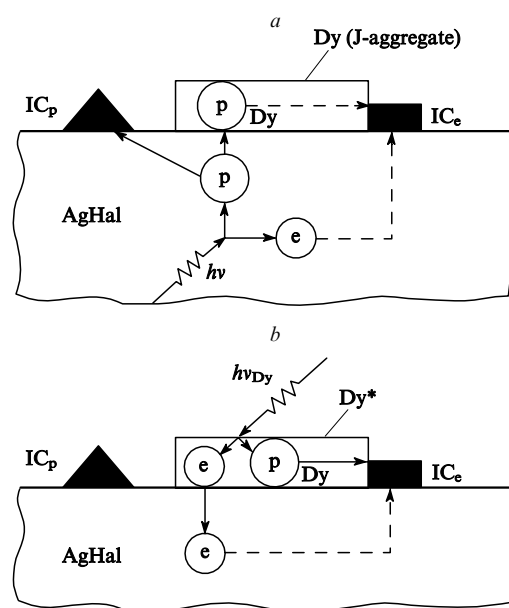


Figure 21. Schemes of desensitisation (a) and type II self-desensitisation (b).¹¹⁸

IC_e is an impurity site as an electron acceptor; IC_p is an impurity site as a hole acceptor; e is a photoelectron; p is a photohole; $h\nu$ is a light quantum absorbed by AgHal; $h\nu_{\text{Dy}}$ is a light quantum absorbed by a dye.

close to the valence band top of AgHal, the dye holes can be injected directly to the valence band.

As opposed to type I desensitisation and self-desensitisation according to the electron-acceptor mechanism, no clear dependence for type II desensitisation and self-desensitisation on the polarographic half-wave oxidation potential $E_{1/2}^{\text{ox}}$, *i.e.*, the potential of a dye hole, was found.^{79, 80, 237} Moreover, structurally similar dyes, which form J-aggregates showing similar absorption maxima and having virtually equal $E_{1/2}^{\text{ox}}$, can differ substantially in the desensitising ability and efficiency of spectral sensitisation.^{6, 80}

In the studies,^{6, 79, 80} the efficiency of type II self-desensitisation was related not only to the energy factor but primarily to the kinetic factor. According to the modern views, sulfite sensitisation affords the $(\text{Ag}_2\text{S})_n$ clusters formed at surface defects of AgHal. Silver sulfide clusters form impurity centres, which exhibit properties of either electron acceptors (IC_e) or hole acceptors (IC_p) depending on n , the charge and the location site. Spectral sensitizer molecules are also adsorbed on the surface of AgHal, the molecules being partially self-organised to form rather elongated J-aggregates. According to the kinetic model of desensitisation,^{6, 79, 80} type II desensitisation and, particularly, self-desensitisation, should substantially depend on the spatial arrangement of the dye aggregates and the recombination centres at which photoelectrons are located. The rate constant of desensitisation (recombination) according to the hole mechanism (k_d) can be described by the equation

$$k_d = A_d \exp\left(-\frac{\alpha \Delta E^\circ}{RT}\right), \quad (3)$$

where A_d is the frequency factor, α is the coefficient and ΔE° is the electrochemical potential difference between the dye hole and the electron trapped by an impurity centre on the surface of AgHal

$$\Delta E^\circ = E_{1/2}^{\text{ox}} - E_{\text{IC}_e}^\circ.$$

It should be noted that the rate constant of recombination for organised systems of J-aggregates, unlike stochastic systems in which a dye exists in the molecular state, is more dependent on the frequency factor A_d than on the energy factor (ΔE°). The frequency factor is a function of the distance r between the J-aggregate and the electron-acceptor impurity centre.

If the transfer of a dye hole to IC_e occurs without the involvement of the valence band of AgHal on the surface across the tunnel junctions under a barrier with a width r , then

$$A_d \approx \exp(-r),$$

i.e., the frequency factor strongly depends on r . In addition, this factor is related to the mobility (μ) of dye holes within the aggregate. The latter is determined by the structure of the J-aggregate, primarily, by the interplanar distance between the dye molecules in the aggregate and the packing angle. Consequently,⁶

$$A_d = f(\mu, r).$$

If self-organisation of dye molecules in J-aggregates is hindered, it starts at surface defects of AgHal, including impurity centres, *viz.*, chemical sensitisation products (Fig. 22 *a*). Due to a contact between J-aggregates and IC_e ($r \rightarrow 0$), the frequency factor and the recombination rate increase, which is manifested as a considerable dye self-desensitisation. On the contrary, if J-aggregation readily occurs and aggregates can be formed not only at defects of AgHal but also at other sites, the probability of contacts between the aggregates and IC_e decreases, the distance r increases (Fig. 22 *b*) and, as a consequence, the recombination rate decreases. Apparently, the difference in the photographic properties of dyes similar in the structure and energy levels is associated with the topography of aggregates formed on the surface of AgHal. Let us note once again that the probability of type II self-desensitisation, which depends on the dye structure, the habit of AgHal microcrystals, pAg and other factors, can be

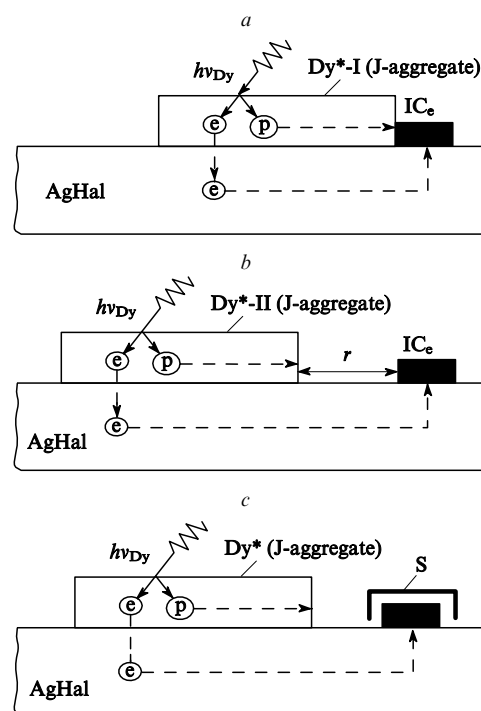


Figure 22. Schemes of self-desensitisation of J-aggregates of dyes (*a*, *b*) and supersensitisation according to the 'isolation' mechanism (*c*).

substantially higher than the probability of desensitisation. Hence, self-desensitisation can to a large degree determine the efficiency of spectral sensitisation of AgHal by aggregating dyes.^{6, 80}

The efficiency of spectral sensitisation can be increased with the use of supersensitisers. Over many years, the results of studies on desensitisation and supersensitisation have not been generalised. Shapiro considered^{79, 80, 126} a generalised chemical concept of spectral sensitisation, in which particular attention is given to secondary oxidative dye self-desensitisation. According to this concept, supersensitisation is considered as deceleration of secondary dark dye self-desensitisation. There are at least three mechanisms of inhibition of type II hole self-desensitisation: (1) dye hole trapping by a supersensitiser; (2) 'isolation' of a hole from an impurity centre acting as a photoelectron acceptor (IC_e); (3) control over aggregation in such a way as to exclude the possibility of existing contacts between aggregates and IC_e .¹²⁶

The mechanism of dye hole trapping by a supersensitiser (the arbitrary reductive mechanism) was considered in detail by Gilman.²³⁸ This mechanism is most typical of J-aggregating dyes, in which holes can migrate to large distances within the aggregates. A bright example of the supersensitising action of the styryl fragment of 2-(*p*-diethylaminostyryl)benzothiazole on J-aggregates of 1,1'-diethyl-2,2'-cyanine iodide was given in the study.²³⁵ A slight change in the absorption band of J-aggregates in the presence of a supersensitiser led to a sharp increase in the photographic sensitivity (by more than an order of magnitude). Measurements of the photoconductivity of photographic layers also demonstrated a considerable increase in photoconductivity in the case of absorption in the J-band, which is indicative of an increase in the quantum yield of Dy^* -derived photoelectrons to the conduction band of AgHal. According to West and Carroll,²³⁵ photoexcitation of J-aggregates gives rise to excitons, whose rate of propagation in the dye layer is so high that the electron transfer to the conduction band of AgHal can be hindered. Hence, excitation is lost due to either thermal energy dissipation or dye fluorescence. The addition of a supersensitiser and inclusion of the latter in J-aggregates hinders exciton motion. Therefore, a super-

sensitiser acts as an exciton trap. Exciton trapping leads to an increase in the probability of electron transfer to AgHal. This phenomenon was considered in more detail by Gilman.²³⁸

According to Gilman, supersensitisation involves oxidation of a supersensitiser (S) by a photoexcited dye Dy_j^* or a dye hole ($Dy_j^{+\bullet}$)



resulting in relocation of a hole to the supersensitiser.

Supersensitisation according to reaction (4) gives rise to the radical anion Dy_j^- . The level ϵ_{LUMO} of the electron in Dy_j^- is higher than that in Dy_j^* due to interelectron repulsion of the extra electron. Hence, the probability of electron transfer to the conduction band of AgHal increases and, as a consequence, the efficiency of sensitisation increases. In the case of supersensitisation according to reaction (5), the probability of recombination processes decreases due to removal of a dye hole and, consequently, the spectral sensitivity can increase. For supersensitisation to occur according to the hole-acceptor mechanism, the supersensitiser must be oxidised more readily than the dye. Therefore, the condition for supersensitisation can be written as follows:²³⁸

$$E_{1/2(S)}^{ox} < E_{1/2(Dy)}^{ox}.$$

The 'isolation' mechanism of supersensitisation^{79, 80, 239, 240} involves selective adsorption of organic compounds on IC_e (generally, on Ag_2S centres), isolation of J-aggregates from IC_e and, consequently, a decrease in the probability of recombination processes (see Fig. 22c). Processes according to the 'isolation' mechanism can occur with supersensitisers, which are more difficult to oxidise than dyes,²³⁹ i.e.,

$$E_{1/2(S)}^{ox} > E_{1/2(Dy)}^{ox}.$$

Various heterocyclic compounds, which are selectively adsorbed on Ag_2S centres, primarily, the well-known stabiliser 4-hydroxy-6-methyl-1,3,3a,7-tetraazaindene, can be used as supersensitisers. Purine bases, for example, guanine and adenine, exert the supersensitising action.^{79, 80} Some monomethinecyanines and nullmethinemercyanines are efficient supersensitisers of the 'isolation' type.

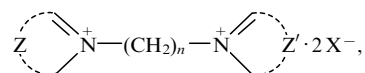
It should be noted that the 'isolation' mechanism substantially differs from the mechanism proposed by Riester.²⁴¹ In the supersensitisation model developed by Riester, dye molecules are isolated from the total surface of AgHal, and the 'isolation' mechanism consists in isolating the molecules from the surface impurity centres, which are chemical sensitisation products. This isolation model takes place in core-shell emulsions and Ir^{3+} -doped emulsions. Photoelectron trapping inside AgHal microcrystals hinders electron-hole recombination. Taking into account this fact, desensitisation and self-desensitisation can be substantially decreased.^{242–244} The formation of an interlayer formed by a supersensitiser between J-aggregates and impurity centres was observed by luminescence techniques.^{245, 246}

Belous and Tolstobrov²⁴⁶ were the first to find that the intensity of luminescence of the Ag_2S cluster in the IR spectral region decreases in a dye- Ag_2S cluster system upon light absorption by dye J-aggregates adsorbed on Ag_2S . Fano attributed²⁴⁷ the observed antisensitisation to the antiresonance effect due to interference of the excited states of the dye and Ag_2S in the case of a direct contact between a sensitiser and an impurity centre. Antisensitisation sharply decreases and the intensity of sensitised luminescence of the cluster increases with increasing distance between the Ag_2S cluster and the dye. 4-Hydroxy-6-methyl-1,3,3a,7-tetraazaindene¹¹⁷ and its alkyl analogues, thiamonomethinecyanines, mercocyanines, styryl dyes and other compounds showing specific adsorption on Ag_2S centres were used as interlayers between dye aggregates and Ag_2S centres.^{248–251}

It was hypothesised^{248, 251} that selective adsorption of organic compounds on Ag_2S centres can be due to the presence of 1,3-dipolar structures involving (in the case of thiacyanines) the nitrogen atoms of heterocycles and the carbon atom of the methine group. It should be noted that the distance between the atoms determining the dipole is 2.6 Å, i.e., it is similar to that between the Ag^+ and S^{2-} ions in the Ag_2S clusters.^{6, 248–251}

It should be noted that a superadditive increase in the light sensitivity is observed if the two above-mentioned modes of inhibition of type II self-desensitisation occur simultaneously.^{79, 80} The superadditive effect of supersensitisation is evidence of the difference between the mechanisms of supersensitisation of photographic layers by two types of compounds in successive steps of dye-hole self-desensitisation. In this case, either dye holes are initially trapped by a readily oxidisable supersensitiser followed by isolation of holes from the photographically active centres with compounds, which are difficult to oxidise and which are adsorbed on these centres, or, alternatively, supersensitisers act in the reverse order.

The third mode of supersensitisation by J-aggregating dyes consists in controlling J-aggregation¹²⁶ by adding such organic compounds to a photographic emulsion that either facilitate aggregation or are involved in 'recrystallisation' of aggregates thus facilitating the growth of more ordered structures of J-polymers. As a result, the distance r (see Fig. 22b) can increase (contacts between J-aggregates and IC_e are absent) or more ordered J-aggregates are formed. In the latter, the probability of energy dissipation of photoexcitation of J-aggregates between structurally different aggregates decreases. For example, bis-quaternary salts of heterocyclic bases of the following general formula can act as regulators of J-aggregation:



where Z and Z' are the groups of atoms, that form the pyridine, quinoline or benzimidazole rings, $n \geq 2$ and X^- is the anion.

It was demonstrated^{122, 123, 125, 126} that the addition of bis-quaternary salts to a photographic emulsion at concentrations comparable with that of the J-aggregating dye enhances the ability of the latter to form J-aggregates, causes a bathochromic shift of the absorption maximum and leads to an increase in the efficiency of spectral sensitisation. In the studies,^{125, 126} the influence of bis-quaternary salts was interpreted as facilitating J-aggregation. Apparently, the fact that the pair positive charges on the nitrogen atoms are not equal to the pair negative charges on the halide ions in the case of adsorption of bis-salts on AgHal microcrystals results in such a relief of the surface potential on the surface of AgHal at which J-aggregation is facilitated not only on defect sites but also on other regions of the surface and which is favourable for ordering of the aggregate structures.

The replacement of the alkyl groups at the nitrogen atoms of cyanine dyes by sulfoalkyl groups⁷⁸ (i.e., the transformation into dyes having a betaine structure) facilitates J-aggregation. Apparently, the presence of dipolar betaine structures in anionic dyes can promote both nucleation of J-aggregates on the dipolar surface of AgHal microcrystals (Ag^+ and Hal^- ions) and subsequent aggregate growth.

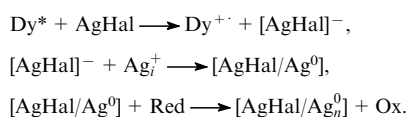
It is known that J-aggregation is affected by various photo-graphically inactive compounds, for example, ketones, nitriles, aromatic alcohols (phenols), etc., which also cause a bathochromic shift of J-bands and an increase in the efficiency of spectral sensitisation.¹²⁶ Generally, the bathochromic shifts of J-bands are related to either a decrease in the packing angle of dye molecules or to an increase in the number of sensitiser molecules involved in aggregates. Both parameters should depend on the aggregation rate. Rapid aggregation should lead to the random formation of particles of different sizes on surface defects of AgHal. Organic compounds cause 'recrystallisation' of J-aggregates. In this case, organic compounds introduced into an emulsion in large amounts

(0.1–1.0 mol per mole of AgHal) serve as a medium (a solvent) facilitating 'recrystallisation'. The latter can give rise to more ordered J-aggregates with bathochromically shifted absorption bands and far removed from IC_e ($r > 0$, see Fig. 22 b), and lead to an increase in the photographic activity of aggregates. J-Aggregation is often facilitated by an increase in the temperature of a molten emulsion and its storage at high temperature before coating.

The formation of numerous new defects, which stimulate J-aggregate growth at sites that are not bound to impurity centres, on the surface of AgHal microcrystals before the introduction of a spectral sensitiser should facilitate J-aggregation. These numerous defects occur, for example, in the synthesis of AgHal microcrystals with a variable halide composition, particularly, of AgBr(I). Hence, an increase in the concentration of iodide ions in AgBr(I) emulsions to a particular limit generally promotes J-aggregation.² This can also account for the influence of the thiocyanate and cyanide ions on J-aggregation. It was demonstrated²⁵² that the addition of iodide ions to an AgBr emulsion leads to the formation of silver iodide at the vertices and edges of microcrystals, thus promoting J-aggregation. According to the results of the studies,^{78, 253} SCN^- and CN^- ions have the same effect. In the studies,^{128–131} it was also demonstrated that J-aggregation of dyes on AgHal increases in the presence of SCN^- . There are also other procedures for controlling the surface imperfection of AgHal.¹²⁵ In addition, J-aggregation can be controlled by decreasing the rate of release of dyes into solution. This can be achieved by adding poorly water-soluble dyes as aqueous sols or by readsorbing dyes from the substrate (SiO_2 , etc.) on AgHal.^{3, 254, 255}

Type I self-desensitisation according to the electron-acceptor mechanism is possible for IR dyes, which form J-aggregates.⁶ It is known that the electron affinity of a dye increases with increasing length of the polymethine chain resulting in a considerable decrease in the efficiency of spectral sensitisation.^{83, 133} According to the modern views,⁶ dyes in the ground state serve as intermediate carriers of electrons to oxygen atoms and protons, *i.e.*, dyes catalyse oxidation by oxygen involving protons of water molecules. The intermediate involvement of dyes in type I self-desensitisation can be determined by such factors as the electron affinity of the molecule and the positive charge of the chromophoric moiety of the dye. In this case, the probability of secondary oxidation processes should increase with increasing electron affinity of dye molecules (which is characterised by the polarographic half-wave reduction potential) and particularly with increasing length of an electron acceptor in aggregates.

The following suggestion was made:^{134, 256} if an efficient procedure were available for assembling unstable silver atoms (or subcentres of a latent image) to form stable particles of a latent image during exposure, the spectral sensitivity of a photomaterial would be substantially increased due to a decrease in the contribution of dye self-desensitisation to spectral sensitisation. The main idea of this method is that the chemical enhancement, *i.e.*, the development of a photomaterial already in the step of exposure, is employed. In this case, latensification of a latent image occurs during exposure. For this purpose, it is necessary to provide a reducing medium in the photographic layer by adding a reductone. The algorithm of this process can be as follows: before exposure, *i.e.*, before the formation of catalytic silver particles, a reductone does not reduce AgHal, apparently, due to kinetic factors. However, after blanket exposure and the formation of silver particles, a reductone reduces pre- and subcentres of a latent image to form stable developed centres of a latent image. This can be described by the following processes:

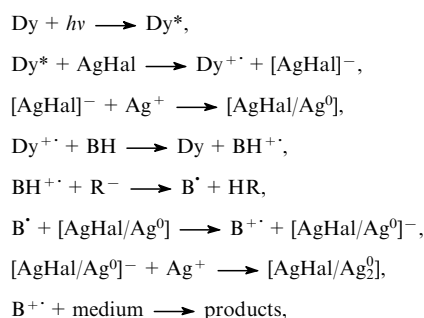


Ascorbic acid is a natural reductone, which has long been used in photographic processes.³ The action of ascorbic acid on infrared photographic layers is a bright example of the efficiency of reducing supersensitisers.^{233, 257–260} Several mechanisms of action of ascorbic acid were described in the literature. It was hypothesised²³³ that an IR dye is oxidised on the surface of AgHal to form a radical dication thus enhancing desensitisation according to the mechanism of photoelectron trapping. The authors observed the appearance of a new hypsochromically shifted absorption band of the radical dication of an IR dye, whose intensity decreased in the presence of ascorbic acid. Consequently, ascorbic acid (in the authors' opinion) reduces the radical dications of the dye to the dye in the ground state, which leads to a decrease in desensitisation. According to the above-considered mechanism, the influence of ascorbic acid occurs before the light action.

The influence of ascorbic acid on numerous IR dyes containing polymethine chains of different lengths in an AgBr(I) emulsion was studied in detail.²⁶¹ Short-wavelength bands of radical dications were found in none of reflection spectra of the dyes, for which a supersensitising effect of ascorbic acid was observed. Hence, it was concluded that the action of ascorbic acid is not associated with reduction of the desensitising radical dication of the dye. It was suggested²⁶ that ascorbic acid acts as an inhibitor of dye self-desensitisation immediately after the light step.²⁶¹

Ascorbic acid was demonstrated¹³⁴ to be adsorbed on silver sulfide sensitivity centres. Latensification of a latent photographic image under the action of ascorbic acid is efficient because silver particles formed on Ag_2S centres are subjected to the primary enhancement by ascorbic acid. Other reductones responsible for the superadditive effect in the photographic development, such as metol, phenidone, dodecyl gallate, *etc.*, behave analogously. Apparently, their action is also associated with specific adsorption on Ag_2S centres and latensification of a latent photographic image.

A new method of inhibition of type II self-desensitisation according to the hole mechanism was considered.^{80, 134, 256} This method is based on the use of a new type of supersensitisers which undergo transformation as a result of oxidation by dye holes accompanied by decomposition of the initial core. This gives rise to a molecule containing a new core, which acts as a reducing agent for AgHal. Chemical transformations of the oxidised form of a supersensitiser lead to the injection of one electron (or several electrons) into AgHal microcrystals, resulting in an enhancement of a latent photographic image. The scheme of the process is as follows:⁸⁰



where BH is a supersensitiser and R^- is a base. According to this scheme, the supersensitiser BH is oxidised by a dye hole to form the radical cation BH^{++} , which reacts with the base R^- to give the radical B^+ . The latter can act as a reducing agent for silver halide, *i.e.*, can inject the second electron into AgHal, resulting in the growth of the centre of a latent photographic image.

The above two-electron scheme was used in the studies.^{262–264} The formate anion (HCO_2^-) served as a hole acceptor. Oxidative decomposition of organic compounds accompanied by electron injection into AgHal was experimentally performed by Muentner and co-workers.^{265–271} Carboxy-substituted amines were gener-

ally used as hole acceptors. Decomposition of the resulting radical cations can occur in decarboxylation, deprotonation, C—C bond cleavage, etc.

In essence, all the above-considered supersensitisation processes under the action of reductones involve reductive latensification of a latent photographic image. This process can be initiated by either a reductone present in a photographic layer (for example, by ascorbic acid) or a reductone formed upon oxidative decomposition of a supersensitiser.

Nowadays, the unique properties of silver halide as a catalytic light-sensitive system are used in full measure only in the dark step of the photographic process (in the step of development). Nevertheless, the use of the unique catalytic properties of AgHal in the light step of the photographic process (as the 'primary development') holds promise. This strategy of spectral sensitisation would be expected to lead to a considerable increase in the light sensitivity of photomaterials.

Various approaches to the explanation of the photographic action and supersensitisation of polymethine dye aggregates were considered in the literature in sufficient detail. A unified theory of spectral sensitisation was developed. This theory is based on redox reactions in a photographic layer, which occur after dye photoexcitation in the secondary dark steps. Of all aggregated forms, the J-aggregated state of cyanine dyes is the most photographically efficient form.

V. Conclusion

Dye aggregates and, primarily, J-aggregates are nanosize molecular ensembles. Aggregates possess collective properties due to formation of a common π -conjugated system, which is reflected in changes in the electronic levels of dyes involved in aggregates, optical absorption bands and the chemical and photochemical activity. Evidently, all these properties depend on the aggregate structure, which is, in turn, determined by the mode of their formation. Nowadays, the architecture, more precisely, the nanoarchitecture of molecular ensembles of dyes can be considered. As in the traditional architecture, the appearance and functional possibilities of nanoarchitectural ensembles are determined by elements of the nanoarchitecture and their combination. In the nanoarchitecture of molecular ensembles of polymethine dyes, molecules, dimers and larger species serve as such elements. It should be noted that numerous elements are available because the class of polymethine dyes is characterised by a great variety of molecular structures and the diversified optical and electronic properties.^{2,3}

The nanoarchitecture of molecular ensembles of polymethine dyes is based on their specific structural features, which determine the tendency of dyes to undergo self-association. A new principle of the construction of complex organised systems from blocks (dimers, which are the simplest organised elements) rather than from individual 'bricks' (molecules) is of particular interest. Presumably, the block principle of construction is widespread in the Nanoworld and occurs in more complicated biological structures.

Investigations of molecular ensembles of polymethine dyes belong to the field of nanochemistry and nanotechnology.²⁷² It should be noted that the notions of nanoscience and nanotechnology are frequently mixed in the literature, although they are obviously different. Molecular ensembles of polymethine dyes are successfully used in nanotechnology for the preparation of photographic materials. Dye J-aggregates have been efficiently used in photographic processes as optical sensors in the spectral sensitisation for approximately seven decades.

Nowadays, in the framework of nanotechnology, aggregates composed of a small number of coloured organic compounds are of particular importance due to the extensive development of optical methods for data recording, processing and reading. In particular, methods for the controlled formation of molecular ensembles of polymethine dyes having desired structures and

required optical and electronic properties are of interest for the use in systems of optical conversion of data, including 'optical' computers.

This review has been written with the financial support of the Russian Foundation for Basic Research (Project No. 04-03-32 009).

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^f — *Opt. Spectroscop. (Engl. Transl.)*

Molecular and crystal design of nonlinear optical organic materials

K Yu Suponitsky, T V Timofeeva, M Yu Antipin

Contents

I. Introduction	457
II. Methods for the assessment of molecular hyperpolarisabilities	458
III. Characteristics of π -conjugated systems related to the efficiency of the second harmonic generation	464
IV. Possible ways to improve thermal stability and optical transparency of NLO materials	476
V. The design of NLO crystals	485
VI. Conclusion	489

Abstract. The results of theoretical and experimental studies on the second-order molecular and crystal nonlinear optical susceptibilities of organic and several classes of organoelement compounds are summarised. Modern methods used in these studies are briefly characterised, their advantages and drawbacks are outlined as regards their application to the systematic search for efficient nonlinear optical materials. Recent achievements and the main challenges in the field are thoroughly discussed and an optimum algorithm of the design of such materials is proposed. The bibliography includes 479 references.

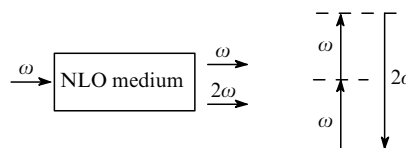
I. Introduction

Investigations into the nonlinear optical (NLO) materials is an actively developing field of the materials science.^{1–10} These materials have to comply with specific requirements, such as manifestation of high quadratic nonlinear optical susceptibilities and thermal stability and transparency in the operational range of wavelengths. Inorganic materials that are most frequently implemented in various devices meet these requirements to a certain degree. However, as early as the 1970s it was realised^{11–15} that organic compounds containing donor and acceptor (D/A) substituents linked through a π -electron system (the so-called D– π –A molecules) are capable of manifesting 1–2 orders of magnitude higher NLO efficiencies (NLO susceptibilities) due to the π -electrons weakly bound to the nuclear framework. This explains the great interest of researchers to the experimental elucidation of nonlinear optical susceptibilities of such compounds and the search for methods enabling prediction of the hyperpolarisabilities and structural simulations of highly efficient NLO molecules. Over the last two decades, the assortment of molecules under study has expanded substantially.^{16–22} A con-

siderable progress has been attained in the field of quantum-chemical calculations of the hyperpolarisabilities of molecules^{23–27} thereby providing valuable insight into the optimum molecular structures and helping to establish the structure–property relationship. The effects of the nature of the π -conjugated system have been monitored using series of polyphenylenes, polyenes, polyynes, their diphenyl-substituted analogues and molecules with heterocyclic π -systems.^{28–36} Various donor and acceptor substituents, in particular, NO₂, C(O)R, CN, OR, NR₂ as well as heterocyclic fragments and their combinations, have been studied in detail.^{37–43}

Only one of numerous possible NLO effects, *viz.*, the second harmonic generation (SHG), which is a special case of the sum frequency generation (SFG) is concerned in the present review. Incident photons with a frequency ω are absorbed by an NLO medium; the majority of photons are re-emitted at the same frequency but, for a small fraction of the incident radiation, the frequency of the generated photons is doubled (Scheme 1). This implies that the nonlinear optical effects can only be detected with powerful radiation sources, such as lasers.

Scheme 1



The dependence of the dipole moment (μ), which describes the perturbation of a system within the dipole approximation, on the external field strength (E) can be represented as a series^{44, 45}

$$\mu_i = \mu_i^0 + \alpha_{ij}E_j + \beta_{ijk}E_jE_k + \gamma_{ijkl}E_jE_kE_l + \dots, \quad (1)$$

where μ_i^0 is the i th component of the dipole moment of the unperturbed system; α_{ij} is the linear polarisability; β_{ijk} and γ_{ijkl} are nonlinear polarisabilities. The polarisabilities are frequency-dependent, which, strictly speaking, has to be reflected in their notation: for instance, $\beta_{ijk}(-\omega_1, -\omega_2, \omega_1, \omega_2)$, where ω_1 and ω_2 are incident radiation frequencies. The second harmonic generation is a particular case as a first-order nonlinear effect and thus it is described by the third term of the series (1), *i.e.*, by the parameter $\beta(2\omega, \omega, \omega)$ [or $\beta(\omega)$], which is a third-rank tensor. Typically, the notation β refers to molecules, *e.g.*, it is used in the studies of the second harmonic generation in solutions or gases or in theoretical calculations. In those cases, the proportionality coefficient is referred to as hyperpolarisability. In the case of crystal, the term

K Yu Suponitsky, M Yu Antipin A N Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, ul. Vavilova 28, 119991 Moscow, Russian Federation. Fax (7-495) 135 50 85, tel. (7-495) 135 92 14, e-mail: kirshik@yahoo.com (K Yu Suponitsky), tel. (7-495) 135 92 15, e-mail: m_antipin@yahoo.com (M Yu Antipin)
T V Timofeeva Department of Chemistry, New Mexico Highlands University, 87701 Las Vegas, USA. Fax (1-505) 454 32 02, e-mail: t_timofeeva@yahoo.com

Received 24 August 2005

Uspekhi Khimii 75 (6) 515–556 (2006); translated by Ya V Zubavichus

second-order nonlineal optical susceptibility is used, which is denoted as $\chi^{(2)}$ or d . Static hyperpolarisabilities extrapolated to the zero frequency [referred to as β_0 , $\beta(0,0,0)$ or $\beta(0)$] are often used for comparative analyses. It is related to the dynamical values by means of the following expression:²³

$$\beta(\omega) = \beta(0)[1 + A\omega^2 + \dots]. \quad (2)$$

The coefficient A depends exclusively on the nature of the molecule. The static hyperpolarisabilities are significantly easier to calculate and they are sufficient for the analysis of trends along various series of compounds, as will be demonstrated below. For the sake of easy comparison and interpretation, the molecular hyperpolarisabilities are usually represented as their vector components

$$\beta_{\text{vect}} = (\beta_x^2 + \beta_y^2 + \beta_z^2)^{1/2}, \quad (3)$$

where

$$\beta_i = \beta_{ixx} + \beta_{iyy} + \beta_{izz}.$$

Such representation is used due to the fact that β_{vect} can be determined experimentally from measurements of the hyperpolarisabilities of molecules. Sometimes, the hyperpolarisability is represented as the tensor norm

$$\|\beta\| = \left(\sum_{ijk} \beta_{ijk}^2 \right)^{1/2}. \quad (4)$$

In many cases, the tensor is degenerated into a vector due to a particular symmetry of the molecule. Thus, all even-order optical susceptibilities of any system with an inversion centre are strictly zero.

In order to compare and interpret the experimentally measured hyperpolarisabilities reported by different research groups, one has to critically assess them for several reasons. First, there are several independent representations of the NLO parameters related to modifications of the formulas (3) and (4), which is not always clearly specified in original papers.[†] Second, different research groups use different reference values of the same standard sample in the measurements. This problem has been specially addressed.⁴⁶ Nevertheless, even after detailed critical assessment, quantitative comparisons of results reported by different research groups is not recommended (see Section 6 in Ref. 46).

Following this guideline, below we compare only those results that were obtained by one research group within the same cycle of measurements. Such an approach made it possible to establish quantitative relationships between polarisabilities of different molecules and correlate their NLO activities with the molecular structure. The relationship between the hyperpolarisability of a molecule and its structure can be deduced from the quantum mechanical description of hyperpolarisability. The Hamiltonian of a system (*e.g.*, a molecule) in an external electric field can be represented as

$$\hat{H} = \hat{H}_0 + \hat{H}',$$

where $\hat{H}_0$ is the Hamiltonian of the unperturbed system and the term $\hat{H}'$ describes the effect of the field applied. If $\hat{H}'$ can be considered as a small perturbation, the hyperpolarisability (assuming only one excited state, which is referred to as the two-level model, and one-dimensional character of the tensor β , which is equivalent to the existence of one prevailing component, *e.g.*, β_{xxx}) can be written in a compact form as³

$$\beta_{xxx} = \frac{3\omega_{ge}^2 \Delta\mu_{ge} |\mu_{ge}|^2}{2\hbar^2(\omega_{ge}^2 - \omega^2)(\omega_{ge}^2 - 4\omega^2)}, \quad (5)$$

[†] In the present review, the notation β is adopted for the hyperpolarisability. By default, β without any additional indices, which was not explicitly commented, means vector component of hyperpolarisability [see Eqn (3)] in the static limit.

where ω_{ge} is the frequency of the transition from the ground (*g*) to the excited (*e*) state, μ_{ge} is the respective transition dipole moment and $\Delta\mu_{ge}$ is the difference between the dipole moments of the molecule in the ground and excited states. This formula clearly shows that β becomes larger with an increase in μ_{ge} and $\Delta\mu_{ge}$. This is achieved for molecules containing donor and acceptor groups linked through a π -conjugated system. Mobile π -electrons in such molecules are readily redistributed upon perturbation with an electric field.

Importantly, as follows from the above relationship, NLO parameters of organic molecular crystals have a straightforward correlation with molecular hyperpolarisabilities. Since intermolecular interactions are significantly (2–3 orders of magnitude) weaker than the intramolecular ones,⁴⁷ the nonlinear susceptibility of a crystal can be represented as a sum of hyperpolarisabilities of the constituent molecules over the unit cell^{48–50}

$$d_{IJK} = \frac{1}{V} f_I f_J f_K \sum_{n=1}^Z \left(\sum_{i=1}^3 \sum_{j=1}^3 \sum_{k=1}^3 \cos \theta_{II}^n \cos \theta_{JJ}^n \cos \theta_{KK}^n \beta_{ijk} \right). \quad (6)$$

Here, V is the unit cell volume; indices I, J and K refer to the crystallographic coordinate system; indices i, j and k define the components of β in the molecular coordinate system; the trigonometric terms $\cos \theta_{II}^n$, $\cos \theta_{JJ}^n$ and $\cos \theta_{KK}^n$ define the transition matrix between these coordinate systems; f_I, f_J, f_K are the factors accounting the local field effects.

The experimental determination of the optical susceptibilities of crystals or polymers, which are of the greatest practical importance, is laborious (especially for single crystals), therefore, the design of NLO materials is based to a large extent on the knowledge and application of the relationship between the NLO susceptibilities of a crystal and hyperpolarisabilities of the constituent molecules.

The present review surveys the approaches to the design of NLO active materials at the molecular and crystal level. We limit ourselves to the consideration of organic and selected classes of organoelement compounds. Supplementary information on the use of organometallics in nonlinear optics can be found elsewhere.^{51, 52}

II. Methods for the assessment of molecular hyperpolarisabilities

1. Experimental methods for measurement of molecular hyperpolarisabilities

One of the most popular method for the determination of molecular hyperpolarisabilities in solution or gas phase based on the measurements of the electrical field-induced second harmonic (EFISH) was developed in the early 1970s.^{53–56} Prior to the measurement, molecules of the compound under study are oriented along a static electrical field. The third-order macroscopic optical susceptibility (Γ) obtained directly from the measurements relates to the respective microscopic value (γ) through the following expression

$$\Gamma = N\gamma f_0 f_\omega f_{2\omega},$$

where N is the number of molecules per unit volume, $\gamma = \gamma_e + \gamma_v + \gamma_r$ is the sum of electronic (γ_e), vibrational (γ_v) and orientational (γ_r) terms; $f_0, f_\omega, f_{2\omega}$ are the local field factors. The hyperpolarisability relates to the orientational term as

$$\gamma_r = \frac{\mu\beta_{\text{vect}}}{5kT}.$$

The orientational contribution can be separated using the temperature dependence $\gamma_r(T)$, and thus the scalar product of the dipole moment and the vector part of the hyperpolarisability $\mu\beta_{\text{vect}}$ can be determined. Often, the orientational term predominates, therefore other two terms can be neglected.⁵⁵ In order to retrieve the absolute value of β_{vect} , one should know the angle between the vectors μ and β_{vect} and the value of dipole moment.

The former can be estimated by means of quantum-chemical calculations, whereas the latter can be determined both theoretically and experimentally.

This means that the accuracy of the resultant value of β depends on the reliability of the quantum-chemical approximation applied and the accuracy of the determination of μ . Other tensor components β_{ijk} remain unknown and thus the formula (6) can only be applied to the calculation of the components of the NLO susceptibility tensor provided that the molecular hyperpolarisability is dominated by a single component (e.g., β_{xxx}).

Yet another problem relates to the transition from the macroscopic (Γ) to the microscopic (γ) level of description, which requires an explicit allowance for the local field factors. In the case of weakly polar solute molecules and non-polar solvents, for which the intermolecular interactions can be neglected, the local field factors can be described within the Onsager model. However, the compounds that are of the greatest interest for nonlinear optics are polar and poorly soluble in non-polar solvents. Solute molecules in a polar solvent are additionally polarised by their solvate environment; furthermore, the formation of molecular associates, in particular, due to the H-bonding, is highly probable. Also there is a concentration dependence of the hyperpolarisability. Such effects have been studied in detail in the case of *p*-nitroaniline (*p*-NA, **1**). Measurements of the molecular hyperpolarisability were performed for solutions in polar methanol⁵⁷ and non-polar melt of *trans*-stilbene⁵⁸ and for a melt of *p*-NA itself.⁵⁷ The ratios obtained

$$\frac{\beta_{p\text{-NA}}^s}{\beta_{p\text{-NA}}^m} \approx \frac{\beta_{p\text{-NA}}^s}{\beta_{p\text{-NA}}^{\text{melt}}} = 0.33$$

(the superscripts s, m and melt denote the values for the solutions in stilbene and methanol and the melt, respectively) suggest a strong influence of the intermolecular interactions on the measured values. Both in the methanolic solution and the melt, *p*-nitroaniline molecules form H-bonded associates, which induce additional polarisation of the molecules thus giving rise to an increase in their hyperpolarisability. A similar relation has been obtained for *trans*-4-dimethylamino-4'-nitrostilbene (DANS, **2**) in *trans*-stilbene and acetone solutions^{58, 59}

$$\frac{\beta_{\text{DANS}}^s}{\beta_{\text{DANS}}^a} = 0.3$$

(the superscript a and s correspond to the acetone and stilbene solutions, respectively).

The concentration dependences of β were studied for systems with both weak (e.g., nitrobenzene–benzene or nitrobenzene–CCl₄) and strong intermolecular interactions prone to the formation of H-bonds (e.g., water–methanol).⁵⁷ For polar and H-bonded systems, it was suggested to describe β with the following equation

$$\beta = \beta_0 + \beta_{\text{dip}}^0(1 - c) + \beta_{\text{solvent}} f_s, \quad (7)$$

where β_0 is the hyperpolarisability of the isolated molecule, the second term quantifies the dipole–dipole interactions and the last term describes specific solute–solvent interactions; c and f_s are empirical parameters. This equation provides only a qualitative description of the real situation. For any specific case, additional measurements are required to estimate the two latter terms quantitatively, which becomes a separate problem.

Yet another experimental method exploits the phenomenon of incoherent scattering of the incident radiation by single molecules, the so-called Hyper Rayleigh Scattering (HRS), which was discovered in 1965.⁶⁰ For the measurements of the second harmonic generation, this method came in use only during the last decade owing to studies of *p*-NA, 4-methoxy- and 4-hydroxy-4'-nitrostilbenes by Clays and Persoons.^{61, 62} The hyperpolarisabilities of these molecules measured using HRS were in agreement with the earlier EFISH results.

A clear advantage of HRS over EFISH is that⁶³ it does not require external static electrical fields for orienting the molecules, i.e., for the induction of a non-centrosymmetric medium. This allows probing of molecules with the zero dipole moment (in particular, octupolar molecules and ions, which are described in more detail below). Furthermore, HRS can yield several components of the molecular hyperpolarisability tensor. Most typically, components β_{ZZZ} and β_{XZZ} in a laboratory coordinate system are determined, which relate to the molecular parameters as follows⁶⁴

$$\langle \beta_{ZZZ}^2 \rangle = \frac{1}{7} \sum_i \beta_{iii}^2 + \frac{6}{35} \sum_{i \neq j} \beta_{iii} \beta_{ijj} + \frac{9}{35} \sum_{i \neq j} \beta_{ijj}^2 + \frac{6}{35} \sum_{ijk} \beta_{ijj} \beta_{jkk} + \frac{12}{35} \beta_{ijk}^2, \quad (8)$$

$$\langle \beta_{XZZ}^2 \rangle = \frac{1}{35} \sum_i \beta_{iii}^2 - \frac{2}{105} \sum_{i \neq j} \beta_{iii} \beta_{ijj} + \frac{11}{105} \sum_{i \neq j} \beta_{ijj}^2 - \frac{2}{105} \sum_{ijk} \beta_{ijj} \beta_{jkk} + \frac{8}{35} \beta_{ijk}^2. \quad (9)$$

Nevertheless, the principal of the aforementioned problems related to the use of EFISH are also typical of HRS, although to a lesser extent. First, even with HRS one cannot determine all the tensor component β_{ijk} . The second problem is due to the neglect of the solvation and association effects. For instance, the following ratios of hyperpolarisabilities were determined for acetonitrile and nitrobenzene in the gas (g) and liquid (l) phases⁶⁵

$$\frac{\beta_{\text{MeCN}}^g}{\beta_{\text{MeCN}}^l} = 0.53, \quad \frac{\beta_{\text{PhNO}_2}^g}{\beta_{\text{PhNO}_2}^l} = 0.77.$$

In the liquid phase, molecules stronger interact with each other and thus are stronger polarised as compared to the gas. More polar molecules are characterised by larger β , which is reflected in the ratios outlined above.

Huyskens *et al.*^{66, 67} applied HRS to study the dependence of hyperpolarisability of *p*-NA and its *N,N*-dimethyl derivative on the solvent nature, in particular, polarity. They tested 50 different solvents and deduced the following formula representing the hyperpolarisability in a solution as a sum of the hyperpolarisability of an isolated molecule (gas-phase) β^g and corrections for the dipole–dipole interactions (the second term) and association (the third term)

$$\beta = \beta^g + \gamma_0 a \sqrt{\frac{\mu}{V}} + (1 - \gamma_0) b \sqrt{\mu}, \quad (10)$$

where γ_0 is the fraction of solute molecules not involved into H-bonding; a and b are empirical coefficients; μ is the dipole moment of the molecule in the gas phase; V is the solvent molar volume. Apparently, Eqn (10) is equivalent to Eqn (7), which was proposed to correct EFISH results for the solvation and association effects. Unfortunately, parametrisation of these equations for any particular compound is very demanding experimentally.

The problem of the interpretation of the solvation effects becomes especially important when the molecular hyperpolarisability has to be further used to estimate the NLO susceptibility of a crystal, in which the molecule is polarised by the crystal field evidently different from that experienced by the molecule in a solution or in a melt.

2. Theoretical approaches to the determination of the molecular hyperpolarisabilities

The major advantage of quantum-chemical methods for the determination of molecular hyperpolarisabilities is that^{68–70} they enable calculation of all the tensor components β_{ijk} . It has to be however noted that the problem of transferability of theoretical values for an isolated molecule to the molecule in a solid phase remains open and deserves a special consideration.

There are two basic approaches to the calculation of β . Within the first approach, the terms describing the interaction of a system

with an electromagnetic field are explicitly included into the Hamiltonian of the system. The second approach exploits the idea that the eigenfunctions of a molecule constitute a complete set and any state of the molecule perturbed by an electric field can be factorised in this basis.

In the first approach referred to as the Finite Field (FF) theory, the Hamiltonian of a system perturbed by an electrical field with a strength E is represented as

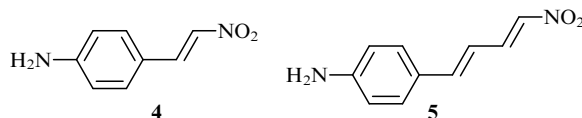
$$\hat{H} = \hat{H}_0 - eE\hat{r}, \quad (11)$$

where $\hat{H}_0$ is the Hamiltonian of the unperturbed system and $\hat{r}$ is the dipole moment operator. The polarisability can be deduced as the derivative of the dipole moment $\mu(E)$ or energy $W(E)$ with respect to the field (E). For the first hyperpolarisability, the following expression can be written

$$\beta_{ijk} = \frac{\partial^2 \mu_i(E)}{\partial E_j \partial E_k} = - \frac{\partial^3 W(E)}{\partial E_i \partial E_j \partial E_k}. \quad (12)$$

The differentiation can be performed either numerically or analytically. In the latter case, an acronym CPHF (Coupled Perturbed Hartree–Fock) is often used instead of FF.

This approach was further developed by Zyss^{71–73} in a combination with the semiempirical approximation INDO/S. The hyperpolarisabilities were calculated as numerical derivatives of the dipole moment with respect to the electric field for a series of mono and disubstituted benzenes [**1**, *o*-NA (**3**), **4**, **5**] and compared to the available experimental data. A direct comparison of contributions made by σ - and π -electrons into the value of hyperpolarisability indicates that it is the π -electrons that are of predominant importance, which is fully in accord with earlier concepts. According to the values obtained for molecules **1**, **4** and **5**, β drastically increases with an increase in the conjugated chain length.



The theoretical values of β reported by Zyss^{71–73} are underestimated by approximately one order of magnitude as compared to the experimental data, however, they correctly reproduce the experimental trends along the series of compounds studied (Table 1).

Kurtz *et al.*⁷⁵ utilised the MNDO approximation with the AM1 and PM3 parametrisation schemes and adopted the FF-based algorithm of the calculation of different-order polarisabilities for the MOPAC code. Matsuzawa and Dixon^{76,77} comprehensively tested this implementation by calculating hyperpolarisabilities of about 150 conjugated polar molecules with the PM3 parametrisation.

As shown in Fig. 1, a reasonably good agreement between the theoretical and experimental values was obtained, although the

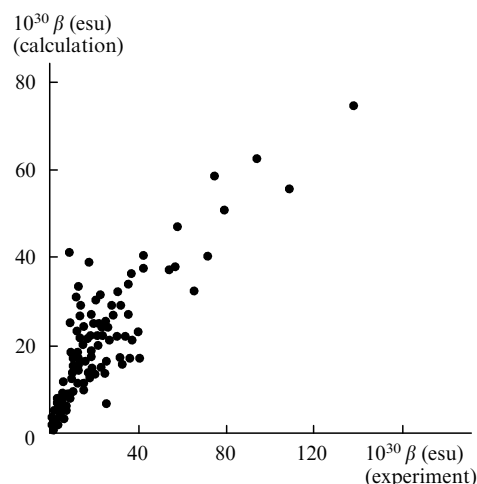
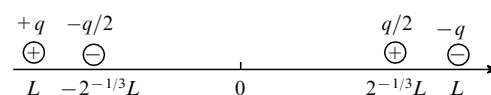


Figure 1. The correlation of calculated (FF/PM3 method) and experimentally determined (EFISH measurements)^{78,79} hyperpolarisabilities of D/A-substituted π -conjugated molecules.

values for molecules with high hyperpolarisabilities were systematically underestimated by the calculation.

Based on the FF theory, Cardelino *et al.*⁸⁰ suggested to simulate the perturbation field with a set of point charges.

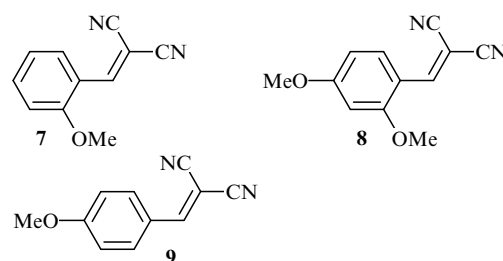


If the separation between the opposite charges $\pm q$ is sufficiently large ($L > 160 \text{ \AA}$), the probe molecule placed into the centre of the system experiences the influence of a constant electric field

$$E = \frac{1}{4\pi\epsilon_0} \left(2 - 2^{2/3} \right) qL^{-2}, \quad (13)$$

the field strength being varied from 0 to $7 \text{ V \AA}^{-1}$.

The calculated values of β obtained for molecules **1**, **3**, *m*-NA (**6**) and **7–9** using this model^{80–83} are in good agreement with the experimental ones (Table 2).



The Sum Over States (SOS) method is also widely applied to the theoretical evaluation of NLO susceptibilities of molecules.

Table 2. Calculated (modified FF/AM1 method, in the static limit) and experimental values of the molecular hyperpolarisabilities (10^{-30} esu) of D/A-substituted benzene derivatives.

Molecule	$\beta(\text{calc.})$	$\beta(\text{exp.})$	Molecule	$\beta(\text{calc.})$	$\beta(\text{exp.})^a$
3	1.7	1.9–10.2	7	13.1	18.7
6	2.8	2.5–6.0	8	30.7	76.3
1	5.3	6.4–46.9	9	32.6	56.5

^a EFISH measurements in 1,4-dioxane at an incident wavelength of $\lambda = 1064 \text{ nm}$.⁸¹

Table 1. Calculated (FF/INDO, in the static limit) and experimental values of the molecular hyperpolarisabilities (10^{-30} esu) of D/A-substituted benzene derivatives.

Molecule	$\beta(\text{calc.})$	$\beta(\text{exp.})^a$	Molecule	$\beta(\text{calc.})$	$\beta(\text{exp.})^b$
3	0.2	1.9–10.2	4	12.9	146.6
1	3.4	6.4–46.9	5	50.6	433.2

^a Hereinafter in this Section: a range of β values is given, if several experimental values were reported in the literature for the molecule;^{46,74} in the case of incident wavelength-dependent calculations, only the experimental data measured at the same wavelength are given; in the case of calculations in the static limit (as in this case), the whole range of experimental values is given. ^b Results of EFISH measurements from Ref. 73.

According to this method, the hyperpolarisability can be represented as⁸⁴

$$\beta(\omega)_{ijk} = -\frac{e^3}{8\hbar^2} \sum_n \sum_{n'} \left\{ \left(r_{gn'}^j r_{n'n}^i r_{gn}^k + r_{gn'}^k r_{n'n}^j r_{gn}^i \right) \times \right. \quad (14)$$

$$\times \left[(\omega_{n'g} - \omega)^{-1} (\omega_{ng} + \omega)^{-1} + (\omega_{n'g} + \omega)^{-1} (\omega_{ng} - \omega)^{-1} \right] +$$

$$+ \left(r_{gn'}^j r_{n'n}^i r_{gn}^k + r_{gn'}^k r_{n'n}^j r_{gn}^i \right) \left[(\omega_{n'g} + 2\omega)^{-1} (\omega_{ng} + \omega)^{-1} + \right.$$

$$+ \left. (\omega_{n'g} - 2\omega)^{-1} (\omega_{ng} - \omega)^{-1} \right] + \left(r_{gn'}^j r_{n'n}^k r_{gn}^i + r_{gn'}^k r_{n'n}^j r_{gn}^i \right) \times$$

$$\times \left[(\omega_{n'g} - \omega)^{-1} (\omega_{ng} - 2\omega)^{-1} + (\omega_{n'g} + \omega)^{-1} (\omega_{ng} + 2\omega)^{-1} \right] \Big\},$$

where the dipole moment operator r and the transition frequencies ω with subscripts correspond to transitions between the ground (g) and excited (n, n') states.

The dependence of the hyperpolarisability on ω is explicitly included in the Eqn (14), which is an advantage of this approach. However, an accurate calculation of β requires that the summation was performed over all excited states, which is associated with enormous computational costs. This approach is of low efficiency, especially as regards calculations for large and medium-sized molecules (*e.g.*, *p*-NA). The contributions of separate electron transitions into the total β value can be isolated and arranged in the descending order of their magnitudes. Then, the summation in the Eqn (14) can be aborted after reaching a preset accuracy level. Utilising of the SOS method makes it possible to analyse separate contributions thereby providing a valuable insight into the origin of the nonlinear susceptibility of a molecule, which is a prerequisite for establishing the structure–property relationship. Nevertheless, it should be kept in mind that the total contribution of neglected terms can prove significant impact despite the smallness of each separate term.

The SOS method within the CNDO/CI approximation was applied by Lalama *et al.*,⁸⁵ Morrell and Albrecht⁸⁶ for the evaluation of the hyperpolarisability of *p*-NA. The values of β (in esu) obtained in these two studies, 6.53×10^{-30} (Ref. 85) and 34.3×10^{-30} (Ref. 86) are significantly different due to the different parameter sets used, however, they both lie within the range of reported experimental values $(6.4–46.9) \times 10^{-30}$ (Refs 57, 58, 74 and 87) measured in different solvents, at different incident wavelengths and using different reference values of d_{11} (for the quartz standard): 0.8×10^{-9} (Refs 57, 58) or 1.2×10^{-9} esu (Refs 74, 87).

The SOS method was further optimised by Morley and co-workers.^{88–90} They parametrised the method for 22 π -conjugated molecules using the CNDO/CIS approximation. The formula (14) was modified by its transformation to a special coordinate system with the origin placed into the centre of gravity of the electron density distribution of the molecule in its ground state. The theoretical results for nitrobenzene (**10**), aniline (**11**), *p*-NA and molecules **12–15** obtained by this method reproduce the experimentally established trends, although the values themselves differ by a factor of 3–4 in some cases (Table 3). Here, it would be appropriate to mention the large scatter in the reported experimental data, which limits the reliability of the parametrisation. The method described above was implemented in the CNDOVSB software code.⁸⁹

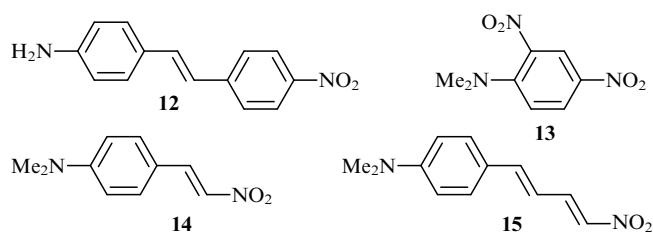


Table 3. Calculated (SOS method within the PPP and CNDO approximations) and experimental values of dynamic ($\hbar\omega = 1.17$ eV) hyperpolarisabilities (10^{-30} esu) of D/A-substituted benzene and stilbene derivatives.

Molecule	β_{PPP}	β_{CNDO}	$\beta(\text{experiment})$
10	5.4	0.62	1.9–2.4
11	2.5	3.66	0.6–1.2
1^a	35.9	12.18	9.6–46.9
12	300.0	69.15	225–295
13	39.1	9.25	21
14	179.3	126	180–260
15	687.9	355	470–790

^a The experimental data for *p*-NA were measured at $\hbar\omega = 0.656$ eV; the photon energy values $\hbar\omega = 1.17$ and 0.656 eV correspond to the incident wavelengths of 1064 and 1907 nm, respectively.

Li, Marks and Ratner^{91,92} combined the SOS method with the PPP/CIS approximation; some of their results are compared with the experimental data and CNDO-based theoretical estimates in Table 3. It is clearly seen that the calculated data agree qualitatively with the experimental ones. The PPP-based theoretical estimates agree with the experiment somewhat better than the CNDO-based ones, although the former approximation is by definition less accurate. Probably, the deficiency in the theory is compensated for by better parametrisation.

Verification of the adequacy of the SOS approach was carried out by Kanis *et al.*^{39,93,94} for 203 polar organic molecules using the ZINDO code^{95–98} (the SOS method coupled with the INDO approximation), the results obtained are shown in Fig. 2.

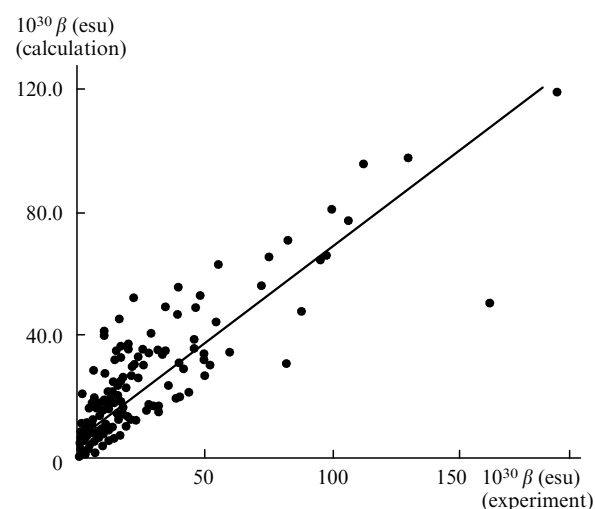


Figure 2. The correlation of calculated (SOS/INDO method)^{95–95} and experimentally determined (EFISH measurements)^{78,79} hyperpolarisabilities of D/A-substituted π -conjugated molecules.

Some common trends can be revealed from the comparison of theoretical (based on the FF and SOS approaches) and experimental results (see Figs 1 and 2). The agreement for lower values of β is better than for higher values (in the latter case, the calculated values are always smaller than the experimental ones). Taking into account that the reported experimental data refer to SHG measurements in solutions,^{78,79} this discrepancy can be rationalised assuming the aforementioned solvation and association effects, which become important for easily polarisable molecules, *i.e.*, for molecules susceptible to the environmental effects. Apparently, the correlation between the theoretical and

experimental values is better described by a function $k\sqrt{x}$ ($y > 1$) rather than a linear dependence.

The majority of calculations of the hyperpolarisabilities with *ab initio* quantum-chemical methods are based on the finite field (FF) formalism. For the calculation of the frequency dependent hyperpolarisabilities $\beta(2\omega, \omega, \omega)$, it is necessary to use the time-dependent Schrödinger equation. Such an approach employing the Hartree–Fock approximation was elaborated by Sekino and Bartlett⁹⁹ and tested on a number of small molecules. The calculated values were found to be ~ 1.5 – 2 times smaller than the respective experimental data. Karna and Dupuis^{100, 101} improved the computational algorithm and accomplished test calculations for molecules CHHal_3 . The algorithm was implemented in the HONDO code.¹⁰¹ Despite good agreement in polarisabilities $\alpha(\omega, \omega)$, the theoretical values of $\beta(2\omega, \omega, \omega)$ were several-fold smaller than the experimental ones. Most probably, this is due to the fact that the reported experimental values refer to measurements in solutions.

Further developments of the theoretical approaches to the determination of molecular hyperpolarisabilities are based on the account of the electron correlation. Sekino and Bartlett proposed¹⁰² a multiplicative static correlation correction to $\beta(2\omega, \omega, \omega)$ calculated at the Hartree–Fock (HF) level. Within the ACES II software code developed by the authors, the correlated dynamical hyperpolarisability was obtained based on the value of $\beta(2\omega, \omega, \omega)$ calculated by the Hartree–Fock method and the values of $\beta(0)$ calculated both by the Hartree–Fock and by higher-level electron correlation methods {the perturbation (MP2) or Coupled Clusters theory [CCSD and CCSD(T)]} according to the formula

$$\beta_{\text{cor}}(2\omega, \omega, \omega) = \beta_{\text{cor}}(0) \frac{\beta_{\text{HF}}(2\omega, \omega, \omega)}{\beta_{\text{HF}}(0)}. \quad (15)$$

Rice *et al.*¹⁰³ suggested to account the electron correlation in the calculations of the dynamic hyperpolarisabilities with an additive correction

$$\beta_{\text{cor}}(2\omega, \omega, \omega) = \beta_{\text{cor}}(0) + [\beta_{\text{HF}}(2\omega, \omega, \omega) - \beta_{\text{HF}}(0)]. \quad (16)$$

Further, Rice and Handy,^{104, 105} Aiga and co-workers^{106–109} elaborated a method for the calculation of the dynamic hyperpolarisabilities within the MP2 approximation with the simultaneous account of the electron correlation and frequency dependence. The validity of the additive scheme was verified¹⁰⁵ by comparing its results with the results of strict *ab initio* calculations of $\beta(2\omega, \omega, \omega)$ for formaldehyde and ammonia. The use of the additive correction underestimates the *ab initio* values for CH_2O and NH_3 by 4% and 13%, respectively, at the incident wavelength of a ruby laser. Hammond and Rice compared¹¹⁰ the additive and multiplicative corrections in the case of HCl molecule by accounting the electron correlation with the CCSD(T) method. The frequency dependent values were calculated within the Hartree–Fock and MP2 methods. The latter approach yielded better (by 3%–8%) agreement with the experimental data and in this case, the additive correction performed slightly better (by 1%) than the multiplicative one. On the other hand, the multiplicative scheme appears preferable if the frequency dependence is taken into account by the Hartree–Fock method (the difference is 4%).

Yet another approach to the assessment of hyperpolarisability with account of the electron correlation was elaborated^{111, 112} based on the CCS, CC2, CCSD and CC3 methods. The following values of $\beta(2\omega, \omega, \omega)$ were obtained for hydrogen fluoride with the t-aug-cc-pVTZ basis set (in a.u. at $\omega = 0.0656$ a.u.):

Method	CCS	CC2	CCSD	CC3	Experiment ¹¹³ (gas phase)
$-\beta(2\omega, \omega, \omega)$	7.760	12.030	8.789	8.321	10.9 ± 0.95

It has to be mentioned that the hydrogen fluoride molecule represents a ‘stumbling block’ as regards the comparison of the theoretical and experimental results. Even after a vibrational correction (-1 a.u.)^{114, 115} is added, the theoretical estimation remains beyond the confidence interval of the experiment. Notwithstanding, the similar vibration-corrected calculations for a series of small molecules, including H_2O , CO, MeCN and HCl, give values of $\beta(2\omega, \omega, \omega)$ in quantitative agreement with the experiment (Table 4).^{116–120}

High-level *ab initio* calculations make it possible to estimate $\beta(2\omega, \omega, \omega)$ to within 10%. It has to be stressed that the accurate

Table 4. The values of $\beta(2\omega, \omega, \omega)$ (a.u.) calculated with the MP2 and Coupled Clusters (CC) methods compared to the respective experimental values for small molecules.

Method	mHyPOL (see ^a)	d-aug-cc-pVDZ	d-aug-cc-pVTZ	d-aug-cc-pVQZ	d-aug-cc-pV5Z	Ref.	Experiment	Ref.
CO molecule								
MP2	31.64	—	31.00	—	—	109	29.9 ± 3.2^b	119
CCSD	—	—	29.56	29.09	—	116		
CC3	—	—	31.91	—	—	116		
H₂O molecule								
MP2	-21.31	—	-19.89	—	—	109		
CCSD	—	—	-21.72	-21.98	—	116	-21.8 ± 0.9^b	119
CC3	—	—	-21.02	—	—	116		
NH₃ molecule								
MP2	-49.16	—	—	—	—	109	-48.4 ± 1.2^b	119
MeCN molecule								
MP2	—	31.5	—	—	—	117	26.3 ± 0.8^c	120
CCSD	—	29.3	—	—	—	117		
CCSD(T)	—	26.7	—	—	—	117		
HCl molecule								
CC3	—	—	—	—	4.57	118	4.9 ± 0.5^b	113

Note. The frequencies used in the calculations correspond to the experimental incident wavelengths (λ). ^a Modified¹⁰⁹ basis POL: (10s6p4d2f)/[5s3p3d2f] for the second-period elements, (6s4p2d)/[3s3p2d] for the hydrogen atoms. ^b Gas phase, $\lambda = 694.3$ nm. ^c Gas phase, $\lambda = 514.5$ nm; the value is multiplied by 3/5.

reproduction of experimental data is the only reasonable criterion for the adequacy of the theoretical method applied. However, the experimental measurements are dependent on the selection of the reference values. Unfortunately, no unambiguous criteria for the correct selection of such standard values have been proposed so far.^{23, 65, 121, 122} Furthermore, the application of highly accurate calculations is restricted to the size of molecules under study. It is evident that the molecules considered above, composed of two–six atoms, are exclusively of theoretical interest.

Thus, two major directions of modern theoretical investigations into the NLO properties of molecules can be distinguished. The first direction implies the development of high-level *ab initio* methods and their verification by comparing the calculation results with the accurate experimental data from gas-phase measurements. Such calculations should use sufficiently broad basis sets that include polarisation and diffusion functions,¹²³ take into account the electron correlation and vibrational corrections,^{124, 125} which can amount up to several per cent of the total value¹²⁶ (this correction is typically neglected in lower-level calculations).

The second direction consists of the use of less accurate but faster methods for the calculation of hyperpolarisabilities enabling studies of larger molecules for the prediction of trends in their NLO properties and selection of promising systems for the experimental study. For instance, Beck and Grummt analysed¹²⁷ 200 different conjugated polar molecules using the FF and SOS methods with semiempirical approximations (AM1, PM3, CNDO/S). They concluded that the semiempirical methods adequately reproduce the experimentally observed trends, and the discrepancies between the theoretical and experimental values are due to the lack of treatment (or insufficient model treatment) of the environmental effects rather than mere theory deficiencies.

The density functional theory (DFT) is widely employed for the evaluation of NLO properties of molecules, in particular, hyperpolarisabilities, since it provides the most efficient means (in terms of computational costs) to account the electron correlation.¹²⁸ Nevertheless, the reliability and validity of DFT-derived results remain disputable. Some authors criticise^{129–132} theoretical hyperpolarisabilities calculated using very well known functionals, such as SVWN, BLYP and B3LYP.^{128, 133} Meanwhile, other research groups (see, for instance, Refs 134–138) advocate the validity of the DFT calculations. Tables 5–9 compare theoretical hyperpolarisabilities of small molecules, benzene diyne derivative **16**, triazines **17–19**, NH₂/NO₂-substituted π -conjugated molecules (compounds **1**, **12**, **20**, **21**), D/A-substituted

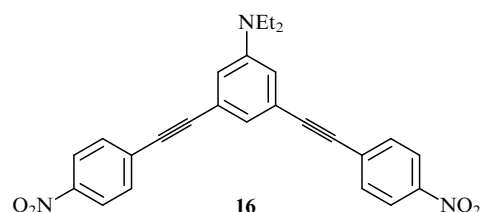
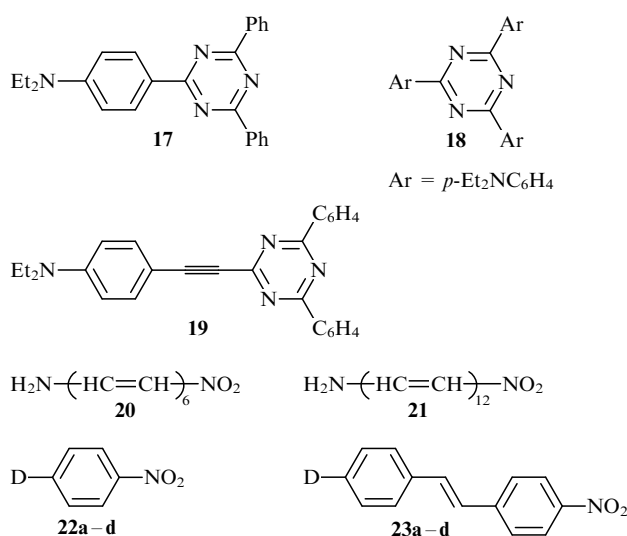


Table 5. Calculated¹²⁹ (DFT) and experimental¹¹⁹ (gas phase, $\lambda = 694.3$ nm) values of $\beta(2\omega, \omega, \omega)$ (a.u.) for small molecules.

Molecule	SVWN/TZ2P + diff	BLYP/TZ2P + diff	LB94/TZ2P + diff	Experiment
NH ₃	−109	−138	−46.0	−48.4 ± 1.2
CO	36.6	37.8	23.4	29.9 ± 3.2
H ₂ O	−34.4	−37.3	−20.3	−21.8 ± 0.9
HF	−10.7	−11.2	−7.68	−10.9 ± 0.95 ^a

Note. The basis TZ2P was augmented with diffuse functions; the frequencies used in the calculations correspond to the experimental incident wavelengths (λ). ^a Data from Ref. 113.

benzenes (**22a–d**) and stilbenes (**23a–d**) calculated within the density functional theory with the respective experimental values.



D = MeO (a), HO (b), Me (c), HC(O) (d).

The application of DFT gives rise to a problem of an inexact asymptotic behaviour of the majority of functionals at distances far from nuclei (*i.e.*, in the region of vacant molecular orbitals): they decrease exponentially rather than as $\sim 1/r$. The functionals with improved asymptotic behaviour [*e.g.*, LB94, HCTH(AC) or BP86-GRAC] often perform better in terms of agreement with the experimental data and accurate *ab initio* quantum mechanical calculations (see Tables 5, 6).

However, an HCTH(AC)-based calculation incorrectly predicts the hyperpolarisability of acetonitrile, whereas the use of the B97-1 functional yields more accurate estimates. An incorrect ratio of the hyperpolarisabilities of molecules **17** and **18** was obtained in a theoretical study of triazine derivatives with the

Table 6. Theoretical values of $\beta(0,0,0)$ (a.u.) for small molecules according to DFT and strict calculations based on the Coupled Clusters method.

Molecule	LDA ^a	BLYP ^a	B3LYP ^a	B97-1 ^a	HCTH (AC) ^a	BP86-GRAC ^b	BLYP ^c	CCSD(T) ^d
NH ₃	−55.66	−58.59	−41.03	−38.93	−33.30	−37.87	−87.09	−34.3
H ₂ O	−24.79	−24.40	−19.19	−18.65	−18.31	−18.2	−28.19	−18.0
H ₂ S	−14.73	−10.48	−7.15	−7.37	−10.22	—	—	−7.7
CO	29.46	29.30	26.86	26.33	22.60	21.9	32.89	23.5
HF	−8.86	−8.73	−7.42	−7.21	−7.35	−7.2	−8.85	−7.3
MeCN	36.97	38.53	31.73	27.77	87.3	—	—	24.2 ^e

^a Data from Ref. 130; The basis set POL was augmented with d-functions for the hydrogen atoms and s- and p-functions for heavier atoms. ^b Data from Ref. 132; the basis sets 7s5p4d for H, 9s7p5d4f for C, N, O and 11s7p5d4f for F. ^c Data from Ref. 135; the basis set DNP + FIP. ^d Data from Ref. 102; the same basis as in Ref. 130. ^e Data from Ref. 120; the basis [4 + 1s3 + 1p2 + 1d/3 + 1s2 + 1p] + (2s2p1d1f/2s).

Table 7. Theoretical dynamic hyperpolarisabilities (10^{-30} esu, $\lambda = 1064$ nm) calculated within the LB94/DZP(fc) approximation for molecules **16**–**19**¹³⁷ compared to results of the HRS measurements in 1,4-dioxane at $\lambda = 1064$ nm.^{139, 140}

Molecule	β (calc.)	β (exp.)	Molecule	β (calc.)	β (exp.)
16	31	43	18	313	383
17	323	259	19	1211	447

Table 8. The values of $\beta(0,0,0)$ (a.u.) for NH_2/NO_2 -substituted π -conjugated molecules calculated using the DFT and MP2 methods.¹³¹

Mole- cule	SVWN/ 6-31G	BLYP/ 6-31G	B3LYP/ 6-31G	LB94/LDA/ TZ2P	MP2/ 6-31G
1	1650	1656	1698	1903	1931
12	29 298	28 349	20 153	36 695	10 110
20	47 090	47 140	54 710	52 040	62 660
21	682 000	677 000	611 000	784 000	184 000

LB94 functional (see Table 7). The hybrid functionals B3LYP and B97-1 perform somewhat better than LDA and BLYP (see Table 6).

Table 8 summarises computational results for a number of molecules with extended π -conjugated bridges. According to the tabulated data, the values predicted by DFT (in particular, in the case of the LB94 functional with improved asymptotic behaviour) are significantly larger than those predicted by MP2. Based on this conclusion, Champagne *et al.*¹³¹ warned against the use of DFT for the evaluation of hyperpolarisabilities. However, we should point out that the hyperpolarisabilities increase by factors of 12 and 5 on going from molecule **1** to **12**, as estimated with B3LYP and MP2, respectively. Meanwhile, according to the experimental measurements, the ratio of hyperpolarisabilities of D/A-substituted stilbenes and benzenes varies in the range from 6 to 10, depending on substituents and experimental conditions (see Table 9). This means that the increase in β with an increase in the conjugation chain length is somewhat underestimated by MP2 and overestimated by B3LYP in the above calculations by Champagne *et al.*¹³¹ It is also of note that β of *p*-NA has been accurately determined experimentally in the gas phase (1787 ± 73 a.u., EFISH, $\lambda = 1064$ nm)⁶⁵ and it is unclear, why Champagne *et al.*¹³¹ did not compare their theoretical results with this experimental value. From Table 8, it is apparent that the B3LYP-based estimate is closer to the experimental value than that of MP2.

As has been mentioned above, the B3LYP functional performs slightly better than the non-hybrid ones and, in this particular case, also proves superior to LB94 (which estimates the increase in hyperpolarisability on going from **1** to **12** to be 19-fold). Unfortun-

Table 9. The values of static and dynamic hyperpolarisabilities (10^{-30} esu, $\lambda = 1907$ nm) of D/A-substituted benzene and stilbene derivatives calculated by the LDA/POL¹³⁶ method compared to the respective experimental values.⁷⁸

Molecule	$\beta(0,0,0)$	$\beta(2\omega, \omega, \omega)$	Experiment ^a
22a	6.74	8.18	15.3
22b	4.91	5.85	9.0
22c	3.56	4.24	6.3
22d	0.32	0.52	1.8
23a	96	153	84
23b	79	123	51
23c	63	95	45
23d	17	27	18

^a EFISH measurements in 1,4-dioxane at $\lambda = 1907$ nm.

nately, the lack of experimental data for **21** prevents the respective analysis of the increase in hyperpolarisability on going from **20** to **21**. We suggest that the use of DFT gives rise to the overestimation of hyperpolarisabilities in the case of extended easily polarisable π -systems, such as polyenes. At the same time, the π -systems containing aromatic rings are less polarisable and can be adequately described within DFT.

Regardless of the aforementioned drawbacks, the majority of functionals correctly reproduce the experimental trends in β (see Tables 5–8). It thus follows that the B3LYP and, especially, B97-1 functionals are slightly superior to others.

It is important to keep in mind the major purpose of the use of various computational methods. Most often, in the search for promising materials for NLO applications it is reasonable to monitor relative changes in hyperpolarisabilities along a specific series of compounds. Apparently, DFT provides the optimum efficiency for this task.

III. Characteristics of π -conjugated systems related to the efficiency of the second harmonic generation

1. Qualitative criteria of hyperpolarisability.

Hyperpolarisability as a function of the conjugated chain length

The condition that an NLO active molecule should contain strong donor and acceptor substituents linked by an easily polarisable π -bridge can be considered as a basic prerequisite in the search for NLO compounds. The optimum combination of the π -system and D/A-substituents provides the maximum NLO efficiency.

Marder *et al.*^{141–145} proposed a convenient criterion for the description of NLO active molecules, which characterises the degree of delocalisation of the electron density over the π -system as a function of the nature (weak/strong) of D/A-substituents, *viz.*, Bond Length Alternation (BLA), calculated as a mean difference between the lengths of formally ordinary and double bonds. This difference can be determined from either experimental data on the molecular structure or quantum-chemical calculations. A series of substituted polyenes was analysed in order to verify the applicability of the criterion.



The distribution of bond lengths in the polyenes shifts either towards the non-polar form (a non-polar solvent, weak D/A-substituents) or towards the zwitter-ionic form (a polar solvent, strong D/A-substituents).

The BLA criterion was used¹⁴¹ to monitor the effects of the strength of D/A-substituents on the degree of the electron delocalisation over the polyene π -chain. The criterion makes it possible to arrange any D/A-substituents in a common scale of their relative strengths and depict the molecular hyperpolarisability as a function of the substituent strength.

Within the two-level model, the static hyperpolarisability can be represented as

$$\beta = \frac{3}{2} (\mu_e - \mu_g) \frac{\mu_{ge}^2}{E_{ge}^2}, \quad (17)$$

where $(\mu_e - \mu_g)$ is the difference between the dipole moments of the molecule in the ground and excited states, μ_{ge} is the transition dipole moment and E_{ge} is the corresponding energy [this is a static analogue of the formula (5)]. Terms in the right part of Eqn (17) are related to the ground state wavefunction (Fig. 3), which in turn correlates with BLA according to the definition of the criterion.^{141, 142}

Hyperpolarisabilities of molecules with identical substituents (*viz.*, NMe_2 and CHO) as a function of BLA and another similar criterion, Bond Order Alternation (BOA), were analysed theoret-

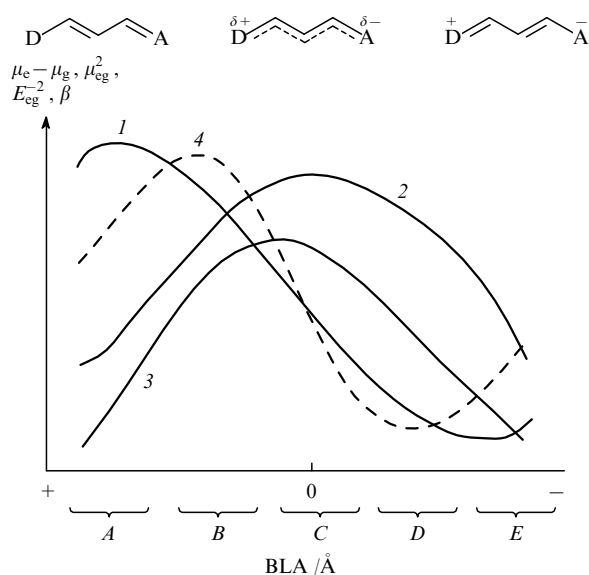
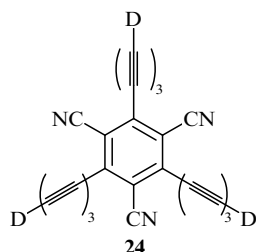


Figure 3. Dependences of $(\mu_e - \mu_g)$ (1), μ_{eg}^2 (2), E_{eg}^{-2} (3) and β (4) on the ground-state wavefunction of a polyene system represented by the BLA parameter.

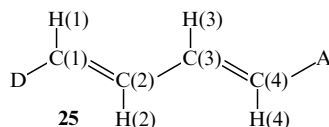
It is commonly adopted that $BLA > 0$ for molecules in the neutral form and $BLA < 0$ for zwitter-ions. A–E are arbitrarily selected regions.

ically using the SOS/INDO/CISD and FF/AM1 methods.^{144–146} Solvent effect were simulated by applying an electric field. The dependence β vs. BOA fully consistent with the curve 4 in Fig. 3 was obtained. The function β vs. BLA was also analysed¹⁴⁷ for the case of octupolar molecules (see below).



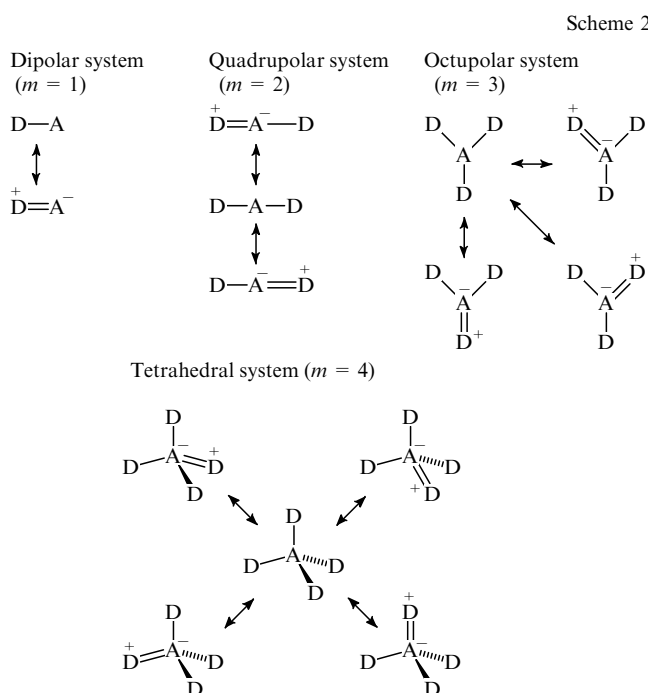
The values of β for molecules **24** with the donor substituent (D) varied over the series H, Me, OH, OMe, NH₂ and NMe₂ were estimated within the CPHF/6-31G approximation. The resultant values of β increase with an increase in the donor strength of the substituent along the above series, but it does not reach the maximum probably remaining in the region A (see Fig. 3).

Yet another criterion, BACS (Bridge Atomic Charge Sum), which characterises the effects of substituents and/or environment on the degree of conjugation over the π -chain linking donor and acceptor groups in molecules of the type **25**, was suggested.^{148–150} It is defined as the sum of charges on the atoms constituting the chain.

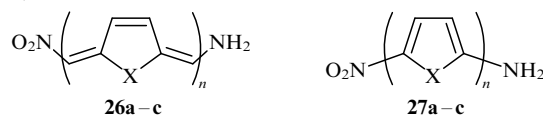


$$BACS = q_{C_i} + q_{H_j}$$

Solvent effects were also simulated by adjusting the external electric field strength. D/A-substituted polyenes and five-membered heterocycles (**26a–c**, **27a–c**) were selected as model systems. The optical characteristics were calculated within the FF/AM1 approximation. The linearity between BACS and BLA criteria was demonstrated for the case of polyenes,¹⁴⁸ which implies that BACS also correlates with the ground state wave-



function. It was established^{149,150} that the dependences β vs. BACS for the substituted heterocycles studied are similar to those for polyenes. Thus, it may be concluded that the curve 4 in Fig. 3 describes the general trend in hyperpolarisability of any π -conjugated system on going from its neutral to the zwitter-ionic form.



X = NH (a), O (b), S (c).

Yet another parameter utilised to represent the ground state wavefunction within the VB-*m*CT model is worth mentioning. A molecule can be represented as a combination of its valence-bond structure (VB) that characterises of the neutral form and *m* charge-transfer (CT) states corresponding to different zwitter-ionic forms (Scheme 2).

The ground-state wavefunction (ψ_g) can be written in the basis of VB (φ_{VB}) and CT (φ_{CT}) functions as

$$\psi_g = \varphi_{VB} \sqrt{1 - ml} + \sqrt{l} \sum_{j=1}^m \varphi_{CTj}, \quad (18)$$

where *m* is the number of zwitter-ionic states, *l* is the parameter quantifying the degree of mixing between the neutral and the zwitter-ionic forms. The latter parameter was selected by some researchers^{151–156} as a criterion for the evaluation of β , whereas another criterion, MIX, was preferred in a series of works^{157–160} for linear molecules. MIX relates to *l* in a simple way

$$MIX = 2l - 1.$$

The linearity between *l* and MIX, on the one side and BLA, on the other was demonstrated for linear,^{151,157–160} quadrupolar,¹⁵² octupolar^{153–155} and tetrahedral molecules.¹⁵⁶ Furthermore, Laage *et al.*¹⁶¹ applied the MIX criterion to the description of hyperpolarisabilities of charged D/A-substituted polyenes.

It has to be noted that the criteria considered above, despite their convenience, have specific limitations and are only of a qualitative character. For instance, the use of BLA for molecules containing heteroatoms is hardly justified. The BACS criterion is more suitable for the comparative analyses of results obtained for different π -conjugated chains but it has to be kept in mind that the values of atomic charges depend on the computational method

and basis sets selected.¹⁶² Probably, the criteria *I* or MIX are more versatile, however, their determination requires special calculations, whereas molecular geometry parameters and atomic charges are listed in default outputs of all major quantum-chemical codes. The common feature of all the criteria considered above is that they correlate with the ground state wavefunction, which primarily defines the efficiency of the second harmonic generation. All the above-mentioned criteria can only be used for the visualisation of the wavefunction.

As has been shown both theoretically (*e.g.*, see Ref. 163) and experimentally,^{78,79} an elongation of the conjugation chain gives rise to a significant increase in the molecular hyperpolarisability. Zhu and Jiang¹⁵⁰ estimated the increase in β with an increase in the number of units (n) in the conjugation chain. Comparative data for molecules with polyheterocyclic chains are shown in Fig. 4. The quinonoid-type polyheterocycles **26a–c** reveal high NLO activity, whereas that in the case of polyheterocycles **27a–c** is significantly lower and the activity increases more slowly with the chain elongation. According to the computation, β increases in the series pyrrole < furan < thiophene, but this empirical observation was not explained.

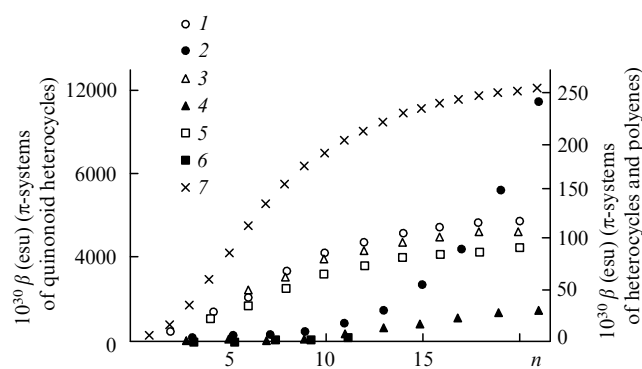


Figure 4. Hyperpolarisability as a function of the number of conjugated chain units for NH_2/NO_2 -substituted polyheterocycles (1–6) and polyenes (7);

(1) polythiophene (**27c**), (2) quinonoid analogue of polythiophene (**26c**), (3) polyfuran (**27b**), (4) quinonoid analogue of polyfuran (**26b**), (5) polypyrrole (**27a**), (6) quinonoid analogue of polypyrrole (**26a**), (7) polyenes.

Similar results were obtained by Morley,¹⁶⁴ who applied the software code CNDOVSB to calculate the polarisabilities of NMe_2/NO_2 -substituted polyheterocycles. The same series of ascending β (pyrrole < furan < thiophene) was obtained. Morley speculated¹⁶⁴ that such a sequence is due to the combined effect of the degree of charge transfer and energy gap between the ground and excited states.

Investigation into the dependence of hyperpolarisabilities of NMe_2/NO_2 -substituted polyenes, polyynes and polyphenylenes on the conjugation chain length under assumption of planarity of the molecules using the SOS/CNDO/CI method (Fig. 5), for molecules with sufficiently long π -chains ($n > 7$), showed that β increases in the series polyphenylenes < polyynes < polyenes. Furthermore, in the case of polyphenylenes, the increase β stops for $n > 8$.^{165–168}

Champagne, Jacqemin *et al.*^{169–174} investigated a number of molecules containing polymethinimine (PMI) π -chains. Since the fragment $\text{CH}=\text{N}$ can be simultaneously regarded as a chain unit and a D/A-pair, they analysed^{169,170} molecules $\text{H}-(\text{CH}=\text{N})_n\text{H}$, *i.e.*, molecules without supplementary substituents. Under assumption of the planar *trans*-structure of the chain, the values of the hyperpolarisability were estimated for n varied from 1 to 20 and the hyperpolarisability increment per $\text{CH}=\text{N}$ unit in an infinite chain was determined

$$\Delta\beta = \beta(n) - \beta(n-1).$$

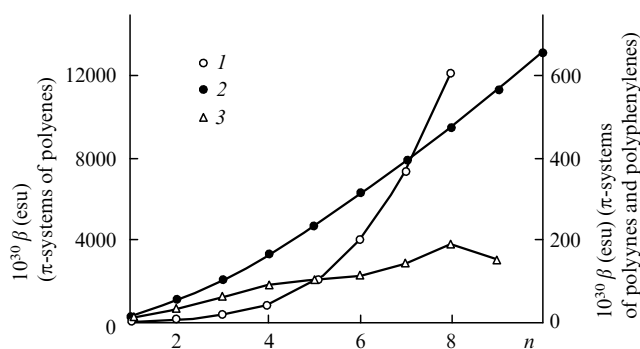


Figure 5. Hyperpolarisability as a function of the number of conjugated chain units for NMe_2/NO_2 -substituted oligomers; (1) polyenes, (2) polyynes, (3) polyphenylenes.

If the lengths of formally ordinary and double carbon–nitrogen bonds are kept fixed,¹⁷⁰ the absolute values of hyperpolarisability significantly diminish with an increase in BLA, in agreement with the general dependence $\beta(\text{BLA})$ (see Fig. 3). Moreover, the increment of $|\beta|$ increase with a chain elongation also decreases

BLA / Å	0.100	0.126	0.150	0.190	0.220
$\Delta\beta_{zzz}(\infty)$ (a.u.)	-2753 ± 129	-1461 ± 51	-869 ± 28	-434 ± 7	-293 ± 2

The authors explained this by a decrease in the degree of the electron density delocalisation. In another study of the same system,¹⁷¹ the bond lengths were allowed to vary in the geometry optimisation procedure and the BLA values were adjusted by allowance for the solvent effects. As expected, BLA somewhat decreased with chain elongation: from 0.132 Å to 0.095 Å and from 0.137 Å to 0.092 Å on going from $n = 2$ to 18 for an isolated molecule and acetonitrile solution, respectively.

The ratio β/M , where M is the molecular mass, was suggested as a convenient criterion to compare unsubstituted PMI (4.2 in units of 10^{-30} esu) with other types of compounds.¹⁷² For instance, $\beta/M = 0.76$, 0.16 and 0.10 for D/A-polyenes,¹⁷⁵ *p*-NA¹⁷⁶ and 3-methyl-*p*-NA,¹⁷⁷ respectively.

PMI and polyenes with identical D/A-substituents were directly compared in a theoretical study within the CPHF/6-31G approximation^{173,174} (Table 10, Fig. 6). The authors considered¹⁷³ the effects of different D/A-substituents and their mutual arrangement (which is especially important for PMI) at a constant length of the PMI and polyene chains ($n = 4$).

Table 10. The values of β_{zzz} for D/A-substituted polymethinimines and polyenes.

Molecule	β_{zzz} (a.u.)	Molecule	β_{zzz} (a.u.)
$\text{O}_2\text{N}-(\text{CH}=\text{N})_4\text{NH}_2$	7598.2	$\text{F}-(\text{CH}=\text{N})_4\text{OH}$	1038.0
$\text{H}_2\text{N}-(\text{CH}=\text{N})_4\text{NO}_2$	−3446.3	$\text{HO}-(\text{CH}=\text{N})_4\text{F}$	198.8
$\text{O}_2\text{N}-(\text{CH}=\text{N})_4\text{OH}$	5650.9	$\text{O}_2\text{N}-(\text{CH}=\text{CH})_4\text{NH}_2$	8330.3
$\text{HO}-(\text{CH}=\text{N})_4\text{O}_2\text{N}$	−2501.0	$\text{O}_2\text{N}-(\text{CH}=\text{CH})_4\text{OH}$	6526.3
$\text{F}-(\text{CH}=\text{N})_4\text{NH}_2$	1495.5	$\text{F}-(\text{CH}=\text{CH})_4\text{NH}_2$	1109.9
$\text{H}_2\text{N}-(\text{CH}=\text{N})_4\text{F}$	−456.6	$\text{F}-(\text{CH}=\text{CH})_4\text{OH}$	707.5

According to the data listed in Table 10, the PMI chain provides higher optical efficiencies with weakly polarising substituents (OH/F, NH_2/F). However, the situation is reversed upon the introduction of strong D/A-groups (*i.e.*, OH/ NO_2 or NH_2/NO_2). The authors explained this by a combined action of three factors: the degree of the electron density delocalisation and the asymmetry in the electron density distribution relative to the unsubstituted polyene either intrinsic (due to the alternating

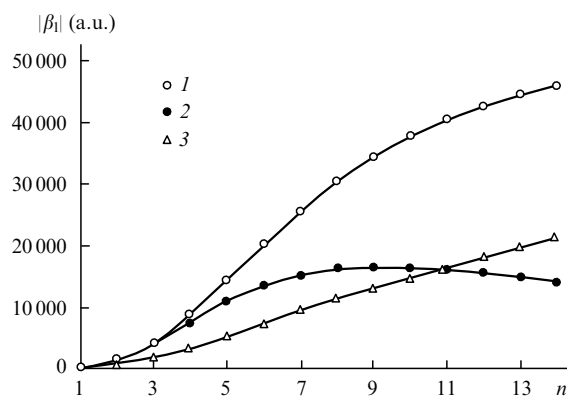


Figure 6. Component of hyperpolarisability parallel to the conjugated chain (β_1) as a function of its length for $\text{H}_2\text{N}-(\text{CH}=\text{CH})_n\text{NO}_2$ (1), $\text{O}_2\text{N}-(\text{CH}=\text{N})_n\text{NH}_2$ (2) and $\text{H}_2\text{N}-(\text{CH}=\text{N})_n\text{NO}_2$ (3). Calculation within the CPHF/6-31G approximation.

$\text{N}^{\delta-}=\text{C}^{\delta+}$ fragments) or extrinsic (induced by D/A-substituents). The higher NLO efficiency of polyenes in the case of strong D/A-substituents (NH_2/NO_2) can be explained by the higher degree of the π -electron delocalisation in polyenes with respect to PMI, which dominates over the asymmetry contribution. The situation is reversed in the case of weak D/A-pairs: the asymmetry effect prevails. The best result upon PMI substitution can be achieved by attaching donor groups from the side of nitrogen atoms (see Table 10), since the asymmetry effects of the D/A-groups and $\text{CH}=\text{N}$ fragments are oppositely directed in this case. A study of changes in hyperpolarisability of NO_2/NH_2 -substituted PMI and polyenes with chain elongation¹⁷⁴ (see Fig. 6) indicated that the attachment of donor groups from the side of nitrogen atoms enhanced the polarisability only for short and medium-length PMI chains ($n < 11$), which is in agreement with the data presented in Table 10. The opposite effect was observed for long PMI chains: the absolute value of β continued to increase for $\text{H}_2\text{N}-(\text{CH}=\text{N})_n\text{NO}_2$, whereas it started to decrease for $\text{O}_2\text{N}-(\text{CH}=\text{N})_n\text{NH}_2$.

These results can be rationalised within the concept of auxiliary D/A-substituents. The terminal nitrogen atom in a PMI chain carries a partial negative charge; the attachment of a donor group to it increases its donor ability, and thus this acts as an auxiliary donor. The partially positively charged terminal carbon atom behaves similarly with respect to acceptor groups attached. In such a situation, the asymmetry induced by the D/A-pair is opposite to the intrinsic asymmetry due to the $\text{CH}=\text{N}$ fragments. For relatively short PMI chains ($n < 4$), the D/A-pair asymmetry prevails. Upon an increase in the chain length, the induced asymmetry becomes weaker and thus the intrinsic asymmetry due to the $\text{CH}=\text{N}$ fragments starts to dominate, which gives rise to a decrease in the hyperpolarisability at $n > 10$; the effect of substitution vanishes for $n \rightarrow \infty$. If D/A-substituents are attached to the opposite terminal atoms, both asymmetry effects act in the same direction. However, the terminal $\text{N}^{\delta-}$ and $\text{C}^{\delta+}$ atoms of the PMI chain deactivate the acceptor and donor properties of the substituents attached, which gives rise to β lower than that of analogous D/A-polyenes. This concept is also supported by results obtained for molecules **28–37** (Table 11).^{4, 178–182}

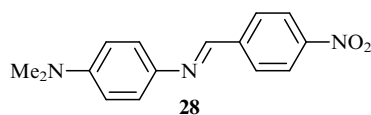
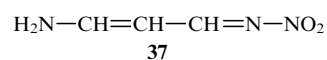
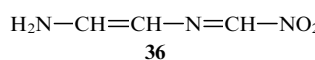
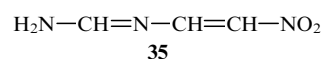
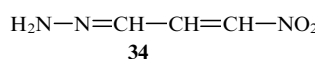
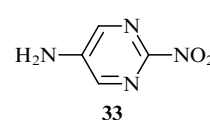
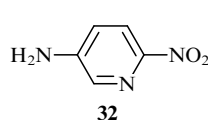
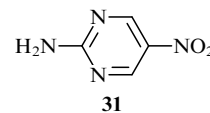
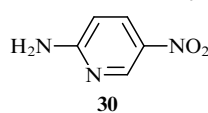
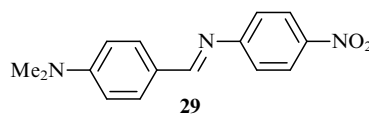


Table 11. Calculated values of static hyperpolarisabilities (10^{-30} esu) for molecules **28–37**.

Molecule	β	Calculation method	Ref.
28	28.0	FF/PM3	178–180
29	36.8	FF/PM3	178–180
30	33.9	SOS/PPP/CI	4
31	25.6	SOS/PPP/CI	4
32	46.7	SOS/PPP/CI	4
33	47.6	SOS/PPP/CI	4
34	4.87	CPHF/6-31G	181, 182
35	3.94	CPHF/6-31G	181, 182
36	6.35	CPHF/6-31G	181, 182
37	4.26	CPHF/6-31G	181, 182



The bridging nitrogen atom in molecule **28** acts as a weak acceptor, and the central CH group acts as a donor. This deactivates the terminal D/A-substituents. In contrast, the central fragments in molecule **29** enhance the strength of D/A-substituents, which gives rise to an increase in the hyperpolarisability.^{178–180} The heterocyclic nitrogen atoms in molecules **30–33** withdraw the electron density thus increasing the partial positive charge on the adjacent carbon atoms.⁴ This attenuates the donor properties of molecules **30** and **31** but enhances the acceptor properties of molecules **32** and **33**. An analogous situation is observed in molecules **34–37**.^{181, 182}

Jacqemin *et al.*^{183–186} published the first estimates (calculated with the CPHF/6-31G method) of the hyperpolarisabilities of molecules $(\text{X}-\text{Y})_n$, where X, Y = B, P, Si, N, C characterised by the *trans*-cisoid structure [except for the $(\text{B}=\text{N})_n$ molecule, which is linear]. In particular, they estimated the values of β/M (Table 12). It is apparent that the PMI systems considered above manifest significantly higher NLO activities.

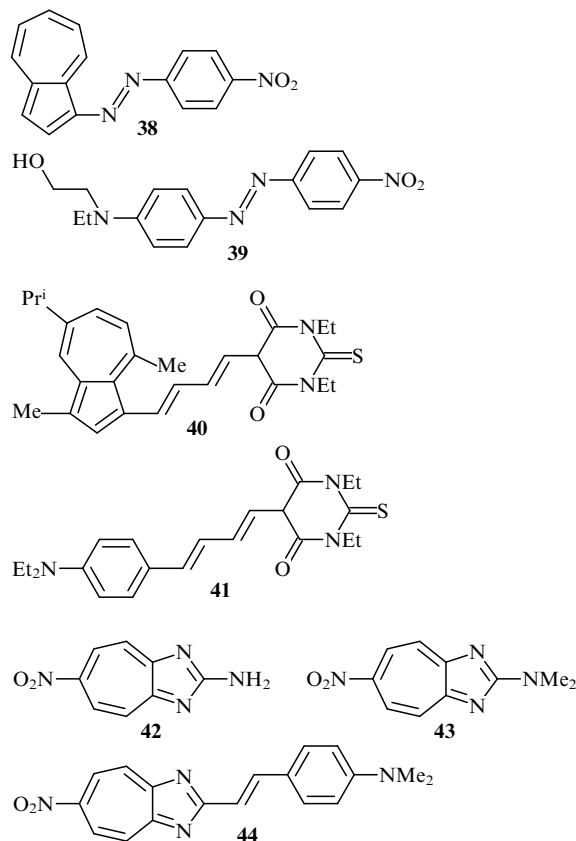
Table 12. Calculated values of β/M (10^{-30} esu) for $(\text{X}-\text{Y})_n$ oligomers.

Molecule	β/M	Ref.	Molecule	β/M	Ref.
$(\text{B}=\text{N})_n$	~ 0	183	$(\text{SiH}=\text{PH}_2)_n$	0.33	184
$(\text{BH}=\text{NH})_n$	0.03	186	$(\text{BH}=\text{PH})_n$	0.95	185
$(\text{BH}_2-\text{NH}_2)_n$	0.01	186	$(\text{BH}_2=\text{PH}_2)_n$	0.02	185
$(\text{N}=\text{PH}_2)_n$	0.03	184	$(\text{CH}=\text{NH})_n$	4.2	172
$(\text{CH}=\text{PH}_2)_n$	0.06	184			

2. Molecules with heteroatoms

Fragments containing heteroatoms, in particular, heterocyclic π -systems, are widely used in the design of NLO-active compounds as both π -bridges and the D/A groups.^{187–190}

The NLO properties of azulene-containing molecules, their heteroanalogues and related reference compounds (**38–44**) have been studied.^{191–193}



The azulene bicyclic system can be used as either a donor or an acceptor or as a unit of a π -bridge. The donor properties of azulene were estimated based on the EFISH measurements in dioxane ($\lambda = 1907$ nm)¹⁹¹ and SOS-based calculations (INDO, $\lambda = 1907$ nm).¹⁹² Its behavior as a π -bridge was considered theoretically using the FF method (AM1 in the static limit).¹⁹³ The donor properties of azulene are comparable to those of RR'N groups (R, R' = Alk or Ar, see molecules **38–41**), which are among the strongest π -donors. Diazaazulene derivatives **42–44** manifest higher hyperpolarisabilities than DANS (Table 13), which indicates the higher NLO activity of azulene-containing molecules. Probably, this is due to the lower energy barrier to the electron delocalisation and enhanced donor and acceptor ability of the substituents attached to the five- and seven-membered rings of azulene, respectively.

Table 13. Calculated hyperpolarisabilities of azulene-containing molecules, their hetero analogues and reference compounds.

Molecule	$10^{30} \beta_0$ (esu)	$10^{48} \mu\beta_0$ (esu)
38	50	—
39	48	—
40	—	1323
41	—	1400
42	20	—
43	36	—
44	106	—
2	43	—

The spectral properties of unsubstituted five-membered heterocycles C_4H_4X ($X = O, S, Se$ and Te) were studied theoretically using *ab initio* calculations at different levels.^{194–196} The hyperpolarisability increases in the following series: thiophene < furan < selenophene < tellurophene. It is of interest that the results of theoretical studies of the D/A molecules with π -systems built up of such heterocycles (see above) manifest the reversed trend, *viz.*, thiophene > furan. As it will be discussed in more detail below, both thiophene and furan can act as a π -bridge of choice depending on the specific structure of the D- π -A molecule. It is of note that the sequence of ascending β for unsubstituted heterocycles partly correlates with the aromaticity series: thiophene > selenophene > tellurophene > furan.¹⁹⁷ The correlation is violated by the position of furan. However, the aromaticity of furan is still a subject of debate: it is estimated to be in the range from 20% to 60% of the benzene value, depending on the theoretical method utilised.¹⁹⁸

For unsubstituted fused heterocycles, β increases¹⁹⁹ and the aromaticity decreases²⁰⁰ on going from benzothiazole to benzoxazole.

Most probably, the following trend is observed: the less aromatic unsubstituted heterocycle is characterised by larger β due to the lower energy barrier to the electron density redistribution.

Jen and co-workers^{201–205} analysed the effects of thiophene for benzene substitution in π -conjugated chain on the spectral properties.

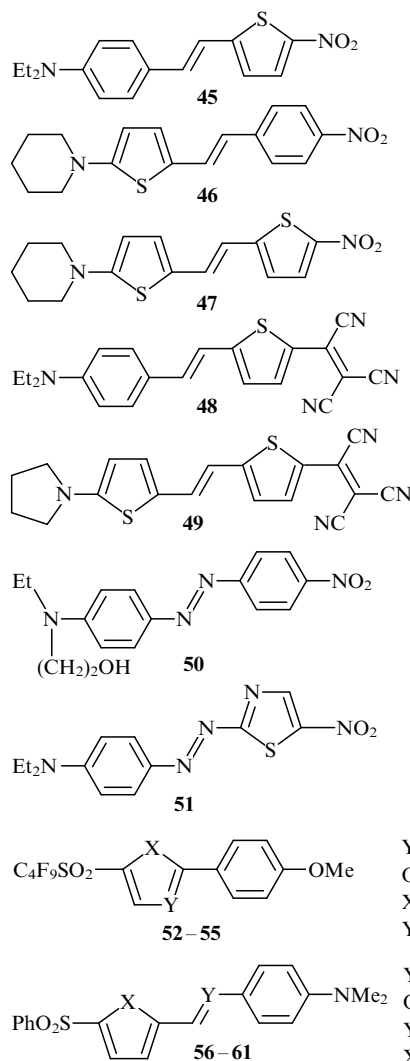
According to the results obtained (Table 14, molecules **2, 45–49**), the substitution for the phenylene fragment from the donor side is more efficient, since the electron-rich thiophene fragment acts as an auxiliary donor in this case. If the bridge is built up of two thiophene fragments, the value of β increases further, since only a readily polarisable conjugated system appears between the D/A groups. The introduction of strong π -acceptors, such as a tricyanoethylene substituent, gives rise to an even further increase in the hyperpolarisability. On the other hand, it has to be

Table 14. Spectral properties [$10^{48} \mu\beta_0$ (esu); $\lambda_{\max}$ /nm] of heterocyclic molecules.

Molecule	$\mu\beta$	$\lambda_{\max}$ (see ^a)	Ref.	Conditions
2	580	424	201, 205	1,4-dioxane, EFISH measurements at $\lambda = 1907$ nm
45	600	478	201, 205	the same
46	660	460	201, 205	"
47	1040	516	201, 205	"
48	6200	640	201, 205	"
49	6900	718	201, 205	"
50	51	480	206	CH ₂ Cl ₂ , EFISH measurements at $\lambda = 1579$ nm extrapolated to $\lambda = \infty$ using the two-level model
51	104	579	206	the same
52	1.8	282	207	1,4-dioxane, EFISH measurements at $\lambda = 1064$ nm extrapolated to $\lambda = \infty$ using the two-level model
53	7.1	312	207	the same
54	8.0	338	207	"
55	8.2	310	207	"
56	119		208, 209	1,4-dioxane, EFISH measurements at $\lambda = 1064$ nm
57	502		208, 209	the same
58	769		208, 209	"
59	314		208, 209	"
60	395		208, 209	"
61	1364		208, 209	"

^a Hereinafter, $\lambda_{\max}$ is the absorption maximum in the UV spectrum.

noted that the increase in β is accompanied by a narrowing of the region of the optical transparency of these compounds.



Y = N: X = NMe (52),
O (53), S (54);
X = CH=CH,
Y = CH (55).

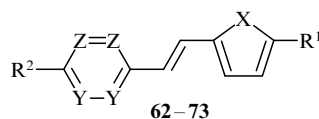
Y = N: X = NMe (56),
O (57), S (58);
Y = CH:
X = NMe (59),
O (60), S (61).

Dirk *et al.*²⁰⁶ proposed to use thiazole as a structural unit of π -bridges. The substitution of this five-membered heterocycle for the benzene ring doubles β (see Table 14, molecules 50 and 51). The authors explained this increase by the lower energy barrier to the electron delocalisation in the case of thiazole. Meanwhile, molecule 51 is less optically transparent.

The hyperpolarisabilities of biaryls 52–54 increase²⁰⁷ in the series 52 (imidazole) < 53 (oxazole) < 54 (thiazole), although they remain lower than β of their biphenyl analogue 55. Similar trends in β on going from π -systems containing nitrogen heterocycles to oxygen and further to sulfur heterocycles were obtained for molecules 56–58 and 59–61.^{208, 209}

It is evident that the aforementioned trends can be explained only by a combined account of the effects of the energy barrier to the electron delocalisation and the π -electron density excessiveness or deficiency (relative to that in benzene) in these heterocyclic systems.

A detailed theoretical background for the results considered above was given^{210–212} taking heteroanalogues of D/A-substituted stilbenes as model molecules. Breitung *et al.*²¹² also analysed five-membered heterocyclic compounds containing two heteroatoms, for which the non-equivalence of positions 2 and 5 in the heterocycles has to be addressed. Albert *et al.*²¹⁰ considered a series of molecules 62–73. Their spectral properties were assessed using the SOS/INDO method ($\hbar\omega = 0.1$ eV) for molecular geometries optimised at the AM1 level (Table 15).



$R^1 = \text{NH}_2$, $R^2 = \text{NO}_2$, $Y = Z = \text{CH}$: X = S (62), O (63), NH (64);
 $R^1 = \text{NH}_2$, $R^2 = \text{NO}_2$, $Y = \text{N}$, $Z = \text{CH}$: X = S (65), O (66), NH (67);
 $R^1 = \text{NO}_2$, $R^2 = \text{NH}_2$, $Y = Z = \text{CH}$: X = S (68), O (69), NH (70);
 $R^1 = \text{NO}_2$, $R^2 = \text{NH}_2$, $Y = \text{N}$, $Z = \text{CH}$: X = S (71), O (72), NH (73).

Table 15. Spectral characteristics of heterocyclic analogues of NH_2/NO_2 -substituted stilbenes.²¹⁰

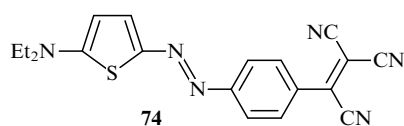
Molecule	$10^{30} \beta_{\text{vect}}$ (esu)	λ_{max} /nm	Molecule	$10^{30} \beta_{\text{vect}}$ (esu)	λ_{max} /nm
62	43.9	402	68	45.0	424
63	46.6	410	69	37.5	424
64	55.7	418	70	33.5	417
65	53.8	423	71	36.1	419
66	53.2	425	72	27.7	414
67	62.5	430	73	24.4	409

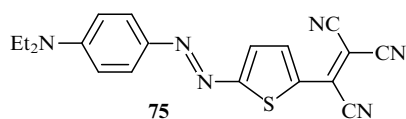
Note. For molecule 12, $\lambda_{\text{max}} = 363$ nm, $\beta_{\text{vec}} = 31.7 \times 10^{-30}$ esu.

According to the data summarised in the left part of Table 15, the heterocyclic substitution for one of the benzene rings at the donor side increases the hyperpolarisability, which is in accordance with the lower aromaticity of the heterocycles. However, the energy of aromatic stabilisation decreases in the series benzene > thiophene > pyrrole > furan,^{213, 214} whereas the hyperpolarisability increases in the series 12 (benzene) < 62 (thiophene) < 63 (furan) < 64 (pyrrole). The latter series conforms to the sequence of ascending π -electron excessiveness.²¹⁵

Therefore, heterocycles act as auxiliary donors; apparently, this factor prevails over the aromatic stabilisation effects. Moreover, both factors act in the same direction. Upon replacement of carbon atoms in the benzene ring from the acceptor side by the nitrogen atoms (molecules 65–67), β further increases. The resultant π -electron-deficient ring enhances the effect of the NO_2 group and, moreover, provides a lower delocalisation barrier. If nitrogen atoms are introduced at the position Z (no such compounds are mentioned in Table 15), the hyperpolarisability increases even further. Meanwhile, if the five-membered heterocycle is located at the acceptor side (right part of Table 15), the order of ascending β is reversed, i.e., 68 > 69 > 70, which corresponds to the decrease in the π -electron excessiveness and does not correlate with the changes in the energy barrier to the aromatic delocalisation. Still, all three molecules 68–70 manifest higher NLO activity than molecule 12, which is due to the lower aromatic delocalisation barrier therein with respect to benzene. In this case, the effects of the π -electron density excessiveness are of low importance. It seems strange that the hyperpolarisability of molecule 68 is larger than that of 62. This violates the concept of auxiliary D/A-substituents and is not supported by other theoretical²¹¹ and experimental^{201–205} estimates.

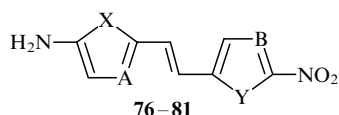
Moylan *et al.*²¹⁶ analysed β as a function of the thiophene location in the π -chain using compounds 74 ($10^{30} \beta = 686 \pm 21$ esu; $\lambda_{\text{max}} = 708$ nm) and 75 ($10^{30} \beta = 867 \pm 35$ esu; $\lambda_{\text{max}} = 719$ nm) as examples.



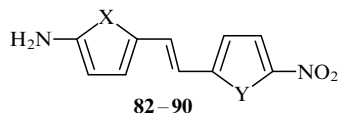


According to the EFISH measurements (at $\lambda = 1907$ nm in chloroform), higher NLO activity is observed for molecule **75**, which contains the thiophene fragment substituted with an acceptor group, despite molecule **74** is more polar, *i.e.*, it possesses a higher dipole moment. This discrepancy can be explained²¹⁶ based on the β (BLA) dependence (see Fig. 3) assuming that both molecules are located in the region *B*. This implies that an increase in the polarity of the π -system, for instance, induced by a stronger D/A group or by a change in the thiophene position, gives rise to a decrease in β . Thus the authors concluded that the concept of auxiliary D/A groups is not versatile. Nevertheless, it remains unclear, why the authors²¹⁶ did not study molecules with weaker substituents. Following the authors' logic, such molecules should fall into the region *A* (see Fig. 3), such that the thiophene location from the side of the donor should appear preferable. This is supported by the experimental data^{201–205} for weaker D/A groups. In our opinion, the results by Moylan *et al.*,²¹⁶ once again corroborate the above statement that the optimum combination of D/A groups and a π -system in a D- π -A molecule is required for the efficient manifestation of the NLO properties. According to the dependences shown in Fig. 3, the majority of NLO active molecules studied fall into the region *A* where all the aforementioned concepts are valid. Meanwhile, for molecules in the region *B*, all these regularities (not only the concept of auxiliary D/A groups) are violated thus giving rise to a decrease in β .

The hyperpolarisabilities of a series of analogues of NH₂/NO₂-substituted stilbene derivatives²¹¹ are listed in Table 16. The calculations were accomplished using different methods, but all qualitative trends were fully consistent.



X = NH, A = CH, B = N: Y = S (**76**), O (**77**), NH (**78**);
Y = NH, A = N, B = CH: X = S (**79**), O (**80**), NH (**81**).



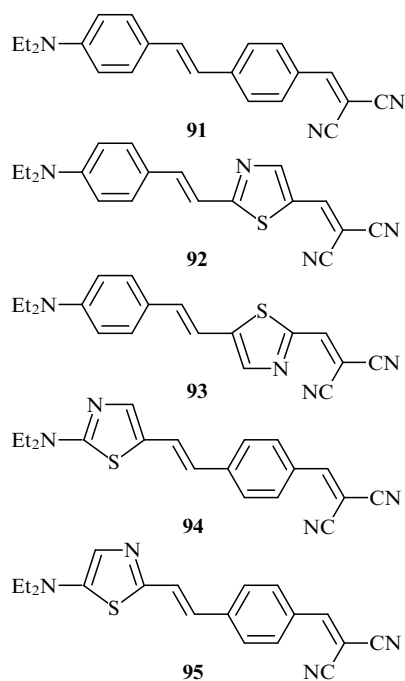
X = S: Y = S (**82**), O (**83**), NH (**84**); X = O: Y = S (**85**), O (**86**), NH (**87**); X = NH: Y = S (**88**), O (**89**), NH (**90**).

These results support the above-mentioned regularities regarding the replacement of the benzene ring by heterocyclic fragments. The hyperpolarisability increases in the following

Table 16. Calculated values of β_0 (CPHF/4-31G) for NH₂/NO₂-substituted stilbenes and their heterocyclic analogues under the assumption of their planarity.²¹¹

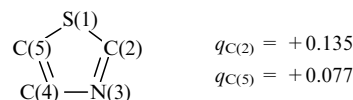
Molecule	$10^{30} \beta_0$ (esu)	Molecule	$10^{30} \beta_0$ (esu)
9	26.0	82	32.9
64	45.2	83	29.0
70	21.6	84	23.0
76	50.8	85	36.9
77	45.3	86	32.1
78	37.3	87	27.5
79	18.0	88	47.1
80	20.2	89	40.8
81	26.3	90	35.0

series **82** < **85** < **88**, **83** < **86** < **89**, **84** < **87** < **90** and decreases in the series **82** > **83** > **84**, **85** > **86** > **87**, **88** > **89** > **90**. In the case of five-membered rings with two heteroatoms, β manifests the following trends: **76** > **77** > **78**, **79** < **80** < **81**. It is of interest that the hyperpolarisability increases in the series **79** < **80** < **70** < **84** < **81** < **87** < **90**. The electron density deficiency decreases in the series thiazole > oxazole > imidazole.²¹⁵ Some authors²¹⁷ consider imidazole already as a weakly electron-rich fragment. Apparently, this is supported by the presented set of molecules where the imidazole ring adjacent to a donor group (**81**) results in higher NLO activity than benzene (**70**) and thiophene (**84**) rings. It is also important to stress that the charges on the carbon atoms in positions 2 and 5 of azoles are different. In molecule **81**, the donor is attached to the carbon atom in position 5, which has a lower positive charge than that in position 2, which is more favourable. Unfortunately, no examples with the reversed situation were considered.²¹¹ Such a study has been carried out by McMahon and co-workers,²¹² who considered D/A-substituted stilbene analogues with one Ph ring replaced by thiazole using the SOS method ($\lambda = 1907$ nm).



Molecule	91	92	93	94	95
$10^{30} \beta$ (esu)	36	54	118	42	57

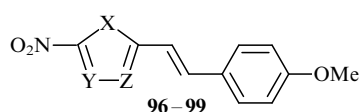
Therefore, the difference in the π -density at the carbon atoms in positions 2 and 5 differently affects the hyperpolarisabilities of molecules.



The maximum value of β is achieved upon the introduction of a π -electron deficient thiazole ring from the side of an acceptor in a way that the latter is bound to the more positive carbon atom at position 2. This was also rationalised by the contribution made by the heterocycle into the total dipole moment of the molecule directed from the acceptor to the donor. The dipole moment vector in the heterocycle is directed approximately from the nitrogen atom to the sulfur atom and thus, in the case of molecule **93**, it makes a certain positive contribution to the total dipole moment. A similar situation is observed in molecule **95**, but the heterocycle, being π -electron deficient, behaves as a 'counter-acting' donor.

It is interesting to note that the replacement of one of the benzene rings by the thiazole fragment both from the donor and acceptor sides gives rise to an increase in the hyperpolarisability of the D/A-substituted stilbene analogue, *i.e.*, the aromaticity effects prevail. For molecules **76** and **79** (see Table 16), where the thiazole fragment substitutes one of the pyrrole rings in molecule **90**, the hyperpolarisability decreases in a different series, *viz.*, **76** > **90** > **79**, which means that the π -electron deficiency of the thiazole ring becomes the dominant factor. Two reasons can be suggested to explain this apparent discrepancy: first, molecules **76** and **79** contain pyrrole as the second aromatic ring involved into the π -system (rather than benzene in molecules **92–95**), and second, different D/A pairs were used. This changes the balance between the aromaticity and the π -electron deficiency effects.

Results similar to those discussed above²¹² were obtained by Jug *et al.*²¹⁸ for imidazole and oxazole analogues of D/A-substituted stilbenes **96–99** (CPHF-based calculations within the VWN/TZVP-FIP approximation).



X = NH, Y = CH, Z = N (**96**); X = NH, Y = N, Z = CH (**97**);
X = O, Y = CH, Z = N (**98**); X = O, Y = N, Z = CH (**99**).

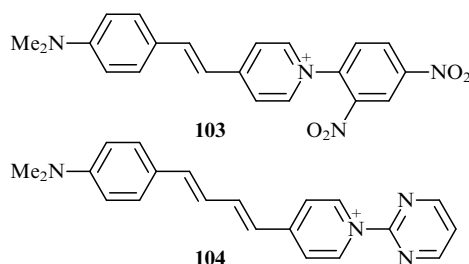
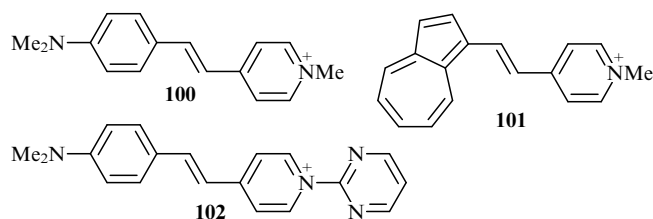
The following values of β_0 were obtained:

Molecule	96	97	98	99
$10^{30} \beta_0$ (esu)	77	78	84	99

The examples discussed above, despite the existence of specific discrepancies, demonstrate the general approach to the design of efficient NLO molecules based on the concept of auxiliary electron donors (acceptors) and fragments with low energy barriers to the electron delocalisation. Notwithstanding, the prediction of a net balance of particular factors on the hyperpolarisability remains a challenging task. In addition, the effects of aromaticity delocalisation barrier and electron deficiency/excessiveness can vary, depending on the computational method or experimental conditions. However, regardless of the method applied, the results can always be rationalised based on the interplay of three factors, *viz.*, the energy barrier to the delocalisation (aromaticity), the π -electron density deficiency/excessiveness and the charge distribution within the heterocycle (*i.e.*, the orientation of the dipole moment of the ring).

It is of note that the hyperpolarisability can be used as a criterion of the combined influence of the π -electron density deficiency/excessiveness and aromatic stabilisation.

Over the recent years, considerable efforts have been put forth to study the NLO properties of organic cations due to the fact that the probability of the crystallisation in non-centrosymmetric space groups for salts is higher than for neutral molecules. This implies that the molecular design step should include an analysis of ions. The hyperpolarisability of a series of cations **100–104** was measured by means of HRS in MeCN (with PF_6^- as a counterion).^{219–222}



The cations reveal the same trends in the spectral properties as analogous D- π -A molecules.

Cation	100	101	102	103	104
λ_{max} /nm	470	477	553	537	579
$10^{30} \beta_0$ (esu)	110	108	130	130	227

The aryl substitution for an alkyl group at the N^+ atom and the elongation of the conjugation chain gives rise to an increase in β and narrowing of the optical transparency range. The cations manifest rather high hyperpolarisabilities. However, an important question arises: what a system is actually probed in these cases. The acceptor ability of the pyridinium cation should depend on the strength of its interaction with a counteranion,²²³ which in turn depends on the experimental conditions, such as the nature of the solvent and of substituents at the N^+ atom and solution concentration. The exact structure of a cation-anion complex can be unambiguously determined in the crystalline state (which has indeed been done for a number of samples), whereas it is impossible for solutions. Thus it remains unclear, whether the regularities revealed reflect changes in the structure of the cation itself or they are due to the counterion effects. Yet another important problem has also to be addressed: how one can utilise the results of measurements in solution to predict the NLO susceptibility of a crystal, which can feature a totally different mutual orientation of the cation and anion? However, taking into account that the basic trends obtained are very similar to those for neutral D- π -A molecules (β increases with an increase in the acceptor strength and the length of the conjugation chain), it might be assumed that the counterion-induced effects are insignificant and the experimental results can well be interpreted in the same way as for the neutral molecules. Quantum-chemical calculations could help to clarify this problem, but no theoretical studies of this kind were carried out.^{219–222}

According to the literature data, vinylene (sometimes, acetylene) and thiophene (or other heterocyclic) fragments are combined in the vast majority of molecules considered as promising NLO materials. In addition, phenylene fragments are also often used as structural blocks of π -bridges. Examples of diverse NLO active molecules are discussed below and their spectral properties are summarised in Table 17.

The molecules considered incorporate heterocyclic fragments (**105–108**), phosphorus-containing groups (**109, 110**), branched π -chains (**111, 112**) and azo-groups (**109, 113**). Unfortunately, the results obtained for them cannot be directly compared; however, the general trend of an increase in β with an increase in the conjugation chain length, strength of D/A substituents, λ_{max} and a decrease in the aromaticity degree are evident. Table 17 also indicates that the molecules transparent in the visible region ($\lambda_{\text{max}} < 400$ nm) typically manifest rather low values of β (*e.g.*, **106a, 108a,b**). Criteria for the selection of specific combinations of fragments should include, in addition to achieving the maximum possible hyperpolarisabilities, high optical transparency, thermal stability and synthetic accessibility. An elongation of a π -bridge typically diminishes the thermal stability and narrows the optical transparency range. The introduction of strong D/A substituents (NR_2 , NO_2 , CN) induces a bathochromic shift of the absorption band. In overall, the design of D- π -A molecules by combining different D/A groups and building blocks of π -bridges is aimed at

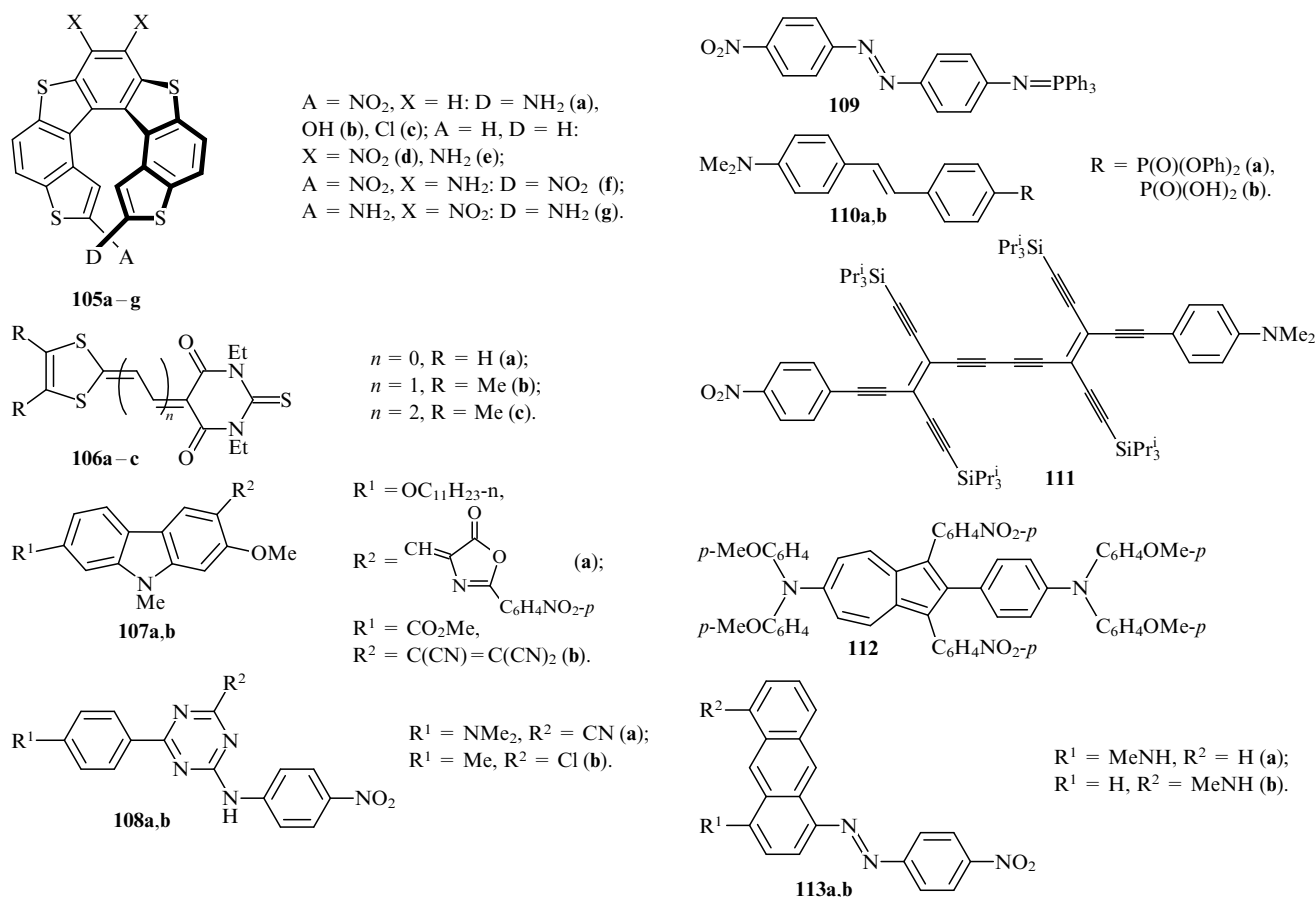


Table 17. Optical characteristics of NLO-active molecules belonging to various classes of organic compounds.

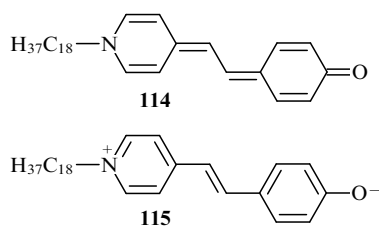
Molecule	β (see a)	$\mu\beta$ (see b)	λ_{max} /nm	Method of calculation or measurement	Ref.
105a	27.6	—	—	CPDFT/B3LYP/6-311G, calculation in the static limit	224
105b	22.9	—	—		224
105c	22.1	—	—		224
105d	63.7	—	—	TDHF/AM1	225, 226
105e	35.8	—	—	TDHF/AM1	225, 226
105f	127.5	—	—	TDHF/AM1	225, 226
105g	107.3	—	—		225, 226
106a	—	–12	403	EFISH	227, 228
106b	—	100	558	(CH_2Cl_2 ; $\lambda = 1907$ nm)	227, 228
106c	—	1100	642		227, 228
107a	—	550	502	EFISH	229, 230
107b	—	280	475	(CHCl_3 ; $\lambda = 1907$ nm)	229, 230
108a	45.8	—	319.6	β : calculation FF/AM1 in the static limit;	231, 232
108b	19.3	—	306.2		231, 232
109	—	1100	490	λ_{max} : calculation ZINDO/S EFISH (DMF; $\lambda = 1579$ nm)	233
110a	94	—	—	CPDFT/VWN/TZVP-FIP,	234
110b	111	—	—	calculation in the static limit	234
111	400	—	481	EFISH (CHCl_3 ; $\lambda = 1907$ nm)	235
112	32	—	458	HRS (CHCl_3 ; $\lambda = 1500$ nm)	236
113a	81.6	—	538	calculation by the	237
113b	56.5	—	553	CNDOVSB code ($\lambda = 1907$ nm)	237

^a In 10^{-30} esu; ^b in 10^{-48} esu.

achieving a desired level of the thermal stability and optical transparency while keeping sufficiently high values of β .

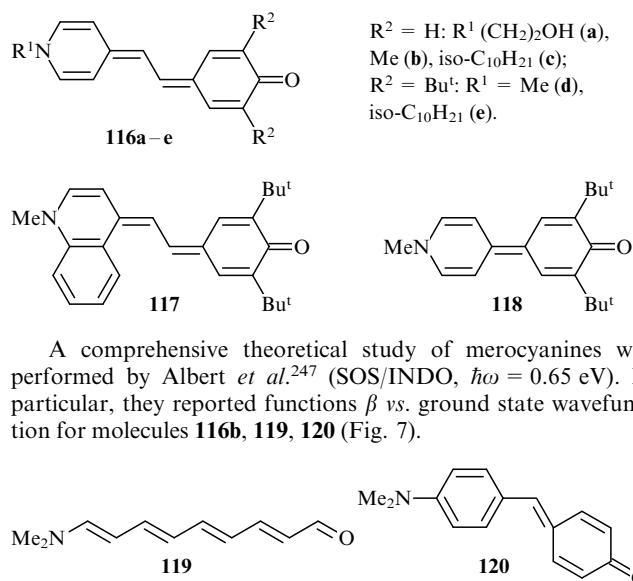
3. Zwitter-ionic molecules

One of the approaches to the design of NLO active molecules implies the use of aromatic D/A groups either directly attached to each other or linked through a short π -bridge.²³⁸ Among this class of compounds, merocyanine dyes are studied most intensely. The ground state of merocyanines can be represented as a superposition of the non-polar quinonoid form (e.g., **114**) and the zwitter-ionic form (e.g., **115**) that makes a significant contribution.



Merocyanines exhibit negative solvatochromism and are exceptionally sensitive to the nature of the solvent.

The first study of the NLO properties of merocyanine was accomplished by Levine *et al.*²³⁹ The absorption maximum was observed at λ_{max} of 605 nm and 440 nm in pyridine and water, respectively. According to the EFISH measurements in pyridine and methanol (which is close to water in terms of polarity), β is negative in both solvents but its absolute value is larger in methanol (-51×10^{-30} esu vs. -34×10^{-30} esu). Similar results were obtained for dyes **116**–**118**; their experimentally measured spectral characteristics are compiled in Tables 18 and 19.



A comprehensive theoretical study of merocyanines was performed by Albert *et al.*²⁴⁷ (SOS/INDO, $\hbar\omega = 0.65$ eV). In particular, they reported functions β vs. ground state wavefunction for molecules **116b**, **119**, **120** (Fig. 7).

Molecule **119** contains no aromatic groups; both the neutral and zwitter-ionic forms of **120** are stabilised by one aromatic ring, whereas in the zwitter-ionic form of **116b**, both six-membered rings are aromatic. The curves obtained have generally the same shape as function β (BLA) depicted in Fig. 3. In the case of molecule **116b**, this dependence differs drastically from those for **120** and **119** because of the aromatic stabilisation of the zwitter-ionic form. This form makes a dominant contribution to the ground state of the molecule already in weakly polar solvents, and an increase in the solvent polarity gives rise to an increase in $|\beta|$.

Table 18. The values of $\lambda_{\max}$ (nm) for merocyanines **116**.^{240–244}

Solvent	116a	116b	116c	116d	116e
Dioxane	—	614	619	626	626
CHCl ₃	—	620	620	633	634
Pyridine	—	605	600	630	632
Acetone	586	585	599	619	620
DMF	584	582	—	—	—
DMSO	—	572	579	617	618
MeCN	571	571	—	—	—
Ethanol	—	514	521	616	617
Formamide	—	494	502	578	581
Methanol	488	483	491	582	601
Water	448	442	447	527	526

Table 19. Experimental values of $\mu\beta$ (10^{−48} esu) for merocyanines **116d**, **117** and **118** from EFISH measurements at 1907 nm.^{245, 246}

Solvent	116d	117	118
Dioxane	—	−45	—
THF	−300	—	—
CHCl ₃	−325	−275	−325 (524)
CH ₂ Cl ₂	−425	—	—
Acetone	−600	−460	−600 (512)
DMF	−525	—	—
DMSO	−1000	−970	—
MeCN	−700	—	−700 (503)
Ethanol	−110	—	—
Methanol	−900	−1000	−900 (482)

Note. The values of $\lambda_{\max}$ (nm) are given in parentheses.

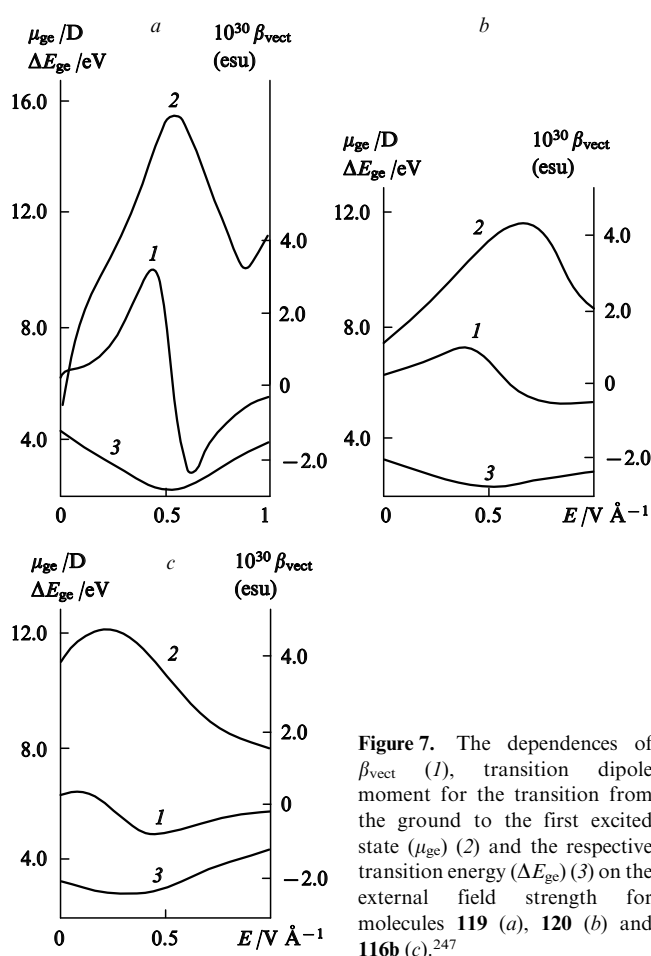
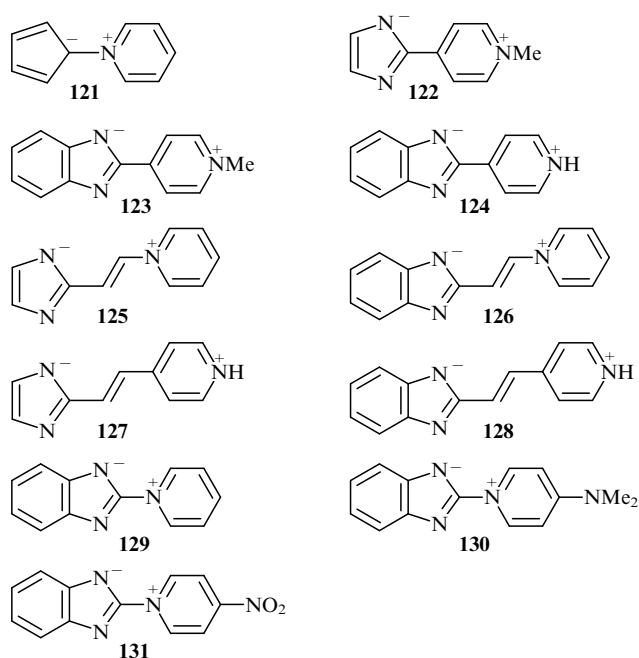
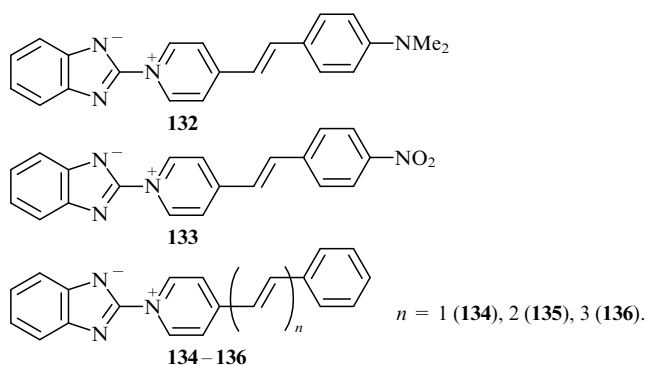


Figure 7. The dependences of β_{vect} (1), transition dipole moment for the transition from the ground to the first excited state (μ_{ge}) (2) and the respective transition energy (ΔE_{ge}) (3) on the external field strength for molecules **119** (a), **120** (b) and **116b** (c).²⁴⁷

The spectral properties of heterocyclic zwitter-ionic molecules **121–129** were the subject of both theoretical (CNDOVSB, $\hbar\omega = 0.95$ and 0 eV; SOS/INDO/S, $\hbar\omega = 0.65$ and 0 eV; CPHF/6-31G) and experimental investigations.^{248–250}





There is qualitative agreement between the results obtained by different methods. According to calculations at the CPHF/6-31G level presented in Table 20, the NLO activities of molecules **121–129** are 3–5 times higher than those of the well-known NLO molecules **1** and **2**. This difference was explained by a larger change in the dipole moment ($\Delta\mu$) upon the transition into the excited state. And this effect is achieved for relatively small molecules, whereas an increase in $\Delta\mu$ for normal D– π –A systems can only be achieved by an elongation of a π -conjugated chain.

Table 20. Spectral properties and dipole moments of heterocyclic zwitterionic molecules in the ground (μ_g) and excited (μ_e) states.

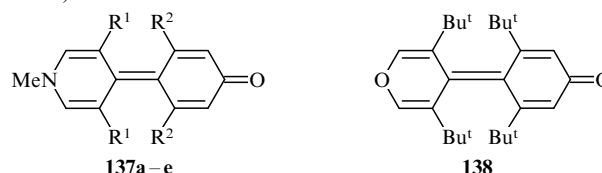
Mole- cule	$10^{30} \beta_0$ (esu)	Mole- cule	$10^{30} \beta_0$ (esu)	$\lambda_{\max}$ /nm	μ_g	μ_e
121	–55.8	129	–33	281	10.3	–5.9
122	–32.6	130	–16	252	14.8	0.1
123	–93.9	131	–132	358	3.5	–15.9
124	–67.5	132	–25	307	17.5	9.1
125	–161.5	133	–100	316	5.9	–14.0
126	–244.7	134	–46	302	13.4	–2.7
127	–9.3	135	28	310	14.3	0.8
128	–78.5	136	11	316	14.9	5.0

Abe *et al.*²⁵⁰ carried out an experimental (measurements of HRS) and theoretical investigation into the behaviour of molecule **124** in solvents of different polarities. The experimental measurements indicated that the hyperpolarisability slightly decreases in more polar solvents. The theoretical values were calculated using the CPHF/6-31G method and the solvent effects were taken into account within the Onsager model by varying the dielectric permittivity (ϵ) from 1 to 90. It was found that the hyperpolarisability decreases from the maximum value of $|\beta| = 33 \times 10^{30}$ esu at $\epsilon = 2$ to nearly zero with an increase in ϵ up to 90. It is of note that the opposite results were obtained for merocyanines, as discussed above. Probably, this difference is due to the fact that the isolated molecule **124** in the ground state falls into the region close to the minimum of $\beta(\epsilon)$ (see Fig. 7), *i.e.*, the contribution of the zwitter-ionic form is significantly larger than that for merocyanines and thus $|\beta|$ decreases with an increase in the solvent polarity.

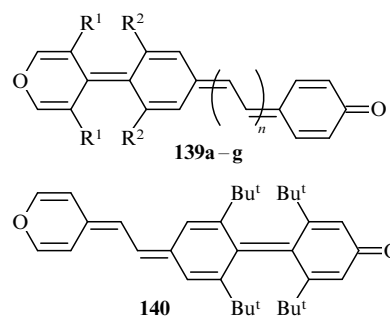
Abe *et al.*²⁵¹ analysed (within the CPHF/6-31G approximation) the spectral properties of molecules **130–136** taking molecule **129** as a reference. An extended conjugated chain was introduced from the side of an acceptor group rather than between the D/A substituents. In addition, some molecules with non-aromatic D/A groups were considered (see Table 20).²⁵¹ Upon introduction of additional π -substituents into the pyridinium fragment, the hyperpolarisability first increases but then starts to decrease after a certain threshold length of the conjugation chain (*cf.* molecules **129** and **134–136**). This phenomenon was explained by competing effects of $\Delta\mu$ and $\lambda_{\max} \sim 1/E_{ge}$. The value of $\Delta\mu$ remains virtually constant on going from **129** to **134**, whereas the transition energy E_{ge} decreases, which results in an

increase in β . Upon further elongation of the π -chain, E_{ge} changes insignificantly, whereas $\Delta\mu$ decreases resulting in a respective decrease in β . Upon introduction of an additional donor group, β decreases (molecules **130** and **132**), since both $\Delta\mu$ and $\lambda_{\max}$ decrease. In contrast, the introduction of an acceptor group (molecules **131** and **133**) leads to the opposite effect due to an increase in $\Delta\mu$ and $\lambda_{\max}$.

Interesting results were reported by Albert *et al.*^{252, 253} for a series of merocyanine dyes and their analogues (molecules **137–140**).



$R^1 = R^2 = H$ (a); $R^1 = H$, $R^2 = Me$ (b);
 $R^1 = R^2 = Me$ (c); $R^1 = Me$, $R^2 = Bu^t$ (d);
 $R^1 = R^2 = Bu^t$ (e).



Using the Hückel method within the two-level model [see Eqn (17)], they demonstrated that an increase in the torsion angle θ at the central double bond from 0° to 90° gives rise to an increase in the difference between the dipole moments of the molecule in the ground and excited states as well as in the transition dipole moment and to a decrease in the transition energy ($E_{ge} = 0$ at $\theta = 90^\circ$). This combination of factors should lead to the existence of a maximum value of β at $\theta = 70–89^\circ$. Figure 8 compares the function $\beta(\theta)$ for unsubstituted molecule **137a** with freely variable θ with the hyperpolarisabilities of molecules **137a–e** in which the respective torsion angles are determined by steric repulsion of substituents. Both the dependences have similar behaviour. The maximum value of β is in the range of $70–80^\circ$ and significantly exceeds that for the planar structure.

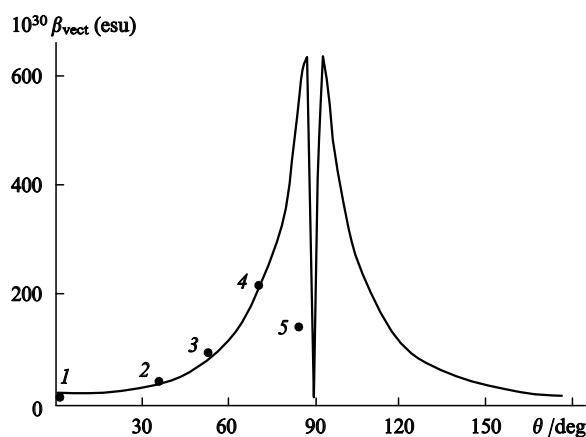
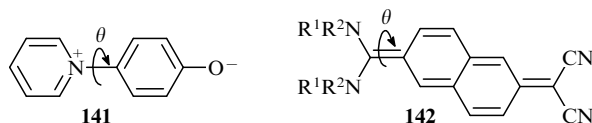


Figure 8. Hyperpolarisability of molecule **137a** (solid line) (SOS/INDO, $\hbar\omega = 0.1$ eV, AM1 optimisation) as a function of an angle between the six-membered rings (θ) and the hyperpolarisabilities of molecules **137a–e** (small circles marked as 1–5, respectively).

Calculations for molecules **141** and **142** with the FF/AM1 method yielded similar results.^{254, 255} Here, the maximum value of β is reached at θ of 60–80°.

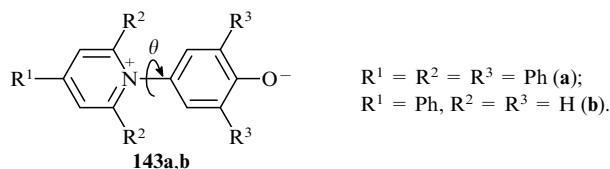


Albert *et al.*²⁵³ also analysed the effects of the elongation of a π -conjugated chain (*cf.* molecules **139** and **140**) on β . The chain fragments were introduced in such a way as to retain the steric effects of substituent resulting in the non-planar structure. Selected results are shown in Table 21. Variation of the torsion angle in molecule **139** by introducing various substituents gives rise to the same type dependence as that for molecule **137** discussed above. It is worth mentioning that the molecule **139e** with the conjugation chain elongated from the side of the acceptor group is characterised by higher β as compared to molecule **140** (the elongation from the donor side), which is probably due to the more efficient stabilisation of the zwitter-ionic (benzenoid) form. A decrease in β with an elongation of the conjugation chain in the series of molecules **139e–g** was explained in a similar way. Unfortunately, trends in β upon chain elongation in **140** were not considered by the authors;²⁵³ however, based on the results discussed above, it might be assumed that β should decrease with an increase in the length of the conjugation chain owing to smaller contribution of the zwitter-ionic form to the ground state of the molecule.

Table 21. Spectral characteristics of molecules **138–140**.²⁵³

Molecule	R ¹	R ²	n	$\lambda_{\max}$ /nm	$10^{30} \beta$ (esu)
138	—	—	—	1206.8	352.8
139a	H	H	1	535.6	34.0
139b	Me	H	1	579.2	1.7
139c	Me	Me	1	643.4	189.8
139d	Bu ^t	Me	1	805.3	391.7
139e	Bu ^t	Bu ^t	1	1204.5	2398.6
139f	Bu ^t	Bu ^t	2	1093.4	1749.0
139g	Bu ^t	Bu ^t	3	971.0	754.5
140	—	—	—	991.6	1119.4

The effects of deviation from planarity for quinonoid molecules were also considered by other research groups.^{256, 257} Bartkowiak *et al.*²⁵⁶ analysed the hyperpolarisabilities of molecules **143a,b** as a function of their conformations using the SOS and FF methods within the AM1 approximation and found that the maximum β is reached at angles θ between the six-membered rings of 60° and 75° for **143a** and **143b**, respectively



According to the results of X-ray crystallographic studies,^{258–260} the angle θ lies in the range of 55–70° for molecules similar to **143** containing phenyl substituents in the *ortho*-positions of the pyridine ring ($R^2 = \text{Ph}$), which is close to the optimum value for the manifestation of the NLO properties. Gangopadhyay *et al.*²⁵⁷ selected 7- R^1 -7'- R^2 -8,8'-dicyanoquinodimethane as a reference molecule.

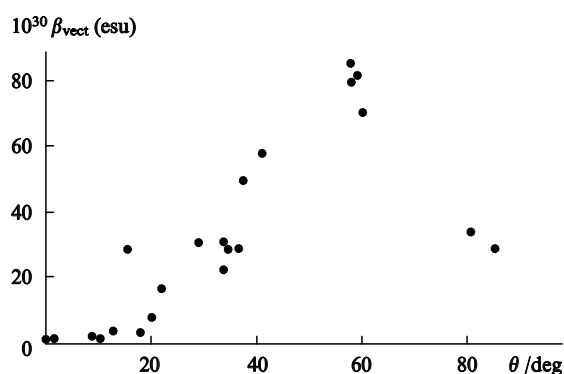
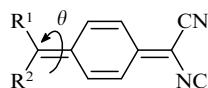


Figure 9. A graphical representation of hyperpolarisabilities (FF/AM1) of various 7- R^1 -7'- R^2 -8,8'-dicyanoquinodimethane derivatives.

They constructed 22 molecules with the torsion angle varying from 0° to 86° by introducing donor groups with different steric volumes (Fig. 9). Assuming that the strengths of donor groups differed insignificantly, it was concluded that the maximum of β reached at $\theta \sim 60^\circ$ suggests the preferred non-planar conformation.

It is of note that in the majority of ordinary D- π -A molecules, the deviation from planarity results in a decrease in the hyperpolarisability due to a break of the π -conjugation chain.^{261–264}

Ravi and Radhakrishnan²⁶⁵ proposed to describe the balance between the quinonoid and zwitter-ionic forms of a molecule with a criterion QBC (Quinonoid-Benzenoid Character) defined as

$$\text{QBC} = 1 - 6 \sum_{i=1}^3 |1.400 - r_i|,$$

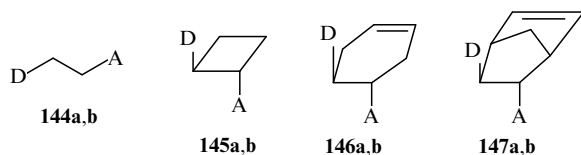
where 1.400 Å is taken as the standard value of the bond length in benzene; r_1, r_2, r_3 are the bond lengths in the six-membered quinonoid ring. The value of QBC can be varied by adjusting the electric field strength. 7,7'-Diamino-8,8'-dicyanoquinodimethane was used as a reference molecule. The calculations were carried out using the SOS/AM1/CISD method. Table 22 summarises the values of hyperpolarisabilities, energies of transitions to the excited states and QBC. It is seen that the absorption maximum appears in the visible region at the QBC corresponding to the maximum value of β ; upon further increase in QBC, β decreases only to 50% of its maximum value, whereas the absorption band shifts to the UV range. It has to be pointed out that the actual values of QBC for quinonoid molecules investigated by X-ray crystallography^{266–269} lie in the range 0.75–0.82, which corresponds to the range of optical transparency.

Table 22. The values of the QBC parameter, hyperpolarisability (10^{-30} esu) and energies of transitions into the first and second excited states for 7,7'-diamino-8,8'-dicyanoquinodimethane.

QBC	β_{vect}	Transition energy /eV	QBC	β_{vect}	Transition energy /eV
0.088	−9.7	2.83 (0.006)	0.358	−75.4	2.65 (0.390)
		3.42 (1.130)			3.72 (0.471)
0.118	−18.5	2.80 (0.044)	0.436	−86.5	2.67 (0.457)
		3.39 (1.065)			3.75 (0.032)
0.190	−35.4	2.77 (0.195)	0.592	−94.0	2.87 (0.583)
		3.44 (0.841)			3.71 (0.050)
0.232	−46.2	2.71 (0.264)	0.730	−67.4	3.17 (0.571)
		3.50 (0.718)			3.75 (0.000)
0.286	−58.6	2.66 (0.326)	0.790	−47.7	3.37 (0.479)
		3.59 (0.599)			3.78 (0.000)

Note. Transition oscillator strengths are given in parentheses.

Rao and Bhanuprakash studied²⁷⁰ molecules **144**–**147** with D/A groups linked by a σ -bridge, $\text{CH}_2\text{--CH}_2$ using the FF/AM1 method.



D = $p\text{-NH}_2\text{C}_6\text{H}_4$, A = $p\text{-NO}_2\text{C}_6\text{H}_4$ (**a**);

D = $p\text{-C}_6\text{H}_4\text{O}^-$, A = $\text{C}_5\text{H}_5\text{N}^+$ (**b**).

The following values of hyperpolarisability were found

Molecule	144a	145a	146a	147a	144b	145b	146b	147b
$10^{30}\beta$	6.3	6.3	6.1	4.2	−625.0	−437.3	−683.5	−301.8
(esu)								

Molecules **144a**–**147a** contain traditional D/A substituents, whereas molecules **144b**–**147b** are of the zwitter-ionic character. The calculated values of β indicate substantial weakening of interactions between the NH_2 and NO_2 groups in molecules **144a**–**147a** since σ -fragments break the conjugation. In contrast, in the case of zwitter-ionic molecules **144b**–**147b**, the σ -bridge stabilises the zwitter-ionic form, which gives rise to an increase in β , i.e., the introduction of a σ -bridge is formally equivalent to a rotation of the phenyl rings (see Fig. 9).

Changes in the hyperpolarisability due to the replacement of a benzene ring by a heterocycle were considered.^{271–273} In contrast to non-quinonoid D– π –A molecules, whose hyperpolarisabilities increase owing to the lower energy barrier to the electron delocalisation in heterocycles with respect to benzene, the opposite trend is manifested by quinonoid molecules. This can be explained in the same way: the higher the energy barrier to the electron delocalisation, the higher the stability of the zwitter-ionic form.

IV. Possible ways to improve thermal stability and optical transparency of NLO materials

The possibility of the use of organic compounds for the second harmonic generation is determined by a number of parameters and, as has been mentioned above, it often happens that an enhancement of one parameter deteriorates others. Therefore, the molecular design of NLO materials has to include simultaneous optimisation of several key molecular characteristics. For instance, most tables in the previous section listed data on the optical transparency of molecules (λ_{max}) in addition to the values of their hyperpolarisabilities. The results discussed above indicate that the function $\beta(\lambda_{\text{max}})$ increases with an increase in the strength of D/A substituents or the length of the π -system or with the introduction of less aromatic fragments in place of more aromatic ones. Several studies were related to investigations within different classes of compounds, such as imidazoles,²⁷⁴ tolans,²⁷⁵ pyrazoles,²⁷⁶ thiazoles,²⁰⁷ coumarins.²⁷⁷ The dependences

$$\beta = k \log \lambda_{\text{max}} + a$$

obtained are nearly linear with the coefficient k varying from 5 to 8. A number of approaches to the search for optimal combinations of the desired properties have been proposed.

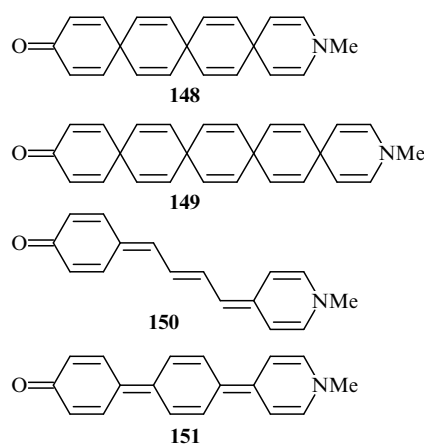
1. Linear molecules with one-dimensional hyperpolarisability

Polyene systems are among the most efficient NLO-active π -systems. Unfortunately, they are characterised by rather low thermal and chemical stabilities (moreover, these characteristics are getting worse with an increase in the length of the π -system²⁷⁸) and absorption maxima in the visible range. Several attempts to improve these characteristics have been undertaken. Thus it was suggested²⁷⁹ to use spiro-conjugated chains (molecules **148** and **149**). Their comparison with polyene and quinonoid polyphenylene-type molecules **150** and **151** showed (Table 23) that the

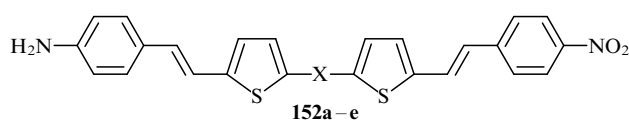
Table 23. Calculated spectral characteristics (SOS/INDO/CI) of spiro-conjugated, polyene and polyphenylene D/A molecules with geometries optimised using the AM1 method and experimental optical characteristics of molecules with σ -fragments (HRS measurements in CHCl_3 at $\lambda = 1064$ nm extrapolated to the zero frequency).

Molecule	$10^{30}\beta_0$ (esu)	λ_{max} /nm	Molecule	$10^{30}\beta_0$ (esu)	λ_{max} /nm
148	1.7	398	152a	69.2	405
149	2.9	430	152b	69.8	395
150	17.6	594	152c	86.4	407
151	16.6	668	152d	80.0	406
			152e	174.4	500

hyperpolarisabilities of spiro-systems are lower by an order of magnitude while the range of their optical transparency is significantly wider.



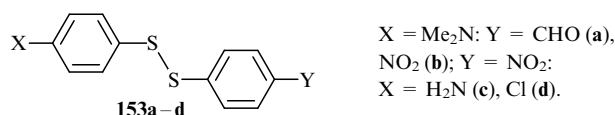
Jerome and co-workers^{280,281} proposed to brake the conjugation chains of conjugated molecules by introducing σ -fragments in order to broaden the range of their optical transparency (see Table 23). The values of hyperpolarisability were both calculated and measured, and qualitative agreement of theoretical and experimental results was observed.



X = CMe_2 (**a**), SiMe_2 (**b**), $(\text{SiMe}_2)_2$ (**c**), S (**d**), $\text{CH}=\text{CH}$ (**e**).

It should be taken into account that the experimental NLO efficiency of molecule **152e** can be strongly overestimated since its absorption maximum is very close to the second harmonic. According to the results obtained, the introduction of a central σ -fragment gives rise to a significant hypsochromic shift of the absorption band but the hyperpolarisability decreases severalfold. The spectral parameters of molecules **152a,b** are close to each other, whereas molecule **152d** manifests a slightly higher hyperpolarisability and its absorption band is shifted to the visible range, which suggests weak involvement of the sulfur lone-pair electrons into the delocalised π -system. It is noteworthy that the value of β for molecule **152c** is larger than those for molecules **152a,b,d**. This can be explained by the involvement of both σ - and $\sigma-\pi$ delocalisation mechanisms in polysilanes.^{282–284}

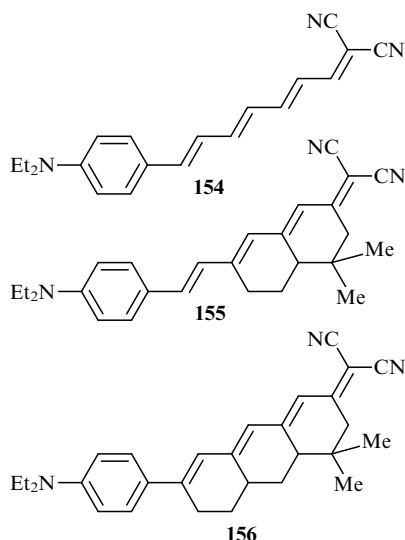
Sudharsanam *et al.*²⁸⁵ utilised the S–S fragment for the break of conjugation chains in a series of molecules **153**. The hyperpolarisabilities of these molecules were measured by HRS method at $\lambda = 1064$ nm in CHCl_3 using a value of 17×10^{-30} esu for **1** as a reference.



Molecule	153a	153b	153c	153d
$10^{30} \beta$ (esu)	36	102	98	44
$\lambda_{\max}$ /nm	304	319	321	317

The data obtained show that the introduction of stronger D/A groups affects β to a larger extent than $\lambda_{\max}$. The values of $\lambda_{\max}$ remain sufficiently low, so that the molecules remain optically transparent in the whole visible spectral range. The authors adopted value 55.4×10^{-30} esu as a reference for **2** for a comparative analysis of the hyperpolarisabilities, however, this value was determined under different conditions and is strongly underestimated. For instance, according to measurements performed under the same conditions,²⁸⁶ the value of β for **2** is almost 9 times larger than for **1**, *i.e.*, it would be more appropriate to use the value of $\sim 150 \times 10^{-30}$ esu for the sake of comparison. Thus the hyperpolarisability of **2** is ~ 1.5 times larger than that for its disulfide analogue, while molecule **2** is less optically transparent ($\lambda_{\max} = 427$ nm in CHCl₃).

The use of sterically stabilised polyenes **154–156** was suggested^{287–289} as a way to improve the thermal stabilities of D- π -A systems with polyene π -bridges.



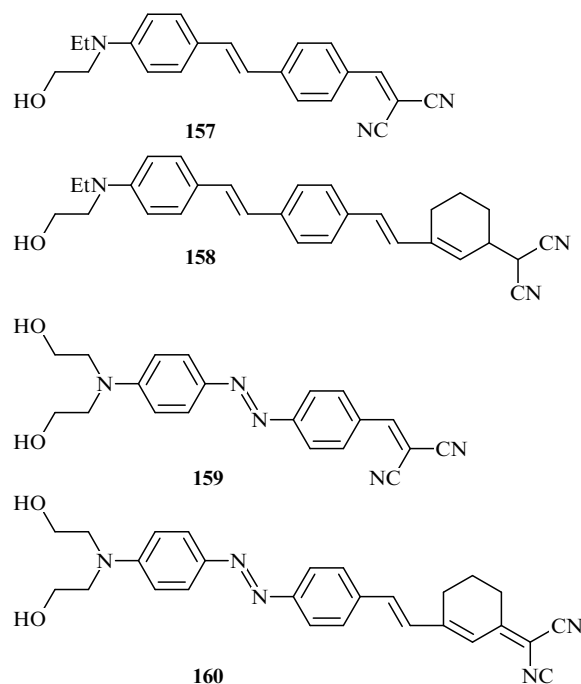
The absorption spectra were measured in 1,4-dioxane, the polarisabilities were determined using EFISH measurements in chloroform ($\lambda = 1907$ nm); the decomposition temperatures (T_d) of molecules **154–156** were 170, 317 and 343 °C, respectively, as estimated by differential scanning calorimetry (DSC).

The following values of spectral parameters were obtained for the sterically stabilised π -conjugated molecules:

Molecule	154	155	156
$10^{30} \beta$ (esu)	453	378	—
$\lambda_{\max}$ /nm	563	538	518

The above data clearly demonstrate that the introduction of cyclohexene fragments simultaneously brings about some increase in the optical transparency and a significant increase in the thermal stability. As expected, this occurs at the cost of a decrease in β , since $\lambda_{\max}$ also decreases.

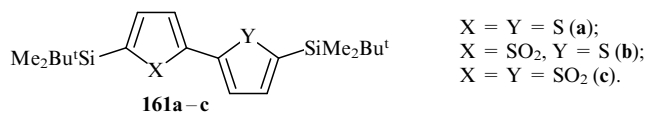
Luo, Hua *et al.*^{290, 291} investigated sterically stabilised π -conjugated molecules **157–160**. Their absorption spectra were measured in chloroform and the hyperpolarisabilities were determined using HRS measurements in methanol ($\lambda = 1064$ nm).



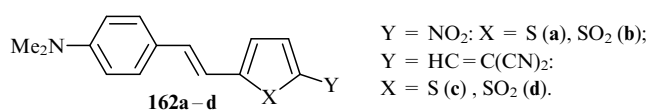
Molecule	157	158	159	160
$10^{30} \beta$ (esu)	1393	1564	1086	2890
$\lambda_{\max}$ /nm	493	474	508	490

Despite the molecules stabilised with a cyclohexene fragment contain longer π -chains, they are characterised by slightly shorter absorption wavelengths and higher β .

It was shown^{292, 293} that the thermal stabilities of molecules **161** increase upon transition from thiophenes to their analogues containing thiophene 1,1-dioxide moiety ($\lambda_{\max}$ were determined for CHCl₃ solutions).²⁹³

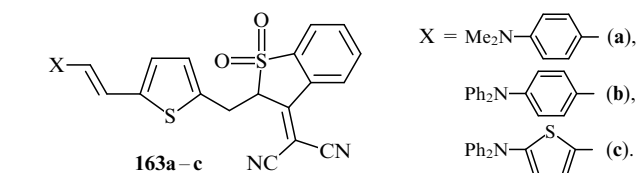


Molecule	161a	161b	161c
$\lambda_{\max}$ /nm	326	390	406
M.p. /°C	118	137	226



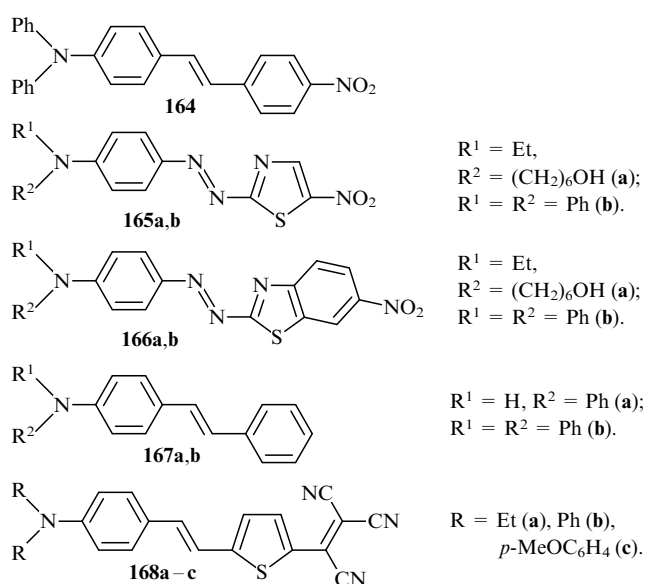
Molecule	162a	162b	162c	162d
$10^{30} \beta$ (esu)	61.4	116.1	84.7	175.7

This also leads to an increase in the hyperpolarisability, as evidenced by the theoretical calculations (FF/AM1 in the static limit)²⁹² for molecules **162**, due to the loss of aromaticity in the five-membered heterocycles. The latter factor, on the other hand, narrows the optical transparency range of these molecules. Likely, the acceptor properties of the SO₂ group are also partly responsible for the increase in β . This suggestion is supported by rather high hyperpolarisabilities of molecules **163** (measurements in CH₂Cl₂ at $\lambda = 1907$ nm extrapolated to the zero frequency).²⁹⁴



Molecule	163a	163b	163c
$10^{30} \beta$ (esu)	3070	2320	4880
$\lambda_{\max}$ /nm	704	660	738

The use of amino or alkylamino groups as donors is preferable for achieving high values of β , however, these compounds are less thermally stable than, for instance, their alkoxy analogues.^{295, 296} With this regard, Moylan *et al.*^{297–299} and other researchers (see Refs 300–302) proposed to use a diarylamino group and showed that its introduction significantly increases thermal stability without narrowing of the optical transparency range (Table 24).



The use of tetra- or pentafluorophenyl groups (molecules **169–171**) as acceptors instead of π -acceptor groups results in broadening of the optical transparency range and an increase in the thermal stability^{303–305} (Table 25, molecules **169a,c,e**, **170a** and **169b,d,f**, **170b**). The data from Table 25 also indicate that it is difficult to unambiguously predict the trend in β upon transition

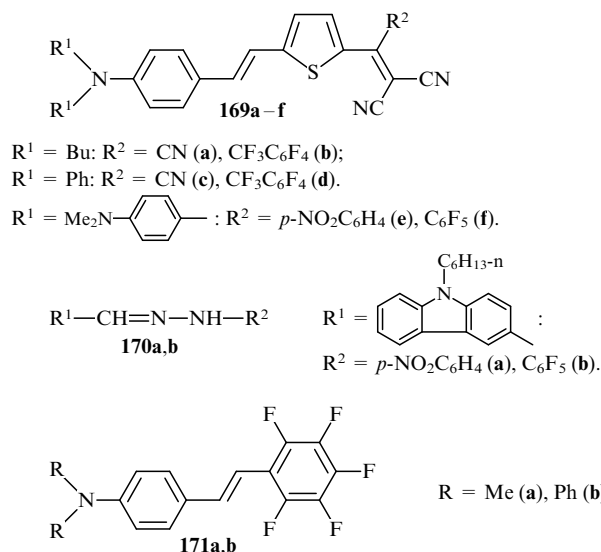


Table 24. Optical and thermal characteristics of D/A-substituted stilbenes and their analogues.

Mole- cule	$10^{30} \beta_0$ (esu)	$\lambda_{\max}$ /nm	T_d /°C	Comments	Ref.
2	42.1	438	290	measurement of optical characteristics in CHCl_3 ; β from EFISH measurements ($\lambda = 1907$ nm) extrapolated to the zero frequency using the two-level model; T_d from DSC measurements	297–299
164	37.3	436	358	the same	297–299
165a	52.2	582	213	"	297–299
165b	68.2	582	295	"	297–299
166a	60.1	548	259	"	297–299
166b	71.8	550	356	"	297–299
167a	17.7	417	288	measurement of $\lambda_{\max}$ in hexane; β calculated by the FF/AM1 method in the static limit; T_d from TGA measurements	300
167b	20.0	411	313	the same	300
168a	6700 ^a	640	240	measurement of optical characteristics in dioxane; $\mu\beta$ (10^{-48} esu) from EFISH measurements ($\lambda = 1907$ nm); T_d from TGA measurements	301
168b	3510 ^a	601	315	the same	301
168c	—	683	295	$\lambda_{\max}$ measured in CHCl_3 ; T_d from TGA measurements	302

^a The value of $\mu\beta$ is given.

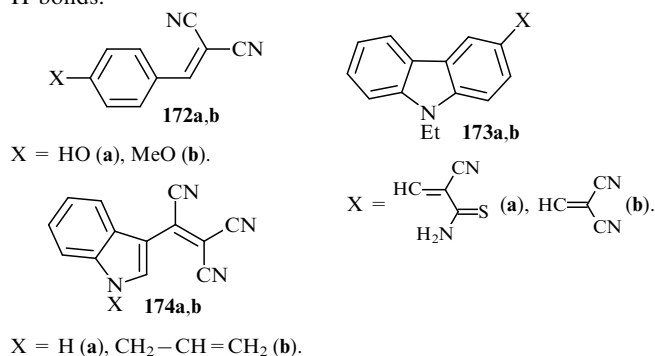
from the nitrophenyl to the pentafluorophenyl acceptors (molecules **169e,f** and **170a,b**). The result depends on the structure of the π -system and the donor type, in addition to the mere strength of the acceptor group to be replaced. It is also evident that the use of NPh_2 groups instead of NAlk_2 leads to a significant increase in the thermal stability (molecules **169a–d**, **171a,b**).

Table 25. Decomposition temperatures (according to DSC measurements), absorption band maxima and hyperpolarisabilities of molecules **169–171**.

Mole- cule	$10^{30} \beta_0$ (esu)	$\lambda_{\max}$ /nm	T_d /°C	Comments
169a	—	640	240	measurement of $\lambda_{\max}$ in dioxane
169b	—	591	310	the same
169c	—	601	315	"
169d	—	553	340	"
169e	95	431	—	β_0 : HRS measurement in methanol at $\lambda = 1064$ nm; $\lambda_{\max}$ measured in methanol
169f	84	344	—	the same
170a	46	423	—	"
170b	62	331	—	"
171a	100 ^a	341	177	$10^{48} \mu\beta$ (esu), EFISH measurements in CHCl_3 at $\lambda = 1907$ nm; $\lambda_{\max}$ measured in CH_2Cl_2
171b	110 ^a	379	> 300	the same

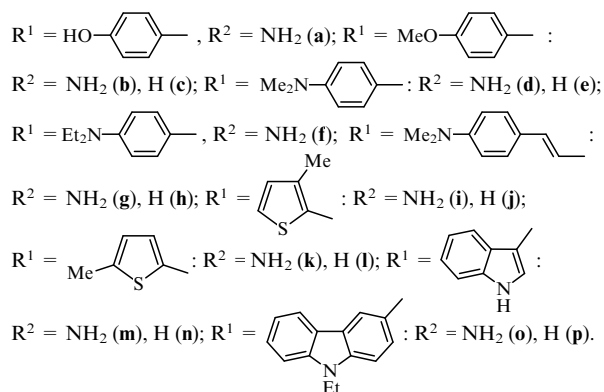
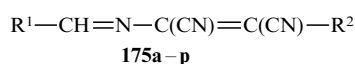
^a The value of $\mu\beta$ is given.

An original approach to increase thermal stability of potential NLO molecules was suggested by Nesterov *et al.*^{306, 307} They used $D-\pi-A-D'$ molecules in which the amino groups liable to the formation of H-bonds were introduced as auxiliary donors D' . Although the melting point of a compound does not correlate directly with crystal lattice energy, nor with the presence of H-bonds in the structure, the literature data (see, for instance, Refs 308–311) indicate that crystals of similar molecules differing from each other only by the presence/absence of H-bonding sites possess higher melting points provided that the crystal structure involves H-bonds. In particular, crystals built up of H-bonded molecules **172a–174a** melt at significantly higher temperatures than crystals built up of molecules **172b–174b**, which do not form H-bonds.



Molecule	172a	172b	173a	173b	174a	174b
M.p./°C	188	114	216	157	275	145

Table 26 summarises the results of theoretical calculations of dipole moments and hyperpolarisabilities (FF/AM1 in the static limit) and experimental characterisation (measurements of λ_{max} in THF)^{306, 307} for imines **175** and their $D-\pi-A-H$ analogues.



It is evident that the substitution of the amino group for a hydrogen atom results in a decrease in the hyperpolarisability, this is also accompanied by a decrease in the dipole moment. The latter factor as well as the availability of active sites prone to H-bonding increase the probability of crystallisation of these compounds in a non-centrosymmetric space group. Indeed, five out of nine compounds studied crystallise in such groups.

2. Molecules with two- and three-dimensional hyperpolarisability

In the case of molecules possessing two- and three-dimensional hyperpolarisabilities, non-diagonal components of the tensor β becomes significant making an additional contribution to the value of β .^{312, 313} In particular, for 1,3-dinitro-4,6-diaminobenzene, the diagonal component β_{zzz} is an order of magnitude

Table 26. Melting points, spectral characteristics and crystallographic data for imines **175** and their $D-\pi-A-H$ analogues.

Molecule	μ /D	$10^{31} \beta_0$ /C m ³ V ⁻²	λ_{max} /nm	M.p. /°C	Space group
175					
a	4.5	54	375	209–210	<i>Pca2</i> ₁
b	5.1	64	374	220–221	<i>Pna2</i> ₁
c	6.0	81	—	—	—
d	6.2	87	414	222–223	<i>P2</i> ₁ / <i>c</i>
e	6.5	109	—	—	—
f	7.4	140	430	211–212	<i>C2</i> / <i>c</i>
g	6.8	189	442	210–211	<i>Pca2</i> ₁
h	8.1	242	—	—	—
i	5.3	34	384	207–208	<i>P2</i> ₁ / <i>c</i>
j	5.7	46	—	—	—
k	5.8	41	387	219–220	<i>P2</i> ₁
l	6.0	55	—	—	—
m	6.8	71	379	217–218	<i>Pna2</i> ₁
n	8.0	83	—	—	—
o	7.3	99	395	213–214	<i>P2</i> ₁ / <i>c</i>
p	8.2	128	—	—	—

smaller than β_{zzz} .³¹⁴ The so-called V- or X-shaped molecules **176–182** were a subject of a series of studies.^{315–319} By comparing characteristics of molecules **176** and **179** with those of molecules **177**, **178** and **180** one may conclude that the attachment of a second donor group, at least, doubles β and enhances the thermal stability but somewhat narrows the range of the optical transparency (Table 27). In contrast, a comparison of characteristics of molecules **181** and **182** indicates that the introduction of a second acceptor group broadens the range of optical transparency in addition to increase in β and T_d .

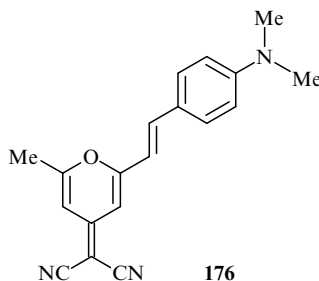
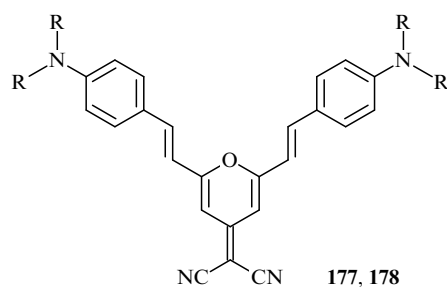


Table 27. Spectral characteristics and decomposition temperatures of molecules **176–182**.

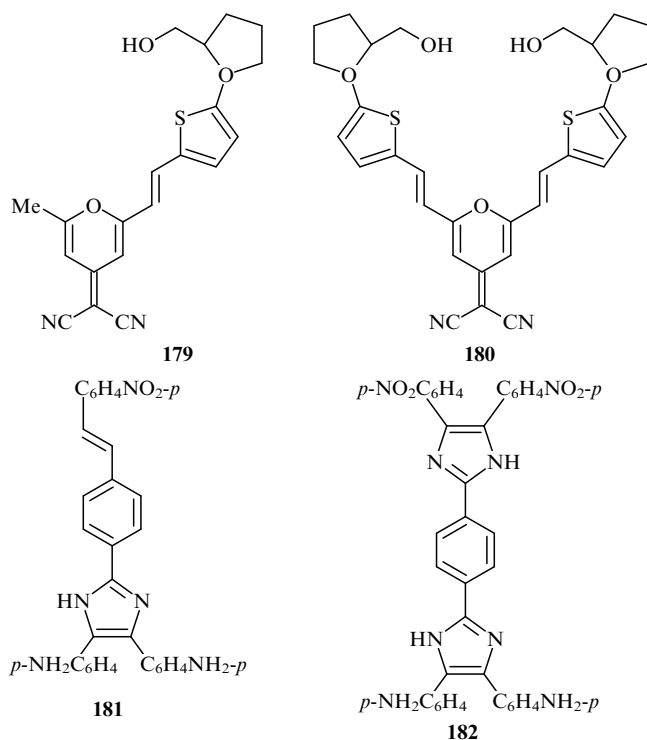
Molecule	$10^{30} \beta_0$ (esu)	λ_{max} /nm	T_d /°C
176	88.8 ± 6.6	468	332
177	175 ± 3	486	404
178	197 ± 2	496	348
179	1043^a	541	301
180	5920^a	564	315
181	34.8	401	335
182	50.9	384	377

Note. The values of β and $\mu\beta$ for molecules **176–180** were measured using EFISH at $\lambda = 1907$ nm in chloroform, for molecules **181**, **182**, these values were calculated theoretically (FF/AM1 in the static limit), T_d were determined from DSC and TGA measurements for molecules **176–178** and **179–182**, respectively.

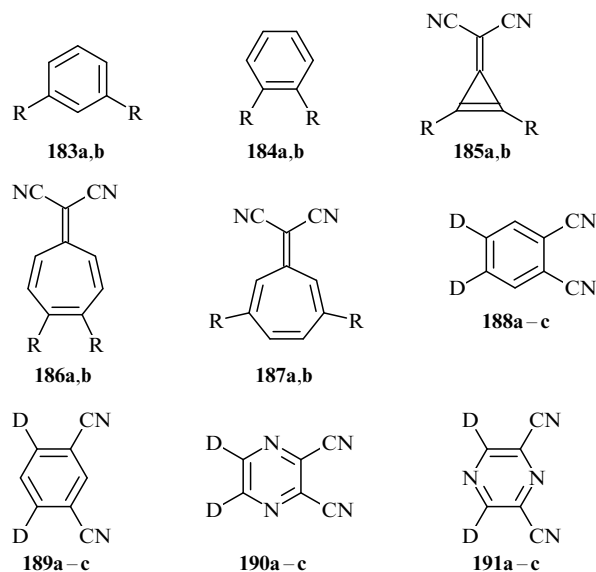
^a The value of $10^{48} \mu\beta$ (esu) is given.



R = Ph (**177**), Bu (**178**).



A detailed theoretical investigation into the trends in hyperpolarisability of X-shaped molecules **183**–**191** was performed by Yang and Champagne³²⁰ for a series of small π -conjugated systems.



R = NH₂ (a), OH (b); D = NH₂ (a), OMe (b), Br (c).

Table 28. Calculated hyperpolarisabilities (in 10^{-30} esu) of X-shaped molecules **183**–**191**.

Mole- cule	β_{xxz}	β_{yyz}	β_{zzz}	β_{tot}	φ /deg	Mole- cule	β
183a	310	42	35	386	121	188a	6.8
183b	218	−63	−38	−320	116	188b	3.4
184a	110	56	362	528	56	188c	3.0
184b	−99	−97	−307	−503	60	189a	3.5
185a	374	−19	−54	301	60	189b	1.9
185b	282	10	107	399	61	189c	1.8
186a	696	−152	2302	2846	27	190a	5.2
186b	566	5	2181	2752	24	190b	3.2
187a	1277	−76	−671	530	76	190c	1.9
187b	725	−25	579	1279	77	191a	2.1
						191b	1.2
						191c	1.6

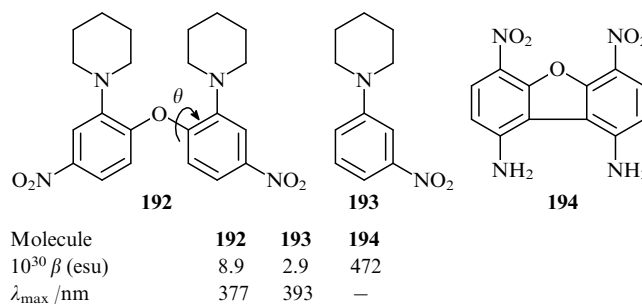
Note. The FF/MP2/6-31 + G*³²⁰ and FF/AM1³²¹ methods were used for molecules **183a**–**187b** and **188a**–**191c**, respectively.

The results of this work are compiled in Table 28. Provided that the coordinate system is selected so as the axis Y is perpendicular to the molecular plane, the components β_{xxz} , β_{yyz} and β_{zzz} make the dominant contributions to the total hyperpolarisability β_{tot} . The optimisation of the hyperpolarisability

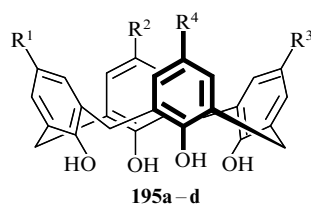
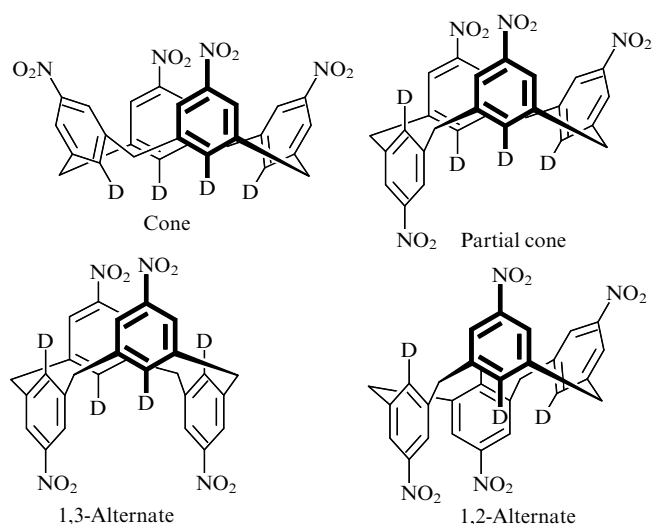
$$\beta_{tot} = \beta_{xxz} + \beta_{yyz} + \beta_{zzz}$$

for such molecules requires a consistent selection of D/A-substituents and the angle φ between the directions of the charge transfer. In particular, the absolute value of β increases on going from molecules **183** to **184** due to a change in φ . A comparison of characteristics of molecules **185b** and **187b** with those of **185a** and **187a**, respectively, indicates that an increase in the strength of a D group (*i.e.*, the use of the amino instead of the hydroxy group) gives rise to a decrease in β , whereas the reversed trend is observed for molecules **186a** and **186b**. It is also worth noting that the relative significance of contributions β_{xxz} and β_{zzz} changes on going from molecule **186** to **187**. A study of didonor/diacceptor-substituted six-membered rings³²¹ (see Table 28) gave similar results. Molecules with donor groups occupying adjacent positions possess higher values of β .

Sudharsanam *et al.*³²² considered molecules **192** and **193** (FF/AM1 in the static limit). Molecule **192** possesses a severalfold higher NLO activity and a broader range of optical transparency. However, it is non-planar. Meanwhile, β should prominently increase if $\theta \rightarrow 0$.³²³ Analysis of molecule **194** with the strictly planar structure revealed a rather high β (SOS/INDO/CIS, $\lambda = 1064$ nm).

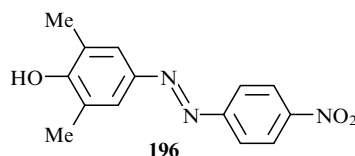


Calix[4]arenes, like V-shaped systems discussed above, also incorporate several D/A pairs in one molecule. These molecules were a subject of several investigations.^{324–326} They can adopt the following conformations:



195a–d

$R^1 = R^2 = R^3 = R^4 = p\text{-NO}_2\text{C}_6\text{H}_4\text{-N=N}$ (a); $R^1 = \text{H}$, $R^2 = R^3 = R^4 = p\text{-NO}_2\text{C}_6\text{H}_4\text{-N=N}$ (b); $R^1 = R^2 = \text{H}$, $R^3 = R^4 = p\text{-NO}_2\text{C}_6\text{H}_4\text{-N=N}$ (c); $R^1 = R^2 = R^3 = \text{H}$, $R^4 = p\text{-NO}_2\text{C}_6\text{H}_4\text{-N=N}$ (d).



196

Interestingly, the absorption band maximum remains constant for all the conformers,³²⁴ which implies that this parameter is weakly affected by the mutual orientation of the D/A-phenyl fragments. In contrast, the value of hyperpolarisability strongly depends on the conformation, which is evidenced by the experimental and theoretical data presented in Table 29.

According to the calculations, 1,2- and 1,3-alternates are characterised by values of β close to zero, which is in agreement with the zero hyperpolarisability experimentally found for the 1,3-conformer. This is due to the complete mutual cancellation of the NLO activity of different D/A-phenyl fragments. The ratio of activities cone/partial cone depends on the inclination angle of the phenyl rings. Brouyere *et al.*³²⁶ additionally compared the hyperpolarisability of NO_2/OH -substituted calix[4]arene in the cone conformation with those of *o,o'*-dimethyl-*p*-nitrophenol and its dimer built up of two parallel molecules. As can be judged from Table 29, additive schemes are applicable to the evaluation of β neither for the dimer nor for calix[4]arene (with a correction for the non-parallel arrangement of the rings), which clearly implies interaction between the π -systems. Further arguments in favour of the substantial influence of the intermolecular π - π interactions on the spectral properties were presented by other authors.^{327–329}

Similar conclusions were derived^{330,331} for NO_2/OH -substituted calix[4]arenes **195a–d** in the cone conformation.

Molecule	195a	195b	195c	195d	196
$10^{30} \beta$ (esu)	296.6	275.2	302.6	233.1	186.7
λ_{max} /nm	374	378	382	378	387

The experimental values (HRS, THF, $\lambda = 1064$ nm) for tetrahydroxycalix[4]arene successively substituted with *p*-nitrophenylazo groups (molecules **195**) were compared with that of the monomeric analogue **196**. The value of λ_{max} for calix[4]arenes is virtually independent of the number of acceptor groups and is slightly smaller than that of the monomer, whereas β is larger. The observed variations in β are probably due to different mutual orientations of the fragments in the calix[4]arene molecule, which is determined by the steric interaction of the substituents.

It is important that the absorption band is blue-shifted and β is increased on going from the monomer to calix[4]arenes (*i.e.*, tetramers). It should be noted that it is possible to achieve a significantly higher NLO activity by sequential coupling of monomers, however at the cost of narrowing of the optical transparency range.

Paracyclophane derivatives **199–201** represent yet another example of molecules possessing non-standard conjugated systems (to be compared with reference molecules **197** and **198**).^{332–334}

Table 29. Calculated and experimental values of β (10^{-30} esu) and λ (nm) for D/A-calix[4]arenes in different conformations.

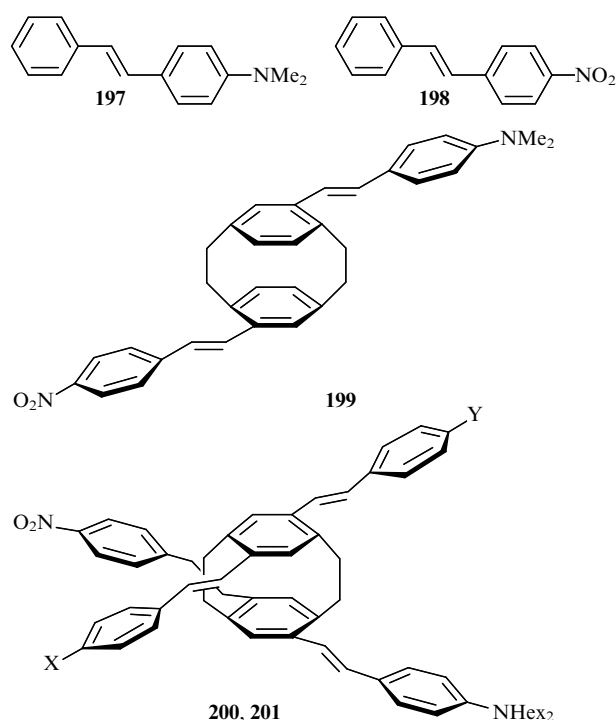
Conformation	Donor	β_{EFISH} (calculation)	β_{HRS} (calculation)	β_{EFISH} (experiment)	β_{HRS} (experiment)	λ_{max} (calculation)	λ_{max} (experiment)
Cone	OH	22.9	23.8	—	—	290	—
Partial cone	OH	12.5	12.8	—	—	290	—
1,2-Alternate	OH	6.3	7.1	—	—	290	—
1,3-Alternate	OH	0.1	0.3	—	—	290	—
Cone	OMe	22.1	24.4	30.0	27.0	290	291
Partial cone	OMe	11.8	13.8	27.0	—	290	291
1,2-Alternate	OMe	1.0	1.1	—	—	290	—
1,3-Alternate	OMe	0.8	0.8	0	0	290	291
Monomer ^a	OMe	12.5	13.1	12.0	—	301	302
Dimer ^a	OMe	18.3	18.3	—	—	284	—

Note. The calculated values of β were obtained³²⁶ using the SOS method within the INDO/CIS approximation;

$$\beta_{\text{EFISH}}(\text{calculation}) = \beta_{\text{zzz}} + \frac{1}{3}(\beta_{\text{zxx}} + \beta_{\text{zyy}} + \beta_{\text{xxz}} + \beta_{\text{yyz}} + \beta_{\text{xzx}} + \beta_{\text{yzy}}); \beta_{\text{HRS}}(\text{calculation}) = \sqrt{\frac{35}{6}} \langle \beta_{\text{HRS}}^2 \rangle, \text{ where } \langle \beta_{\text{HRS}}^2 \rangle = \langle \beta_{\text{zzz}}^2 \rangle + \langle \beta_{\text{xzz}}^2 \rangle.$$

see Eqns (8), (9); experimental measurements were performed in CHCl_3 at $\lambda = 1064$ nm.^{324,325}

^a Data for *o,o'*-dimethyl-*p*-nitrophenol.

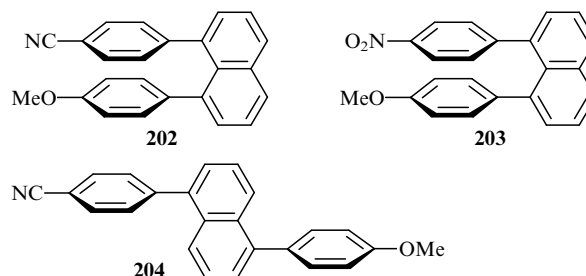


X = NHex₂, Y = NO₂ (**200**); X = NO₂, Y = NHex₂ (**201**);
Hex = n-C₆H₁₃.

The experimental data in Table 30 unambiguously confirm the through-space electron density transfer between the two phenyl rings. The hyperpolarisability of molecule **199** estimated within the additive scheme as a sum of values for molecules **197** and **198** appears three times smaller than the experimental value. Molecule **199** manifests relatively high β and remains optically transparent in virtually entire visible range. On the other hand, the additive model applied to molecules **200** and **201** describes the vector part of the hyperpolarisability tensor ($\beta_j = 1$) relatively well but fails to estimate the septor component ($\beta_j = 3$), which makes the predominant contribution. It is of note that the charge transfer in substituted paracyclophanes was also confirmed by the topological analysis of the electron density distribution based on high-precision X-ray diffraction studies.³³⁵ The introduction of an OH group (which is a strong donor) into one of the benzene rings of the paracyclophane molecule gives rise to the emergence of a critical point (3, -1) between carbon atoms of different benzene rings,³³⁵ which is indicative of a chemical interaction according to the Bader theory.[‡] Meanwhile, the correspondent critical points

are observed neither in unsubstituted paracyclophane nor in its quinonoid analogue, which means that in these cases, no direct through-space charge transfer is involved.^{336, 337}

Bahl *et al.*³³⁸ reported experimentally measured spectral characteristics (HRS in CHCl₃, $\lambda = 1064$ nm) of naphthalene derivatives **202–204**.



Molecule	202	203	204
$10^{30} \beta$ (esu)	26	32	18
$\lambda_{\max}$ /nm	298	308	312

Probably, the reason for the larger value of β in the case of molecule **202** as compared to molecule **204** is again the direct through-space interaction. According to X-ray crystallographic results,³³⁸ the phenyl rings in molecule **203** are nearly parallel to each other and rotated by 62.6° relative to the central naphthalene fragment. The absorption bands of molecules **202** and **203** are blue-shifted with respect to that of molecule **204** and their hyperpolarisabilities are 1.5–2 times larger. Therefore, it may be concluded that the involvement of the direct through-space electron density transfer increases β but does not result in narrowing of the optical transparency range.

Octupolar molecules that are characterised by a three-fold symmetry axis and zero dipole moments represent yet another promising class of molecules for the design of NLO materials. Some representatives of this class were considered by Zyss and Ledoux.^{339, 340} The vector part of the tensor β is zero for octupolar molecules, whereas the septor part remains significant³⁴¹ thus determining the macroscopic spectral properties of the compound. Due to the absence of dipole–dipole interactions, octupolar molecules crystallise in non-centrosymmetric space groups with higher probability than other classes of molecules, which is one of their major advantages.^{342, 343}

Under the assumption of non-interacting substituents (*i.e.*, provided that the effects of D/A pairs are additive), the hyperpolarisability increases by a factor of 1.5 on going from a dipolar to the respective octupolar molecule (featuring the same substituents and π -bridge).³⁴⁴

Bredas *et al.*³⁴⁵ performed a comparative analysis of the spectral characteristics of *p*-NA and triaminotrinitrobenzene (TATB). The hyperpolarisabilities β estimated as norms of the respective tensors [Eqn (4), FF/AM1] were equal to 12.1 and 22.2×10^{-30} esu, and absorption band maxima were located at 4.6 eV and 5.3 eV for *p*-NA and TATB, respectively,³⁴⁴ which means that TATB is characterised by a broader optical transparency range.

Andraud *et al.*³⁴⁶ compared the spectral characteristics of dipolar and octupolar systems for a series of molecules **205a–d** and **206a–d**.

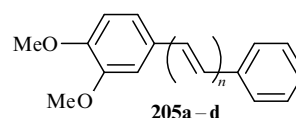
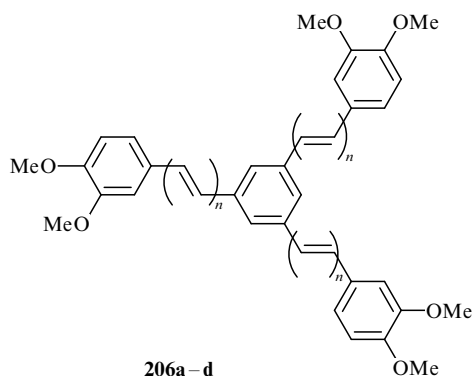


Table 30. Spectral characteristics [$10^{30} \beta$ (esu)] of monosubstituted stilbenes and D/A-substituted paracyclophanes.

Mole- cule	β	$\lambda_{\max}$ /nm	Mole- cule	$ \beta_j = 1 $	$ \beta_j = 3 $	$ \beta_{j=1}^{\text{ad}} $	$ \beta_{j=3}^{\text{ad}} $
197	9	320	200	190	430	170	620
198	9	345	201	260	580	290	0
199	60	378					

Note. All measurements were performed in chloroform; the results of EFISH measurements extrapolated to the zero frequency are given for molecules **197–199**; the measurements were performed at $\lambda = 1907$ nm for **197** and **198** and at $\lambda = 1064$ nm for **199**;³³² HRS results measured at $\lambda = 1320$ nm are given for molecules **200** and **201**.^{333, 334}

[‡] R Bader *Atoms in Molecules: A Quantum Theory* (Oxford: Clarendon Press, 1990)

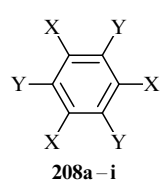
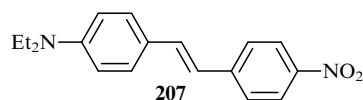


$n = 1$ (a), 2 (b), 3 (c), 4 (d).

Molecule	205a	205b	205c	205d	206a	206b	206c	206d
$10^{30} \beta$ (esu)	18.5	29.0	40.4	52.0	27.4	44.4	58.6	72.0
$\lambda_{\max}$ /nm	391	426	455	480	396	434	458	484

The results obtained [SOS/INDO/S, β estimated according to the Eqn (4)] reveal some general trends also typical of one-dimensional polar molecules. In particular, β and $\lambda_{\max}$ increase with an elongation of the conjugation chain. A systematic comparison of molecules **205a–d** and **206a–d** indicated that octupolar molecules are characterised by higher NLO activities and small bathochromic shifts of the absorption bands.

Spectral and thermal properties of octupolar molecules were also studied by Cho *et al.*^{347–351} The experimental HRS data extrapolated to the zero frequency within the three-level model are presented in Table 31 together with the results of thermogravimetric analysis (TGA). Additionally, the spectral characteristics of dipolar molecules **207** and octupolar molecules **208a–i** were compared.³⁴⁷



X = NO₂; Y = *p*-Et₂NC₆H₄–CH=CH (a);
 X = OMe; Y = *p*-O₂NC₆H₄–CH=CH (b),
p-[(NC)₂CH]C₆H₄–CH=CH (c);
 X = CN; Y = NMe₂–CH=CH (d),
p-Et₂NC₆H₄–CH=CH (e),
p-Ph₂NC₆H₄–CH=CH (f),
p-Bu₂N–(C₆H₄–CH=CH)₂ (g),
p-Hex₂N–(C₆H₄–CH=CH)₂ (h),
p-Et₂NC₆H₄–N=N–C₆H₄–CH=CH (i).

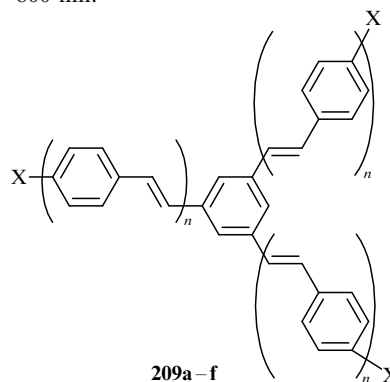
The hyperpolarisabilities β of octupolar molecules **208** are larger than those of their dipolar counterpart **207**. Furthermore,

Table 31. Spectral and thermal characteristics of molecules **207** and **208**.

Molecule	$10^{30} \beta$ (esu)	$\lambda_{\max}$ /nm	T_d /°C	Experimental conditions	
				λ /nm	solvent
207	43	450	—	1560	CHCl ₃
208a	63	428	278	1560	CHCl ₃
208b	11	370	305	1560	CHCl ₃
208c	35	415	354	1560	CHCl ₃
208d	25	389	340	1560	CHCl ₃
208e	65	493	390	1560	CHCl ₃
208f	124	488	422	1560	CHCl ₃
208g	116	499	340	1560	CHCl ₃
208h	348	480	—	1064	THF
208i	246	485	—	1064	THF

the octupolar molecules manifest broader optical transparency ranges. As expected, the hyperpolarisability increases and the optical transparency range becomes narrower with an elongation of the conjugation chain (*cf.* molecules **208d,e** and **g**) and the introduction of stronger acceptors (*cf.* **208b** and **c**). It is of note that the introduction of the phenyl fragments in place of the Et groups at the nitrogen atom (*cf.* **208e** and **f**) gives rise both to a significant increase in β and a hypsochromic shift in the absorption band. The replacement of a CH=CH fragment (**208h**) by N=N (**208i**) results in a decrease in β due to a decrease in the degree of conjugation of the π -bridge. It seems unusual that the hyperpolarisabilities of molecules **208g** and **208h** differing only in the alkyl substituents differ as much as by a factor of 3. In the experimental measurements, solvents with similar polarities were used and, as has been mentioned above, the measured values were extrapolated to the zero frequency. Most probably, this discrepancy reflects the inadequacy of the three-level model to the extrapolation of the experimental data measured at different incident wavelengths. An analysis of the literature data shows that the use of two- and three-level models for the extrapolation of hyperpolarisability values can indeed yield incorrect results.³⁵²

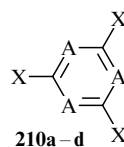
A similar dependence of β on the structure of dipolar and octupolar molecules was obtained for a series of compounds **209** and **210**. Molecules with long conjugation chains (*e.g.*, **209e,f**) manifest larger β and $\lambda_{\max}$ (Table 32). A comparison of hyperpolarisabilities of molecules **209a** and **209b** confirms the validity of the concept of auxiliary D/A groups. The introduction of a donor into the electron-rich thiophene ring is energetically more favourable than the introduction of an acceptor. Molecules **210a–d** contain σ -fragments, such as CH₂ and CH₂–CH₂, providing high optical transparencies of these compounds ($\lambda_{\max} < 300$ nm), and the introduction of the CH₂–CH₂ fragment proves more efficient. The introduction of an acceptor sulfo group instead of a donor amino group (*cf.* molecules **209c,e** and **209d,f**) both increases β and broadens the optical transparency range. According to the results³⁵⁸ devoted to the design of 1,3,5-substituted benzene derivatives with acceptor groups at the terminal positions of π -conjugated substituents, these molecules are optically transparent in a broader range. For instance, $\lambda_{\max}$ is equal to 317 nm ($\beta = 39 \pm 5 \times 10^{-30}$ esu) for 1,3,5-(*p*-CF₃C₆H₄C $\equiv$ C)₃-2,4,6-(MeO)₃C₆, according to the HRS measurements in CHCl₃ at $\lambda = 800$ nm.



X = Me₂N–S–CH=CH–C₆H₄-*p* (a), $n = 0$;

X = O₂N–S–CH=CH–C₆H₄-*p* (b), Hex₂N (c), SO₂Me (d), $n = 1$;

X = Hex₂N (e), SO₂Me (f), $n = 2$.



X = *p*-Me₂NC₆H₄CH₂; A = CH (a), N (b);

X = *p*-Me₂NC₆H₄(CH₂)₂; A = CH (c), N (d).

Molecule	$10^{30} \beta$ (esu)	$\lambda_{\max}$ /nm	Method of calculation or measurement	Ref.
209a	79	392	the SOS method in the	353
209b	29	437	INDO/CISD approximation at $\lambda = \infty$	
209c	29	387	HRS measurements	354
209d	30	342	(in CHCl_3):	355
209e	150	407	$\lambda = 1060$ nm for 209c,d ;	356
209f	250	377	$\lambda = 1340$ nm for 209e,f	
210a	12.1	269	FF/AM1 calculation in	357
210b	16.1	267	the static limit	
210c	17.4	268		
210d	23.4	267		

211a-c

$R = H$ (**a**), NO_2 (**b**), SC_8H_{17-n} (**c**).

Table 33. Spectral characteristics [$10^{30} \beta$ (esu)] of subphthalocyanines.^{357, 359, 360}

Molecule	$\lambda_{\text{max}}/\text{nm}$	β ($\lambda = 1064 \text{ nm}$)	β ($\lambda = 1340 \text{ nm}$)	β ($\lambda = 1460 \text{ nm}$)
a	565	92	296	—
b	586	—	2000	144.3
c	584	—	—	76.5

closo-Carboranes possess a great potential in the design of NLO materials due to their thermal and chemical stability.^{363–366} Experimental and theoretical investigations into the NLO properties of carboranes were started only in the early 1990s.^{367, 368}

Table 34. Calculated optical characteristics of $[\text{B}_{12}\text{H}_{11}-\text{C}_2\text{B}_{10}\text{H}_{11}]^{2-}$ isomers compared to those of *p*-NA.

Compound	$10^{30} \beta$ (esu) (HF/6-31G**)	λ_{max} /nm (CIS/6-31G**)
[B ₁₂ H ₁₁ - <i>o</i> -C ₂ B ₁₀ H ₁₁] ²⁻	3.4	271
[B ₁₂ H ₁₁ - <i>m</i> -C ₂ B ₁₀ H ₁₁] ²⁻	3.6	265
[B ₁₂ H ₁₁ - <i>p</i> -C ₂ B ₁₀ H ₁₁] ²⁻	3.6	260
<i>p</i> -NA	6.2	374

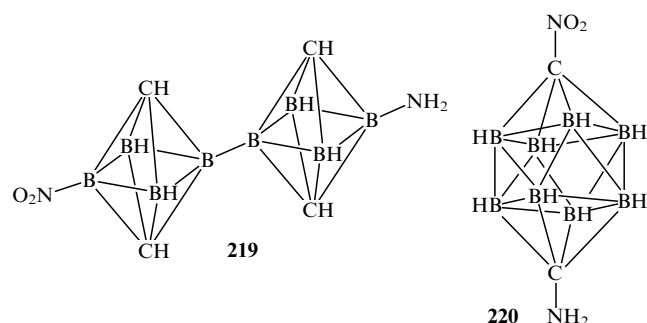
Chemical structures of molecules 212, 213, and 214 are shown. Molecule 212 is a C₈₀ fullerene with a phenyl group and a positive charge. Molecule 213 is a C₈₀ fullerene with a phenyl group and a negative charge. Molecule 214 is a C₈₀ fullerene with two phenyl groups, one positive and one negative charge.

Molecule	212	213	214
10 ³⁰ β (esu)	236 ± 50	682	503
λ _{max} / nm	340	—	—

Molecule	215	216	217	218	219	220	1
β_{vect}	683	1154	808	403	3675	677	1745

Chemical structures of four nido-pentaborane derivatives are shown:

- 215**: A nido-pentaborane derivative with a square pyramidal boron core. The open square face is capped by a carbon atom (C) bonded to a nitro group (NO₂) and an amino group (NH₂). The other four vertices of the square face are capped by BH groups. The remaining two vertices of the pentagonal face are capped by HB and BH groups.
- 216**: A nido-pentaborane derivative with a square pyramidal boron core. The open square face is capped by a CH group and a BH group. The other four vertices of the square face are capped by BH groups. The remaining two vertices of the pentagonal face are capped by O₂N-B and NH₂-B groups.
- 217**: A nido-pentaborane derivative with a square pyramidal boron core. The open square face is capped by a CH group and a BH group. The other four vertices of the square face are capped by BH groups. The remaining two vertices of the pentagonal face are capped by H₂N-B and NO₂-B groups.
- 218**: A nido-pentaborane derivative with a square pyramidal boron core. The open square face is capped by a CH group and a BH group. The other four vertices of the square face are capped by BH groups. The remaining two vertices of the pentagonal face are capped by H₂N-C and NO₂-B groups.



These results show again that the hyperpolarisabilities of carboranes and *p*-NA are comparable. This suggests the conjugation between substituents and the carborane cage and three-dimensional delocalisation of electrons over the carborane core. This suggestion is supported by the results of the topological analysis of the electron density distribution function in carborane derivatives (based on the experimental high-precision X-ray diffraction data)³⁷⁶ and by mandatory utilisation of the resonance structures for the description of chemical bonding in carboranes within the concept of three-centre bonds.³⁷⁷ Furthermore, according to calculations of magnetic properties³⁷⁸ and an analysis of chemical properties,³⁷⁹ carboranes can be regarded as aromatic systems. A significant increase in β upon introduction of another carborane cage into the conjugation chain (molecules **216** and **219**) gives an additional argument in favour of the analogy between the two- and three-dimensional aromaticity. It can seem strange that molecule **220** is characterised by smaller hyperpolarisability than molecule **215**, despite the presence of a longer conjugated bridge. The probable reason for this is the higher degree of aromaticity of 10-vertex carboranes as compared to 6-vertex ones.³⁸⁰

The above data clearly show that the use of carboranes as building blocks of conjugation bridges gives rise to relatively high values of hyperpolarisability with a simultaneous broadening of the optical transparency range. Taking into account the high thermal stability of carboranes, they should be recognised as a very promising class of compounds for applications in nonlinear optics.

V. The design of NLO crystals

The search for crystalline materials with high nonlinear optical susceptibilities d_{ijk} includes two principal steps. In the first step, most promising compounds are selected based on the information regarding their molecular spectral properties. In the second step, d_{ijk} has to be estimated, which can be done with a number of theoretical³⁸¹ and experimental^{3,382} methods.

1. Experimental methods for the determination of the NLO susceptibilities of crystals

The NLO susceptibility of a crystal can be measured both for single crystals and polycrystalline powders. In the former technique, the interference pattern (also referred to as the Maker fringes) produced by the second harmonic radiation transmitted through a single crystal is registered and the intensities in its maxima are compared to a standard reference.^{383–385} This method enables independent determination of all components of the susceptibility tensor. For the determination of specific components d_{ijk} , polished parallel-sided plate crystals are used, which were carefully cut along the respective crystallographic directions.

Generally, the incident wave with a frequency ω and the secondary wave with a frequency 2ω propagating in a crystal are characterised by different phase velocities, so that the interaction area is small and thus the measured intensity of the second harmonic is low. Nevertheless, in the majority of organic crystals, there are specific crystallographic directions, the so-called synchronism directions,³ along which the phase velocities are identi-

cal and thus the second harmonic intensity is amplified proportional to the squared distance traveled by the secondary wave in the crystal. This makes it possible to significantly improve the accuracy of the measurements. However only the effective susceptibility coefficient (d_{ef}) can be determined in this way, whereas every single component of the susceptibility tensor become inaccessible. However, it is the effective susceptibility that is of greatest practical importance. Provided that the refractive index of the material and all the tensor components d_{ijk} are known, the synchronism directions can be approximately found and the value of d_{ef} can be assessed.

A method for the determination of the NLO susceptibility in polycrystalline powders is based^{386–388} on the registration of intensity of the second harmonic transmitted through a cell filled with a powder under study and its comparison with a reference signal. Such measurements are significantly simpler since they do not require time-consuming manipulations with optical-quality single crystals, *i.e.*, their growth, cutting and polishing.

A detailed description of both experimental methods can be found elsewhere.^{3,382} Here, we only mention their major advantages and drawbacks as regards their application to the design of NLO materials.

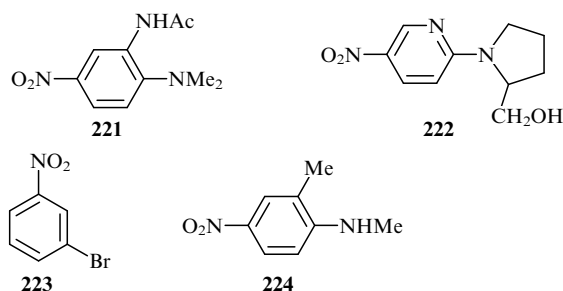
It is evident that the Maker fringe method provides comprehensive information on the NLO properties of a material. Its main disadvantage consists of the necessity to grow and process relatively large optical-quality crystals (with a volume of up to $\sim 1 \text{ cm}^3$), which is very demanding. Therefore, this method is not applicable to the systematic search for the NLO materials. The powder method is by far simpler; it makes it possible to find out whether a crystal possesses synchronism directions and assess its potential in a rather straightforward way. The drawbacks of this method include the relatively low accuracy (50% at most) and the lack of information on single components of the susceptibility tensor.

It has to be noted that the experimental determination of the NLO susceptibility of a crystal does not generally require the detailed knowledge of its crystal structure. In particular, only space group is required for the interpretation of the Maker fringes. Nevertheless, X-ray diffraction data are indispensable, since the measured susceptibility cannot be ascribed to a specific material if its crystal structure is unknown. First of all, this is due to the frequently occurring polymorphism. In particular, a powder under study can actually be a mixture of several polymorph modifications of one compound. Second, it often happens that solvent molecules enter the crystal structure and thus the experimental NLO susceptibility has to be attributed to a solvate rather than pure compound.

Theoretical methods for the evaluation of NLO susceptibilities are typically based on the oriented gas model^{48,49} [see Eqn (6)], which assumes that the susceptibility of a crystal can be represented as a sum of molecular hyperpolarisabilities. The calculation of single components d_{ijk} of the crystal susceptibility tensor requires the knowledge of the hyperpolarisabilities of constituent molecules, local field factors (the approximate formula $f_i f_j f_k = 3$ can be employed in the case where no experimental data to estimate these factors are available)³⁸⁹ and orientation of the constituent molecules in the unit cell.

The basic difference between the existing methods consists of the degree of neglect of the intermolecular interactions. The utilisation of Eqn (6) based on the values of β of an isolated molecule means the complete neglect of the intermolecular interactions. Zyss and Oudar⁴⁹ derived formulas for the calculation of d_{ijk} for the most common space groups under the assumption of the two-dimensional character of the hyperpolarisability, which is suitable for all nearly planar molecules. These formulas have relatively simple forms for monoclinic space groups but become increasingly complicated for higher symmetries. Furthermore, the original paper contains several misprints. This approach was further refined and implemented in the software code NLOP.^{50,390} This code operates with the full molecular hyper-

polarisability tensors and thus it makes possible to calculate the optical properties of any molecular crystal without restrictions to molecular geometry and space group. Furthermore, the probability of errors due to manual calculations with formulas from Ref. 49 is minimised [e.g., see Ref. 391, where d_{xyz} of 2,5-di(benzylidene)cyclopentanone was overestimated twice due to a misprint in the original formula]. According to the calculations for model molecules **221**–**224**, for which the experimental values of d_{ijk} are also available, the theoretical approach agrees with the experiment at a semiquantitative level provided that the crystal structures reveal no specific strong intermolecular interactions (Table 35).^{50,390} No doubt, this is sufficient for a preliminary evaluation of the potential of a compound under study and its appropriateness for a more thorough analysis.



Recently, the oriented gas model was improved by the introduction of a supermolecule concept, which means that the hyperpolarisabilities of molecular associates rather than isolated molecules are taken as input for the calculation of d_{ijk} . This makes it possible to include the dependence of the NLO properties of a molecule on its intermolecular environment into consideration to a certain accuracy level defined by the size and shape of the associate.

In particular, dimers of *p*-NA,³⁹⁶ 2-methyl-4-nitroaniline (MNA, **225**)³⁹⁷ and urea (**226**)³⁹⁸ were considered. The structure of the H-bonded *p*-NA dimer was obtained by the geometry optimisation at the HF/6-31+G** level; those of the MNA dimer (formed by weak stacking interactions) and the H-bonded urea dimer were taken from the experimental X-ray crystallographic data.^{399,400} The hyperpolarisabilities β_z of the dimers calculated within the supermolecule approximation and by the additive scheme were 27.6×10^{-30} esu and 15.4×10^{-30} esu for **1** (CPHF/6-31+G**), 10.5×10^{-30} esu and 15.3×10^{-30} esu for **225** (CPHF/6-31G with the frozen core) and 0.26×10^{-30} esu and 0.38×10^{-30} esu for **226** (CPHF/DZV), respectively.

As has been noted in the previous Section, in the case of molecular associates formed by the stacking interactions between π -systems, the additive scheme for the calculation of hyperpolarisabilities is violated. In particular, the values of β for a stacking dimer of *p*-NA at a distance between the benzene rings of 3.5 Å are 20.5×10^{-30} esu and 24.6×10^{-30} esu, as calculated within the supermolecule approximation and by the additive scheme, respectively.³²⁷ Therefore, it becomes apparent that the additive scheme can be violated in different ways, depending on the dimer structure: the chain-like structure is more favourable than the columnar structure. However, in the case of urea, the super-

molecule value of β for the H-bonded (chain-like) dimer is 1.5 times smaller than the additive one. Several authors^{177,401,402} considered larger molecular clusters of MNA and urea. For a cluster of urea composed of 7 molecules (generated on the basis of crystallographic data),⁴⁰¹ the additive NLO susceptibility was smaller than the supermolecule value only by 15%. In the case of molecular associates of MNA (generated on the basis of crystallographic data), the additive susceptibility was 5 times smaller than the supermolecule value along the crystallographic axis *a* (which approximately conforms to the direction of the molecular dipole moment) but 30%–50% larger than the supermolecule value in the perpendicular directions. On average, the additive scheme underestimated the NLO susceptibility by a factor of two as compared to the supermolecule model.

As has been mentioned above (see Section II), the desired level of accuracy should be considered as the basic appropriateness criterion in the selection of the theoretical method to be applied. The theoretical evaluation of the NLO properties at a semiquantitative level is well sufficient for the majority of tasks related to the systematic search for promising NLO compounds. In such a case, either the mere additive scheme or the supermolecule model based on a small molecular associate, depending on the presence of short intermolecular contacts in the molecular structure, will provide adequate results.

2. Methods for the design of NLO crystals

As has been mentioned above, only non-centrosymmetric crystals are capable of generating the second harmonic. Therefore, the major problem within the design of NLO crystals consists of the search for compounds that crystallise in non-centrosymmetric space groups. The use of chiral molecules is one of the most evident ways to meet this requirement. However, a non-centrosymmetric space group is the only necessary condition for the manifestation of the NLO activity, whereas the sufficient condition implies an optimum arrangement of molecules in a crystal in such a way that individual contributions of molecular hyperpolarisabilities are mutually enhanced.⁴⁹ Unfortunately, many chiral crystal packings are actually pseudo-centrosymmetric (with two crystallographically independent molecules in a unit cell) (see, for example, Refs 307, 403–405). The efficient design of NLO crystals is thus hampered by two major factors. First, there are currently no general approaches to the prediction of crystal structures.^{406–408} Second, the vast majority of organic compounds tend to crystallise in centrosymmetric space groups.^{409,410} The latter fact is traditionally explained by the influence of dipole–dipole interactions favouring the antiparallel orientation of the molecular dipole moments.¹⁶ Nevertheless, the role of dipole–dipole interactions in the formation of crystal structures remains a subject of debate. Some authors^{411,412} argue that the contribution of these interactions is small, while other authors^{413,414} consider it significant. Interestingly, both the viewpoints are substantiated by statistical analyses of crystal structures retrieved from the Cambridge Structural Database (CSD).⁴¹⁵ Adopting the latter viewpoint, it becomes apparent that it is necessary to introduce specific intermolecular interactions which would prevent antiparallel orientation of dipoles in order to obtain a non-centrosymmetric crystal. Even assuming that the

Table 35. Calculated and experimental NLO susceptibilities [$10^9 d_{ij}$ (esu)] in crystals of selected D/A-substituted benzene derivatives.

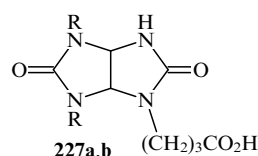
Molecule	d_{21}	d_{22}	d_{23}	d_{25}	Ref.	Molecule	d_{31}	d_{32}	d_{33}	Ref.
221						223				
calculation	67.4	16.5	3.1	16.0	50	calculation	0.73	4.83	6.93	50
experiment	119 ± 36	12.4 ± 2.4	3.6 ± 4.8	3.6 ± 4.8	392	experiment	9.6 ± 1.8	11.0 ± 3.0	19.2 ± 2.4	394
222						224				
calculation	119.2	12.9	1.0	4.5	50	calculation	34.2	4.5	2.2	50
experiment	114 ± 26	40 ± 10	—	—	393	experiment	31 ± 7	—	6.2 ± 1.4	395

dipole–dipole interactions are insignificant and the inversion symmetry of the majority of crystals is a net result of diverse factors, the involvement of specific forces overcoming these factors is a prerequisite for the formation of a non-centrosymmetric crystal. It would be appropriate to mention here that the NLO active molecules, which are in the focus of the present discussion, are typically characterised by large dipole moments, often exceeding 10 D,[§] and thus the effects related to the dipole–dipole interactions are more pronounced for them than for a ‘statistical average’ case.

Several approaches to the problem of construction of non-centrosymmetric crystals exploiting specific intermolecular interactions counteracting the forces that favour the centrosymmetric structures have been suggested. These include the utilisation of molecules containing fragments prone to H-bonding; the use of salts composed of charged ions for which the electrostatic interactions become significant; co-crystallisation with an inert component giving rise, for instance, to a ‘dilution’ of the structure and consequent attenuation of the dipole–dipole interactions between molecules of the NLO-active component. Various combinations of these approaches are also possible. But another question then arises: what kind of crystal packing should be anticipated, taking into account that rather strong specific intermolecular interactions are involved? Presently, this question cannot be unequivocally answered. A comprehensive survey of this problem would be a subject of a separate review. With this regard, below we attempt to critically assess this important problem only with a few representative examples.

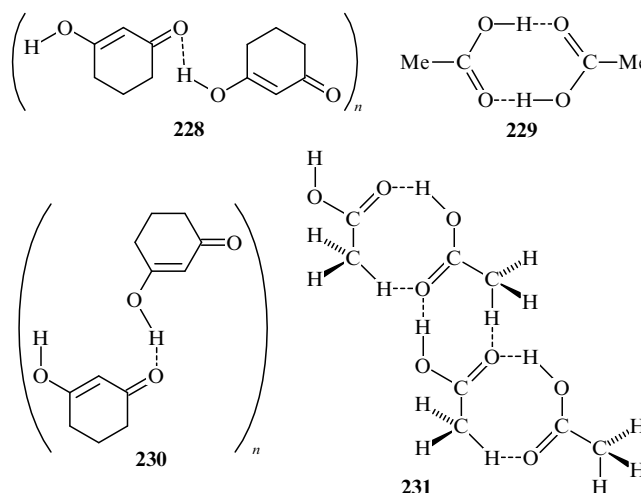
The importance of H-bonds as a key factor in the design of crystal structures is well documented.^{410, 416–422} The following regularities of H-bonding in the crystal structures were formulated: (1) the most active proton donors and acceptors have to be involved in H-bonding; (2) H-bonds are preferably formed between the most efficient donor and acceptor.

As for crystalline NLO-active compounds, the principal role played by H-bonds in the formation of non-centrosymmetric structures has been addressed in numerous studies.^{306, 307, 423–429} However, in all these cases, the conclusions were derived after the completion of X-ray crystallographic study and subsequent analysis of the crystal packings. It is also of note that weak intermolecular forces, such as van der Waals or C–H...X interactions, are always present in the crystal structures in addition to stronger ones. In the studies cited above, the strong specific interactions were responsible only for the formation of a basic motif of the crystal packing, whereas the mutual arrangement of these motifs was governed by weaker forces. Even if a certain basic motif is retained to a high confidence level over a wide series of compounds upon the variation of substituents, the prediction of fine effects of weaker interactions on the supramolecular organisation in the crystal is hardly possible. For instance, a comparative analysis of the crystal structures of more than 40 conjugated molecules with NH₂/NO₂-substituents retrieved from CSD showed that, in all cases, an aggregation of molecules along a specific direction to form H-bonded polar chains can be suggested, whereas the mutual orientations of such chains cannot be easily controlled.⁴³⁰ Lyssenko *et al.*⁴³¹ reported the crystal structures of compounds **227a** and **b** differing from each other only in alkyl groups. Both the structures are built up of identical non-centrosymmetric H-bonded layers. Nevertheless, the neighbouring layers are stacked in parallel and thus are related by a translation in the structure of **227a**, whereas they are antiparallel and related by an inversion centre in the structure of **227b**. No specific interactions stabilising this particular chiral packing in the case of **227** were revealed.⁴³¹



R = Me (**a**), Et (**b**).

The problem of interpretation of quantum-chemical calculations on H-bonded associates occurring in crystal structures was specifically addressed by Turi and Dannenberg.^{432–435} Their aim was to verify the predictive power of calculations by systematically checking whether the energetically most favourable associate, as predicted by means of quantum chemistry, actually occurs in the real crystal structure of the compound. They considered the following H-bonded associates of cyclohexane-1,3-dione and acetic acid



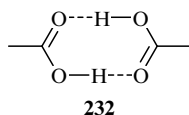
The crystal structure of the associate **228** is composed of molecules in the enol form adopting the *anti*-conformation. At the same time, according to the quantum-chemical calculations (HF/6-31G** and AM1), the stability of an isolated molecule decreases in the series ketone form > enol form/*syn*-conformation > enol form/*anti*-conformation. The relative gain in energy upon the formation of H-bonded associates with respect to the monomers in the ketone form can be analysed based on the results of AM1 calculations compiled in Table 36.

Table 36. Total energies (kcal mol^{−1}) for associates **228**, **230** composed of *N* molecules.

<i>N</i>	Molecule		<i>N</i>	Molecule	
	228	230		228	230
2	1.5	0.1	6	−3.1	−3.0
3	−0.7	−1.4	7	−3.5	−3.3
4	−1.9	−2.2	∞	−5.7	−4.9
5	−2.6	−2.7			

It is seen that at least three cyclohexane-1,3-dione molecules should associate to an H-bonded chain of either *syn*- or *anti*-conformers to become energetically more favourable than the same number of non-interacting isolated molecules in the ketone form. Furthermore, the chain of *anti*-conformers **228**, which actually occurs in the crystal, becomes the most energetically favourable structure only after association of no less than six molecules. H-bonded molecular associates of acetic acid (**229**, **231**) was yet another subject of studies by Turi and Dannenberg.^{434, 435} The simulation of acetic acid dimers was unsuccessful in explaining its crystal structure. No H-bonded dimer with the expected structure

[§] Unfortunately, to the best of our knowledge, no statistical studies regarding the distribution of centrosymmetric and non-centrosymmetric space groups for highly polar compounds have been reported so far.



is realised in the crystal because one of the $C=O\cdots H-O$ H-bonds is replaced by the $C=O\cdots H-CH_2$ bond, which gives rise to the H-bonded chain **231** as the main motif of the crystal packing. A calculation of a three-dimensional cluster that included several chains and 36 molecules in total was required to demonstrate that such a structure is indeed energetically more favourable than that composed of H-bonded dimers. This result clearly illustrates the importance of cooperative effects in the formation of associates and implies that the energy additivity can be violated upon the attachment of a next molecule to the existing cluster.

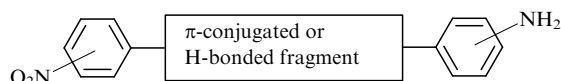
Similar conclusions were derived based on the analysis of crystal packings of nitroanilines, urea and *p*-benzoquinone.^{436–438} It is of note that the quantum-chemical simulations described above were accomplished only for compounds with known crystal structures. For instance, the following statement is valid for carboxylic acids (distinctive features of their crystal structures were comprehensively analysed for the first time by Leisero-witz⁴³⁹): it is impossible to judge on the association pattern of molecules even in one dimension, not mentioning the full three-dimensional crystal structure, based exclusively on the molecular structure.^{410, 440}

Nevertheless, in specific cases, the theoretical approach based on the atom – atom potential method makes it possible to establish the relative energies of centrosymmetric and non-centrosymmetric dimers. The formation of a non-centrosymmetric crystal structure can be anticipated if the latter proves preferable.^{81, 82}

Unfortunately, in overall, the predictive power of contemporary methods for the theoretical crystal packing simulation is rather low. According to recent results devoted to testing of modern specialised software tools for the crystal structure prediction,^{441–444} the correct structure is typically present among 5–10 energetically most favourable structures suggested by the codes, but in many cases it is not the most favourable structure.

Certain regularities in the formation of crystal structures can be revealed using a statistical analysis of the structural information stored in CSD for specific classes of compounds. Within the framework of the search for compounds that are crystallised in non-centrosymmetric space groups, Etter and Huang⁴⁴⁵ accomplished such statistical analyses for nitroanilines, co-crystallisation products in the system phenol–pyridine⁴⁴⁶ and benzoic acids.⁴⁴⁷

For NH_2/NO_2 -substituted molecules of the type



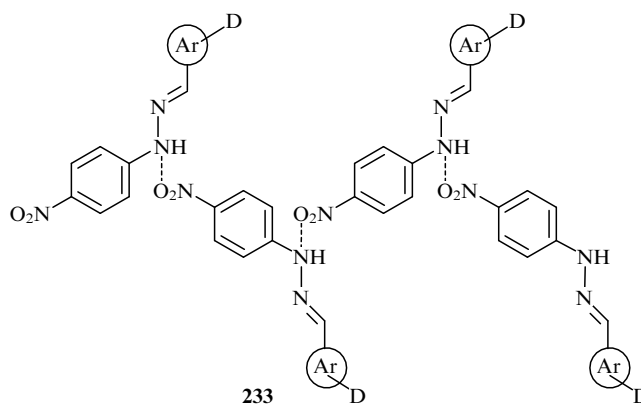
non-centrosymmetric packings are observed in 46% of all cases. Meanwhile, according to CSD, the probability of the crystallisation of an achiral compound in a non-centrosymmetric space group is only 11%.⁴⁴⁵ NH_2/NO_2 -substituted compounds typically reveal H-bonded non-centrosymmetric chains as the basic structural motif. Etter and co-workers⁴⁴⁶ reported results of the NLO susceptibility measurements using the powder method for 22 co-crystallisation products in the system phenol–pyridine. The second harmonic generation was observed for four samples, which amounts to 18% of all cases, *i.e.*, slightly exceeds the statistical average value. According to analysis of the crystal packings of benzoic acid,⁴⁴⁷ centrosymmetric structures occur in 98% of all cases provided that the H-bonded dimer **232** acts as the basic structural block. On the other hand, if infinite H-bonded chains are observed, non-centrosymmetric packings occur with a probability of 52%. The probability of the formation of such chains is substantially higher for *ortho*-substituted acids due to,

first, probable intramolecular H-bonding and, second, steric effects favouring the exit of the COOH group out of the ring plane.

The formation of centrosymmetric dimers can be prevented^{448, 449} by esterification of acids, *e.g.*, by the synthesis of 3-(4-nitrophenyl)-2-phenylacrylates. The compounds, in which *p*-MeO–C₆H₄ and Me groups substitute for the proton, crystallise in non-centrosymmetric space groups. Furthermore, the crystal packing occurring in the case of the Me-derivative appears to be close to the optimum one.

Studies on hydrazones were reported.^{450, 451} According to measurements of the NLO susceptibilities of powders, 20 out of 28 synthesised compound crystallised in non-centrosymmetric space groups.

Several compounds from this series were examined using X-ray crystallography. It was shown that in the vast majority of cases, λ -shaped non-centrosymmetric H-bonded chain **233** is formed as the basic structural motif, although the reasons responsible for the emergence of this particular structure were not identified.



Partly, this issue was clarified in studies of $D-\pi-A-D'$ -imines^{306, 307} (see Section IV). As in the case of hydrazones, the crystal structures of imines were found to be built up of λ -shaped chains. Based on a detailed analysis of the crystal packing of imines, the authors^{306, 307} solidly argued the formation of non-centrosymmetric groups. An isolated single H-bonded chain contains voids that tend to be filled with molecules constituting neighbouring chains thus giving rise to their non-parallel mutual arrangement, which excludes the formation of an antiparallel centrosymmetric packing.

X-Ray crystallographic data on other hydrazone derivatives^{452–456} support the conclusions derived in other studies (Refs 450 and 451). It is worth mentioning that this series of crystal structures obeys the aforementioned main rule of H-bonding. Indeed, if an Ar–D group contains no auxiliary active H-bonding sites, the intermolecular $N-H\cdots O(NO)$ bonds are formed in all cases. On the other hand, the pattern of hydrogen bonds is altered upon introduction of donor OR groups; this can result in the formation of both non-centrosymmetric and centrosymmetric space groups.

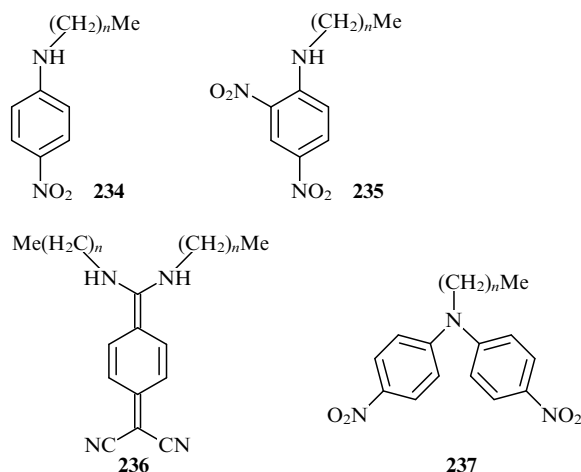
Crystal structures of salts composed of the organic cation, 2-amino-5-nitropyridinium ($2A5NP^+$), and an anion (An^-) of either organic or inorganic nature were investigated.^{457–467} According to the results obtained, the probability of occurrence of a non-centrosymmetric space group correlates with the shortest $H_2N\cdots NH_2$ distance (Table 37). If this distance is longer than 4 Å, then a non-centrosymmetric packing is realised, whereas in the distance range of 3.8–4.0 Å, both centrosymmetric and non-centrosymmetric structures are possible. The authors suggestedly explain this correlation by an attenuation of the effects of dipole – dipole interactions with an increase in the $H_2N\cdots NH_2$ distance. In our opinion, this explanation is insufficient since it ignores the fact that it is the strong hydrogen bonds present in all structures that form the basic structural motifs therein. Additionally, it is currently impossible to predict *a priori* the $H_2N\cdots NH_2$ distance

Table 37. Correlation between the shortest $\text{H}_2\text{N}\cdots\text{NH}_2$ distance (r) and probability of the occurrence of a non-centrosymmetric space group in the crystal structures of $2\text{A5NP}^+ \cdot \text{An}^-$.

An^-	$r/\text{\AA}$	Space group	An^-	$r/\text{\AA}$	Space group
HSO_4^-	3.454	$Pbca$	Cl^-	4.702	$P2_1$
InCl_6^{3-}	3.465	$P2_1/a$	Br^-	4.807	$P2_1$
BF_4^-	3.528	$P2_1/n$	H_2PO_4^-	6.747	$Pna2_1$
H_2PO_3^-	3.809	$C2/c$	H_2AsO_4^-	6.941	$Pna2_1$
I^-	3.955	$P2_1/a$	$\text{Cr}_2\text{O}_7^{2-}$	3.896	$P2_1nb$
Br^-	4.029	$P2_1/a$	$\text{CHCl}_2\text{COO}^-$	3.949	$P2_12_12_1$
$\text{CCl}_3\text{CO}_2^-$	3.956	$P2_1/n$	$[(\text{HO})_3\text{PCH}_2\text{CO}_2\text{H}]^-$	7.070	$P2_12_12_1$

for a specific compound and, respectively, to conclude on the most probable packing type.

Gangopadhyay *et al.*^{468–471} analysed compounds **234–237** for which non-centrosymmetric packing occurs only for a certain length of the alkyl fragments. The authors distinguished three major contributions to the lattice energy: H-bonds, dipole–dipole and dispersion interactions.



In the case of dinitro derivatives, only dipole–dipole and dispersion interactions contribute to the lattice energy due to the formation of intramolecular H-bonds. According to calculations with the atom–atom potential method, the dispersion contribution increases and dipole–dipole contribution decreases with an elongation of the alkyl group. The authors established that a balance between these interactions is settled in the case of the formation of a non-centrosymmetric structure. The dipole–dipole interactions evidently induce a centrosymmetric molecular packing. But what kind of structure is induced by the dispersion interactions? If one assumes that the dispersion interactions induce a non-centrosymmetric structure, it becomes puzzling, why that compounds resume to crystallise in centrosymmetric space groups upon further increase in the alkyl chain length after the balance point. As has been mentioned above, the effects of the dispersion forces on the packing of molecules in a crystal are difficult to predict, which is probably the main reason for the poor efficiency of modern approaches to the crystal structure prediction.

Yet another approach to the design of NLO crystals employs the polymorphism phenomenon^{472,473} and implies the search for the optimum conditions for the growth of a particular modification that crystallises in a non-centrosymmetric space group. Kuleshova and Antipin^{474,475} analysed some of the most common centrosymmetric–non-centrosymmetric polymorph pairs ($P2_1/c-P2_12_12_1$; $P2_1/c-P2_1$; $P2_1/c-Pc$; $P2_1/c-Pna2_1$) based on the structural information retrieved from CSD and derived several

general conclusions. Typically, if one of the two polymorphs crystallises in a chiral space group, the crystal structures of both modifications include chiral structural fragments (*e.g.*, layers or chains). In such a case, the polymorphism relates to different mutual arrangements of these fragments induced, as has been discussed above, by weaker intermolecular interactions. These polymorphs are often accompanying and can be prepared under identical experimental conditions (solvent, temperature, concentration). This detailed analysis is definitely useful but it nevertheless does not answer the most important question: how can a non-centrosymmetric modification be purposefully prepared? Unfortunately, two (or more) polymorphs of a compound very often appear to be centrosymmetric.^{476,477}

Probably, one of the best substantiated approaches to the design of non-centrosymmetric crystals elaborated by Leiserowitz and Lahav^{478,479} employs ‘tailor-made’ additives that selectively inhibit the growth of undesired polymorph modifications. Such an approach is based on the assumption that nuclei of all possible modifications are present in the solution but only the most stable nucleus survives to give rise to the resultant crystal. If a small amount of an additive capable of interacting with the most rapidly growing crystal faces of a certain polymorph and thus inhibiting its growth is introduced to the mother liquor, this will greatly favour the formation of other modifications.

VI. Conclusion

The optimum route to the design of NLO materials should be based on the knowledge and effective utilisation of the contemporary experimental and theoretical methods for the elucidation of structure and properties of NLO-active compounds.

It is evident that the combinatorial approach to the search for new materials by synthesis and experimental testing (for instance, by the powder method) can hardly be accepted as the optimum one. In this case, the step of the evaluation of molecular hyperpolarisabilities (which is actually of no practical importance) is skipped, but it is extremely costly in terms of time and chemicals expenses. Furthermore, the powder method yields only the effective value of the NLO susceptibility and gives no information on factors affecting this value, which makes further purposeful optimisation impossible.

In our opinion, it would be logical and convenient to subdivide the problem of the design of highly efficient NLO materials into two successive steps: molecular design and crystal design.

Taking into account the recent advancement of experimental techniques for the determination of the NLO properties of molecules in solution, the major factor limiting the accuracy of the experimental results relates to the fact that the measurements are performed not for the isolated target molecule, but rather for a product of its interactions with solvent molecules, which is characterised by an unknown structure. The measured hyperpolarisability of a molecule can change severalfold, depending on the solvent. The gas-phase experiments provide a higher accuracy but the majority of polar organic compounds promising for NLO applications do not vaporise due to the decomposition. There are a lot of issues related to different ways of data representation [see formulas (3) and (4)] and the use of different reference values for standard samples. This complicates any comparative analysis of the experimental results obtained by different research groups. However, the data obtained by one research group within the same cycle of measurements can well be compared and analysed at a semiquantitative level. Furthermore, the independently measured characteristics of a certain compound can often be referenced to the respective parameters of a previously studied molecule measured under identical conditions. Therefore, in the present review, we systematically compared and analysed the NLO properties of a broad assortment of molecules reliably determined either theoretically or experimentally, taking the above constraints into account. The reported experimental and theoretical values for the same

molecule are typically in accordance with each other to at least a semiquantitative level. According to the literature data, DFT calculations based on hybrid functionals, such as B3LYP or B97, is the theoretical method of choice for the systematic exploration of the NLO properties of molecules.

The molecular design of NLO materials should differentiate between zwitter-ionic and neutral molecules (*i.e.*, molecules with a negligible contribution of the zwitter-ionic form into the ground state). In a schematic diagram showing hyperpolarisability as a function of intermixing between the neutral (ψ_{VB}) and zwitter-ionic (ψ_{CT}) forms (Fig. 10), zwitter-ionic and neutral molecules are located in the right-hand (*i.e.*, in the range of negative β) and left-hand parts, respectively. The hyperpolarisability of a neutral molecule is governed by the following key parameters: the strength of D/A groups, the energy barrier to the electron delocalisation over the π -system (aromaticity), the length of the conjugation system and the degree of its electron-deficiency(excessiveness). These parameters jointly determine the overall degree of the electron delocalisation over a D- π -A molecule. The majority of NLO molecules in the neutral form fall into the region to the left from the maximum. This gives a key to the construction of molecules with the optimum structure.

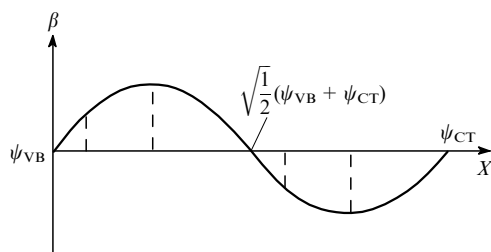


Figure 10. Hyperpolarisability as a function of key parameters (X); X is an increase in the strength of D/A groups, an elongation of the conjugation chain, a decrease in the degree of aromaticity of the π -system and an increase in the degree of electron-deficiency(excessiveness) of the π -system from the acceptor(donor) side.

In contrast, zwitter-ionic molecules containing aromatic D/A groups typically fall into the region to the left from the negative maximum, and thus a decrease in the degree of conjugation between the D/A groups, which additionally stabilises the zwitter-ionic form, gives rise to an enhancement of the NLO properties.

The results discussed in the present review indicate that the algorithm of the search for a molecular structure providing an ultimate hyperpolarisability is generally established.

Nevertheless, any NLO material should meet a number of additional requirements, including optical transparency (the lack of resonance absorption at the second harmonic frequency), thermal and chemical stability, stability towards laser irradiation, accessibility of large (up to 1 cm³) optical-quality single crystals, *etc.* Two former properties can already be estimated at the molecular level (see Section IV). Unfortunately, it turns out that, as a rule, the modifications of molecules resulting in an enhanced hyperpolarisabilities simultaneously give rise to narrower ranges of the optical transparency and lower stabilities. Therefore, the greatest research efforts are currently put forth to locate the proper compromise between the desired spectral and thermal properties, on the one hand and sufficiently high hyperpolarisabilities, on the other.

The most important task within the design of crystals manifesting NLO properties consists of the elaboration of methods for growing of non-centrosymmetric crystals with the optimum molecular packings. Since X-ray crystallography is still the only source of unambiguous information on crystal structures, the current approach to the design of NLO active crystals is based on

the 'trial-and-error' method. The contemporary theoretical methods for the crystal structure simulation are capable of providing the required information only to a limited extent.

The extended array of structural information stored in CSD makes it possible to analyse the regularities of molecular packings along series of closely related compounds and thus make probabilistic predictions. A complex approach combining the CSD-based data mining with available software capabilities of crystal structure simulations and quantum-chemical calculations on molecular associates can be of much help to reduce the probability of errors and increase the number of fruitful trials within the 'trial-and-error' approach.

Summarising all the above results and discussion we propose the following stepwise algorithm for the optimum design and construction of NLO materials.

1. Preliminary selection of molecules and evaluation of their hyperpolarisabilities on the basis of quantum-chemical calculations. The preliminary selection should take into account the literature data on the relationship between the structure of molecules and their spectral and thermal properties. An allowance should be made for the possibility of their crystallisation in non-centrosymmetric space groups. It is also advisable to perform in this step crystal packing simulations and a statistical analysis of the structural data on related compounds from CSD.

2. The synthesis of the selected compound and growing of its single crystals suitable for the X-ray crystallographic characterisation. The crystal structure determination and analysis aimed at the exploration of possibilities to obtain a non-centrosymmetric structure. The crystal structure simulation also can prove useful in this step for a more detailed interpretation of the X-ray crystallographic results. The achievable accuracy of crystallographic data gives indirect information on the accessibility of large optical-quality crystals of the compound.

3. The evaluation of components d_{ijk} of the NLO susceptibility tensor within the oriented gas model or supermolecule approximation. This can be done, for instance, using the software code NLOP. The results obtained can be supplemented with experimental measurements of NLO susceptibility on powders, which additionally enables the determination of the synchronism directions and evaluation of the radiation stability of the material.

4. Growing of large optical-quality single crystals of those compounds that successfully passed all the previous steps for the determination of their NLO susceptibility along different crystallographic directions, including the synchronism direction, using the Maker fringe method. Based on the results obtained the final conclusion concerning the potential of the material for NLO applications can be derived.

This review was written with a partial financial support from the Russian Foundation for Basic Research (Project Nos 02-07-90322 and 03-03-32716), the Federal Programme for the Support of Leading Scientific Schools (NSh-1060.2003.3) and the NASA Alliance for Nonlinear Optics (NAG5 6532).

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^a — *J. Exp. Theor. Phys. Lett. (Engl. Transl.)*

^b — *Opt. Spectroscop. (Engl. Transl.)*

^c — *Crystallogr. Rep. (Engl. Transl.)*

^d — *Exp. Theor. Phys. (Engl. Transl.)*

^e — *Russ. Chem. Bull., Int. Ed. (Engl. Transl.)*

Nuclear magnetic resonance studies of translational diffusion in thermotropic liquid crystals

S V Dvinskikh, I Furó

Contents

I. Introduction	497
II. NMR methods for measuring diffusion in liquid crystals	498
III. Theoretical models and computer simulations of diffusion in liquid crystals	500
IV. Experimental studies of diffusion in thermotropic liquid crystals	501
V. Conclusion	504

Abstract. The experimental NMR techniques for studies of translational diffusion in anisotropic systems and the results of their applications to thermotropic liquid crystals are reviewed. The main approaches to the theoretical description and computer simulations of diffusion are discussed. The experimental results are compared with computations. The bibliography includes 194 references.

I. Introduction

Liquid crystals (LC) represent substances that exist, under certain conditions, in a particular state that is intermediate between the solid and liquid states.

Liquid crystals or mesophases are formed by asymmetric rod-like or discotic molecules.¹ Depending on the method of preparation of LC, thermotropic and lyotropic systems are distinguished. The former result from thermal influence on mesogenic solid crystals, while the latter are formed upon dissolution of mesogenic molecules in certain solvents. Liquid-crystalline ordering stems from the anisotropic pair potential among mesogenic molecules. As a result of this interaction, molecules tend to align preferentially along the same spatial direction called a director. Quantitatively, this orientational order is characterised by the order parameter $S = 0.5\langle 3\cos^2\vartheta - 1 \rangle$, where ϑ is the angle between the molecular symmetry axis and the director. Depending on the spatial arrangement of the mesogenic molecules, LC are subdivided into nematic, cholesteric, smectic and columnar phases.¹ Nematics exhibit one-dimensional orientational order. In smectic and columnar phases, in addition to the orientational order, a positional molecular order is present (molecules are arranged to form layered or column-like structures, respectively).

Molecules in liquid crystals exhibit high translational mobility. Combination of spatial ordering of the molecules with their high mobility opens the prospects for the practical applications of

LC, which, in turn, stimulates the interest in fundamental studies of mesophases.^{1–7}

In contrast to isotropic liquids where the self-diffusion is described by a scalar diffusion coefficient D , the translational self-diffusion in LC is characterised by a tensor $\mathbf{D}$.^{8–11} In LC with the axial symmetry, two of the three principal components D_{xx} , D_{yy} , D_{zz} of the diffusion tensor are equal in magnitude.^{11,12} Conventionally, diffusion coefficients $D_{\parallel}$ and $D_{\perp}$ denote diffusion along and perpendicular to the director, respectively.

Diffusion in LC has been studied by a variety of experimental techniques including nuclear magnetic^{8,9,11,13} and electron spin^{14–16} resonances, quasielastic neutron scattering (QENS),^{17–26} forced Rayleigh scattering,^{27–35} optical microscopy^{36–42} and radioactive tracer method.^{43–45} NMR is currently the predominant method in diffusion studies of liquid crystals primarily because in most of the other techniques it is the diffusion of the molecular labels that is measured, which reflects only indirectly the diffusion of the molecular species in LC.

The past decade has witnessed significant advances in the NMR techniques. Novel procedures for the diffusion studies in LC have been developed;^{46–60} that based on the magnetic pulsed field gradient spin-echo technique is unique because it is molecularly selective and requires neither foreign probes nor changing the LC properties.^{61–67} Molecular positions and their changes are encoded by the NMR frequency, which becomes a function of the position in the presence of a magnetic field gradient.

The development of new techniques has allowed much more accurate measurements in a far broader range of diffusion coefficients. This has stimulated studies of ‘difficult’ and less conventional LC phases and determination of the diffusion tensor components in the phase transition region. With these new improved techniques it was also shown that some previous diffusion data were erroneous. New experimental results have motivated the development of new theoretical models and computer simulations of the diffusion process in liquid crystals.

In the present review, the experimental NMR techniques for diffusion studies in thermotropic liquid crystals are considered. The experimental results are compared with those derived from theoretical modelling and computation. The previous exhaustive review of diffusion studies in liquid crystals was published more than 20 years ago by Krüger⁸ and was followed by brief recent surveys^{9,10} and a methodological review.¹¹

S V Dvinskikh Institute of Physics, St Petersburg State University, ul. Ul'yanovskaya 1, 198504 St Petersburg, Russian Federation. Fax (7-812) 428 72 40, tel. (7-812) 428 75 59, e-mail: sdvinskikh@mail.ru

I Furó Department of Chemistry, Royal Institute of Technology, Teknikringen 30/36, SE-10044 Stockholm, Sweden. Fax (46-8) 790 82 07, tel. (46-8) 790 85 92, e-mail: ifuro@physchem.kth.se

Received 17 March 2006

Uspekhi Khimii 75 (6) 557–568 (2006); translated by S V Dvinskikh

II. NMR methods for measuring diffusion in liquid crystals

In ordinary liquids, the NMR spectra consist of narrow lines because anisotropic spin interactions are all motionally averaged to zero due to rapid isotropic tumbling of the molecules. In contrast, in liquid crystals this local motional averaging is incomplete³ and anisotropic spin couplings, such as the dipole–dipole or quadrupole interactions, are averaged to non-zero residual value. Hence, experimental NMR spectra usually exhibit line broadening and splitting. Spectral broadening translates into a quick decay of spin coherences in the time domain, which has a direct detrimental bearing on field-gradient NMR experiments for diffusion.

1. Pulsed-field-gradient NMR experiments

The determination of diffusion in conventional NMR experiments in isotropic liquids usually employs the pulse gradient spin echo (PGSE)^{64–67} or the pulse gradient stimulated spin echo (PGSTE)[†] (Ref. 68) radio-frequency (rf) pulse sequences depicted in Fig. 1. Irrespective of the specific experiment, NMR detects displacement *via* gradient-assisted de- and re-phasing of spin coherences. Diffusion coefficients can be measured only if the spin coherences are sufficiently de-phased by the applied field gradient.

In isotropic liquids, the resulted spin echo amplitude is described by the well-known Stejskal–Tanner^{62,69} expression

$$A(g, \delta, \Delta) \sim \exp \left[-D\gamma^2 g^2 \delta^2 \left(\Delta - \frac{\delta}{3} \right) \right], \quad (1)$$

where g and δ are the strength and the length of the applied gradient pulses, respectively, Δ is the diffusion time (the delay between gradient pulses), D is the self-diffusion coefficient and γ is the gyromagnetic ratio of the observed nuclei.[‡] In anisotropic systems, this expression is modified to accommodate for the diffusion anisotropy [Eqn (2)]:^{11,69,70}

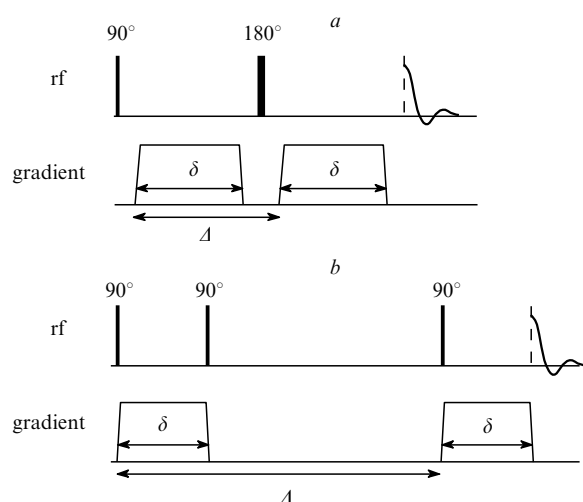


Figure 1. Pulse sequences for conventional pulsed-field-gradient spin echo (a) and stimulated echo (b) NMR experiments; δ is the length of the gradient pulses, Δ is the time delay between the gradient pulses.

[†] In the absence of motion, all de-phased magnetisation can be recovered in the form of echo signal.⁶⁸

[‡] Since dephasing is proportional to γ^2 , the majority of NMR diffusion measurements have been carried out on high- γ nuclei, mainly ^1H .

$$A(g, \delta, \Delta) \sim \exp \left[-\gamma^2 \delta^2 \left(\Delta - \frac{\delta}{3} \right) g D g \right]. \quad (2)$$

The quick decay due to relaxation processes sets an upper limit for the length of applicable gradient encoding/decoding pulses and, thereby, a lower limit for the measurable diffusion coefficients. Whether or not the line broadening can be suppressed depends on the dominant spin interaction and the magnitude of the residual coupling.

2. Spin interactions and the NMR spectral shape

The residual spin interactions depend on the orientation of local LC director with respect to the applied static magnetic field B_0 . If this orientation varies at short distances, spectral splitting by residual couplings may even vanish due to molecular reorientation induced by translational displacement. The director orientation with respect to the direction of the external magnetic field can be homogeneous or randomly distributed in the sample. Low-viscous LC can be prepared in a homogeneous state with the same director orientation all over the sample volume by applying suitable electromagnetic fields. For example, in many nematics the molecular axes orient spontaneously along the field vector in the magnetic field. This is a consequence of the positive anisotropy of the magnetic susceptibility $\Delta\chi = \chi_{\parallel} - \chi_{\perp}$ of molecules ($\chi_{\parallel}$ and $\chi_{\perp}$ are susceptibilities parallel and perpendicular to the director, respectively). The contribution to the free energy

$$\Delta G = -\frac{1}{6} \Delta\chi B_0^2 (3 \cos^2 \vartheta - 1)$$

(ϑ is the angle between the director and the field vector) due to coupling to a magnetic field B_0 is minimised for the director alignment parallel to the field. Although $\Delta\chi$ is relatively small, the collective effect in the bulk sample is sufficient to overcome thermal fluctuations. Such oriented systems are contrasted to ‘powder’ samples with the random angular orientation of the director.

The appearance of the spectrum also depends on the involved spin couplings. The pairwise dipole–dipole interactions usually act in LC among a manifold of nuclei. Hence, even in uniformly oriented LC samples [e.g., in 4-cyano-4'-pentylbiphenyl (5CB)] ^1H NMR spectra of dipole–dipole coupled ^1H nuclei are wide because they consist of many overlapping split lines (Fig. 2).

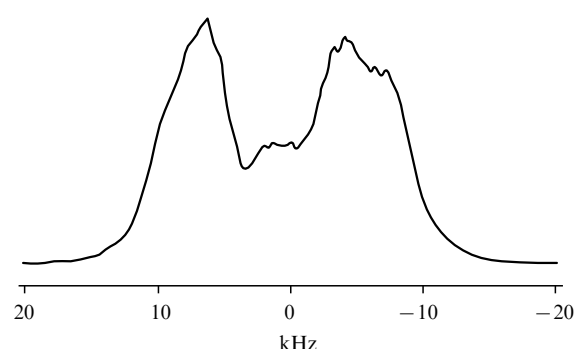
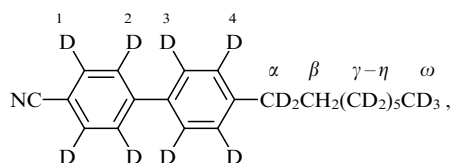


Figure 2. ^1H NMR spectrum of nematic 4-cyano-4'-pentylbiphenyl (5CB).

The exception is LC where the director of a sample is oriented at the ‘magic angle’ ϑ_m to B_0 , since at this condition the splitting and the resulting spectral broadening are suppressed.[§] Single-spin quadrupole interactions for spin $I = 1$ nuclei in a macroscopically

[§] At $\vartheta_m = \arccos(1/\sqrt{3}) \approx 54.7^\circ$ (ϑ_m), the angular factor in the dipole–dipole interaction term is equal to zero; hence, the corresponding contribution to the spectral line width vanishes.

oriented LC may result in spectra split into sharp lines. For example, the ^2H NMR spectrum of partially deuterated 4-cyano-4'-octylbiphenyl (8CB)



consists of quadrupolar split doublets (Fig. 3).

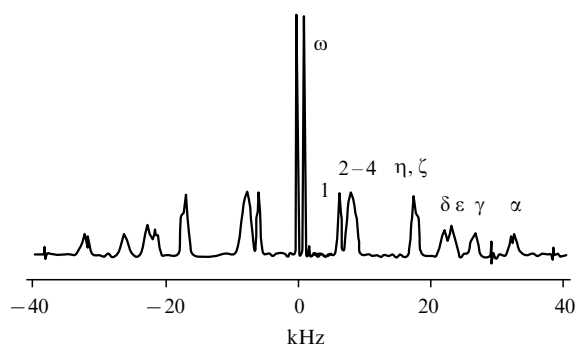


Figure 3. ^2H NMR spectrum of partially deuterated smectic 4-cyano-4'-octylbiphenyl (8CB).

Powder samples exhibit, irrespective of the type of the involved spin interaction (dipole–dipole and quadrupolar), large broadening but often, for the latter case, with a discernible ‘powder pattern’ line shape with the characteristic singularities.⁷¹

3. Measurement of diffusion coefficients in liquid crystals

Diffusion in thermotropic liquid crystals has been addressed by a broad range of NMR techniques,^{8,9,11} including static-field-gradient method,^{47,59,60} as well as various techniques combining pulsed field gradients with a ‘nematic’ echo sequence,^{72–74} multiple-pulse spin decoupling,^{11,49–55,75–77} magic-angle sample orientation,^{46,56–58,73,78–82} deuterium stimulated (alignment) echo,⁵³ soft-pulse excitation⁸³ and multiple-quantum NMR.^{55,84,85} The optimum choice depends on the type of spin interaction, spectral shape and macroscopic sample orientation. Thus, conventional PGSE and PGSTE techniques have been used for weakly oriented solutes in liquid crystalline matrices.^{3,8,86–88}

a. Sample alignment at the magic angle

The simplest and earliest method for the diffusion coefficient measurement involves the preparation of a homogeneously oriented sample, which is then placed by its director at the magic angle (54.7°) with respect to the magnetic field B_0 .⁷⁹ In LC with the uniaxial symmetry of the orientational order, this rotation suppresses the dipole-dipole broadening. The limitation of the method is the required uniform orientation at a given oblique angle to the magnetic field; hence, this technique is not available in liquid-crystalline phases that reorient in the magnetic field or cannot be uniformly oriented. Hence, this approach has mainly been used for studies of viscous smectic phases formed upon cooling of nematic phases.[¶] For nematic phases, the electric field has been employed to hold the director along the magic angle.⁷⁸

In yet another approach, fast switching of the B_0 direction in a field-cycling spectrometer⁴⁶ creates the magic-angle condition. A

late offspring of magic-angle technique, appropriate for studies of unoriented powder-like LC samples, is a diffusion experiment performed under magic angle spinning (MAS) conditions⁸⁹ with the gradient field set along the spinning axis.

b. Suppression of anisotropic spin interactions by echo techniques

In the case of small anisotropic dipole–dipole ($I = 1/2$) or quadrupole couplings ($I = 1$), one may apply the solid or quadrupole echo^{90,91} instead of a conventional spin echo. In some cases, the so-called nematic echo^{92,93} generated in a $90^\circ - \tau - \beta - \tau$ sequence with $\beta < 54.7^\circ$ has been observed in ^1H NMR and employed in diffusion experiment.^{73,74,94} For ^2H NMR experiments, the stimulated echo sequence with modified pulse flip angles has been suggested to suppress the effect of the quadrupolar coupling on the echo amplitude.⁵³

c. Spin decoupling

Line broadening effects for systems of nuclei with $I = 1/2$ are in most cases significant due to homonuclear dipolar interactions. In solids, static dipolar line broadening is usually suppressed by appropriate radio frequency pulse sequences.⁹⁵ The same strategy has been explored for anisotropic diffusion experiments. The problem is that dipolar decoupling sequences perform inefficiently in the presence of a large frequency offset induced by the applied field gradient.⁹⁶ Hence, initially only very short (and, hence, weak due to instrumental limitations) gradient pulses in-between the rf pulses of the homonuclear decoupling sequence have been applied.^{75,76} As a consequence, only relatively fast diffusion could be measured this way. A better choice is to apply magic-echo (Fig. 4)^{53,97} decoupling during evolution periods of the stimulated echo pulse sequence.⁹⁸ In this sequence, longer windows are available for gradient pulses. Magic echo, originally devised to remove multi-spin dipole–dipole coupling, has also been shown to suppress simultaneously static quadrupole effects.⁹⁹ Hence, this strategy has been applied to quadrupolar spins with non-vanishing dipolar couplings.^{53–55} The disadvantage of the experiment is the limited time available for gradient encoding: at most, one-third of the coherence evolution periods.

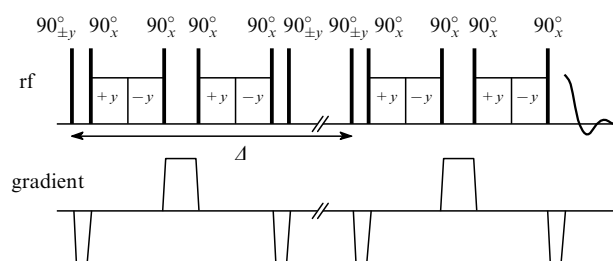


Figure 4. Stimulated echo sequence combined with magic-echo decoupling for measuring diffusion coefficients in the presence of static dipole–dipole and/or quadrupole interactions in LC.⁵³

Decoupling in the presence of uninterrupted gradient pulses^{100,101} is more effective. However such experiments can only be made accurate if the resonance frequency offset effects of decoupling are correctly dealt with. This can be achieved using slice selection by a soft 180° pulse (Fig. 5), which limits the active sample volume to the region with sufficiently small frequency offset.^{49–51} Applied to homonuclei,^{49,51} this strategy suffers from two shortcomings: down-scaling of the gradient by the decoupling sequence, which limits the efficiency of gradient encoding and a decrease in the signal intensity as a result of slice selection. In the case of heteronuclei,⁵⁰ there is no down-scaling of gradient and the slice selection scheme can be ‘multiplexed’ thereby collecting the signal from most of the sample volume.

¶ Once oriented by the magnetic field in the nematic phase and subsequently transformed upon cooling to the smectic state, many samples preserve a homogeneous director orientation even when turned away from B_0 .

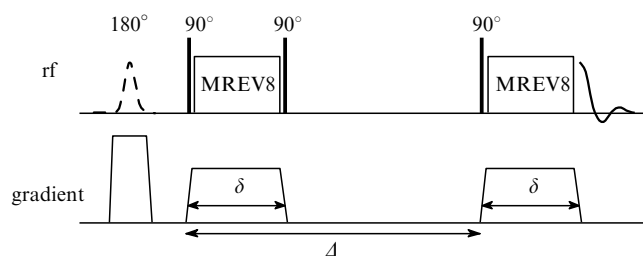


Figure 5. Pulse sequence for diffusion measurements using stimulated echo experiment with homonuclear decoupling (by MREV8 sequence)⁹⁵ applied simultaneously with the field-gradient pulses.⁴⁹

d. Multiple-quantum NMR

An additional possibility, explored not only in the case of $I = 1$ nuclei,⁵⁴ but also in the situation of dipolar coupled spins $I = 1/2$,^{84,85} is to perform an experiment where gradient pulses are employed during the evolution of multiple-quantum spin coherences. The highest-order coherences are not influenced by static quadrupolar and dipolar effects and, hence, exhibit longer decay.¹⁰² As an additional advantage, the field gradient affects higher-quantum coherences proportional to their quantum order thereby increasing the efficiency of gradient encoding/decoding.

e. Strong field gradient

Instead of suppressing line broadening, one may try a ‘brute force’ approach, *viz.*, to increase the strength of the gradient field. One way is to use a small gradient coil in combination with a high-current generator.^{103–111} The other solution is to exploit static gradients such as the one present in the fringe field of a conventional NMR superconducting magnet.^{112,113} The rf pulse sequence in this case is similar to that shown in Fig. 1 b, but with the gradient field constantly present instead of the pulsed gradient.^{47,59,60,114} An obvious disadvantage is small signal-to-noise ratio, which is a consequence of the limited range of excitation of the applied rf pulses and of the spectral broadening by the gradient during detection. Moreover, one cannot conveniently vary the gradient strength and direction.

f. Spectral selective excitation

Spatial slice selection can be replaced by spectral slice selection by long selective rf pulses.⁸³ It has been shown that weak rf pulses can excite sharp proton signals in ^1H NMR spectra of liquid crystals,¹¹⁵ which can be exploited for measurements of their diffusion coefficients.⁸³ Just as for spatial slice selection, the signal loss is a disadvantage of this approach.

g. Relaxation

Diffusion coefficients can be estimated from the NMR spin relaxation rate measurements.^{116–123} An access to diffusion *via* relaxation, however, requires the separation of contributions to the relaxation rates of intra- and intermolecular interactions as well as contributions of different modes of molecular reorientations. The contribution of the intermolecular interaction to spin relaxation processes originates from the modulation of dipole–dipole interactions upon molecular diffusion.^{124–127} Diffusion coefficients extracted from the relaxation data characterise the translational motion on the molecular length-scale in contrast to the micrometre-scale diffusion coefficients obtained by the field-gradient techniques.

h. Spectral shape analysis

Chiral mesophases (cholesterics) exhibit helical spatial modulation of the molecular orientation. If the NMR spectral shape is dominated by the anisotropic spin interactions, the resonance frequency turns out to be spatially encoded even without the application of an external field gradient.^{128–137} Modulation of the spin resonance frequency as a result of molecular diffusion is

reflected in the shape of the NMR spectrum, akin to chemical exchange effects.¹³⁸ Note, this approach can only measure the diffusion component along the modulation direction, *i.e.*, along the helical axis.

4. Accessing the diffusion tensor components

Characterisation of the diffusion tensor $\mathbf{D}$ requires experiments performed at several field gradient orientations with respect to the director. In a homogeneously oriented sample, $D_{\parallel}$ and $D_{\perp}$ can be measured either by using orthogonal gradient coils^{52,53,55,57,58,139} or by changing the sample orientation provided that the director is not re-oriented by the magnetic field.^{46,60,78,82} The other option, applicable in non-oriented samples, exploits the spectral broadening itself by anisotropic spin interactions, such as quadrupole coupling⁹⁰ or chemical shift anisotropy.^{51,140} Since the anisotropic interactions provide correspondence between the spectral resonance frequency and the domain orientation, the intensity decay at different frequencies in the spectrum for just one gradient direction reveals the principal components of the diffusion tensor $\mathbf{D}$.

If diffusion within individual domains of non-oriented powder samples cannot be orientationally assigned (as is typical of the ^1H nuclei), the diffusional decay becomes the composite of decays for different gradient orientations.^{11,141} If the orientational distribution is completely random and other effects, such as restricted diffusion, do not complicate the evaluation, the diffusion tensor can also be extracted either from the composite decay or from diffusion–diffusion correlation (or exchange) experiments using orthogonal field gradient pulses.^{142–144}

III. Theoretical models and computer simulations of diffusion in liquid crystals

1. Diffusion models in nematics

Several theoretical approaches have been developed to describe the translational diffusion in nematic liquid crystals. The hydrodynamic theory of Franklin¹⁴⁵ evaluates the molecular diffusion in terms of viscosity coefficients, friction constants and detailed molecular geometry. Using this approach, the temperature dependence of the anisotropic radio-tracer diffusion in the nematic phase of *p*-azoxyanisole (PAA) was correctly predicted.¹⁴⁵ In contrast, the results obtained for nematic 5CB were found to be incompatible with this model.^{52,55} Since the approach involves many parameters not readily available with sufficient accuracy, its predictions cannot be easily verified by experiments.

In yet another approach, the diffusion coefficients in nematic phases have been derived *via* a parameterised form of the momentum time-autocorrelation function in the system of perfectly ordered clusters and subsequent transformation of the diffusion tensor from the cluster frame to the laboratory frame.¹⁴⁶ The theory relates the components of the diffusion tensor to the molecular geometry (molecular axial ratio) and the order parameter S . It predicts that the arithmetic (isotropic) average of the diffusion coefficient

$$\langle D \rangle_a = \frac{2D_{\perp} + D_{\parallel}}{3} \quad (3)$$

is independent of orientational order and geometry and changes continuously across the nematic–isotropic phase transition. The model has previously been applied with varying success to nematic liquid crystals. Particularly, a satisfactory agreement with the results in PAA was found.¹⁴⁶

Hess and co-workers¹⁴⁷ have applied the affine transformation from the isotropic diffusion of hard spheres to the space of aligned uniaxial ellipsoids to derive the diffusion coefficients in terms of the molecular axial ratio and the phase order parameter. In contrast to the previous approach, the geometric average

$$\langle D \rangle_g = D_{\parallel}^{1/3} D_{\perp}^{2/3} \quad (4)$$

rather than the isotropic average $\langle D \rangle_g$ is predicted to be independent of the molecular shape and order and to coincide at the phase boundary with the diffusion coefficient in isotropic phase. This model has been successfully tested using molecular dynamics computer simulations^{147, 148} and describes well experimental NMR results.^{52, 53}

A mean-field kinetic approach to anisotropic translational diffusion in nematics has also been proposed.¹⁴⁹ Similarly to the affine transformation model, the predicted value of $\langle D \rangle_a$ increases with the increase in the molecular order.

2. Diffusion models in smectics

The diffusion in the smectic A phase has been modelled under the assumption of a periodic temperature-independent potential $V(z)$ along the smectic director^{150–152}

$$V(z) = \frac{V_1}{2} \cos\left(\frac{2\pi z}{d}\right), \quad (5)$$

where d is the layer spacing. Thus, diffusion parallel to the director requires the molecule to overcome not only the viscous drag of the medium, but also the potential barrier. In-layer diffusion remains essentially unaffected. Molecular diffusion along the director is given by the equation

$$(D_{\parallel})^{\text{sm}} = (D_{\parallel})^{\text{nem}} \left[I_0\left(\frac{V_1}{2RT}\right) \right]^{-2}, \quad (6)$$

where I_0 is the modified Bessel function of the first kind and of the zero order. For the non-zero potential amplitude, V_1 , this model predicts a discontinuity of $D_{\parallel}$ at the nematic–smectic A phase transition. This approach has successfully described diffusion data obtained by QENS and NMR methods in some smectic LC with a pronounced discontinuity of $D_{\parallel}$ at the nematic–smectic phase transition.^{8, 94}

Recently,⁵⁵ this model has been modified to include a temperature-dependent potential in the parameterised form:

$$V_1(T) = V_0 \left(1 - \frac{T}{T^*}\right)^{\gamma} \quad (7)$$

in keeping with the temperature dependence of McMillan's smectic order parameter.¹⁵³ The value of the parameter T^* is close to the smectic–nematic transition temperature. This modified model provided a correct description of the experimental results in smectic A phases with a weak second order nematic–smectic phase transition as is typical of systems exhibiting a significant nematic range.^{55, 80, 81}

3. The temperature dependence of the diffusion coefficients

Arrhenius-type descriptions are commonly applied to the temperature dependence of the individual components of the diffusion tensor in liquid crystals.^{8, 9}

$$D_{\parallel, \perp} = D_{\parallel, \perp}^0 \exp\left(-\frac{E_{\parallel, \perp}}{RT}\right). \quad (8)$$

However, the energy parameter E does not have a simple physical meaning in the case of liquid crystals, in contrast to solids where it corresponds to the height of the potential barrier for particle jumping between the lattice sites. The values $E_{\parallel, \perp}$ in mesophases may be dependent on the temperature through the order parameter, especially near the phase transitions.⁵² Thus, although Eqn (8) has often been found to fit well the experimental data recorded in mesophase temperature ranges, the numerical results lack physical interpretation.

4. Computer simulation of the diffusion by molecular dynamics

In molecular dynamics (MD) simulation of diffusion in liquid crystals,^{148, 149, 154–164} the diffusion coefficients were determined either from the mean-square molecular displacements or from the

velocity autocorrelation functions. The results are commonly compared to those predicted based on the affine transformation model and to experimental data.

A non-monotonic temperature dependence of $D_{\parallel}$ in nematic phase was observed,^{148, 164} which was attributed to the competition between a decrease in molecular ordering and mobility. The geometric average of the diffusion coefficient $\langle D \rangle_g$ was found to be continuous and linearly temperature-dependent across the nematic–isotropic phase transition. In contrast, the isotropic average $\langle D \rangle_a$ depends on molecular order,¹⁶⁴ as illustrated in Fig. 6.^{163, 164}

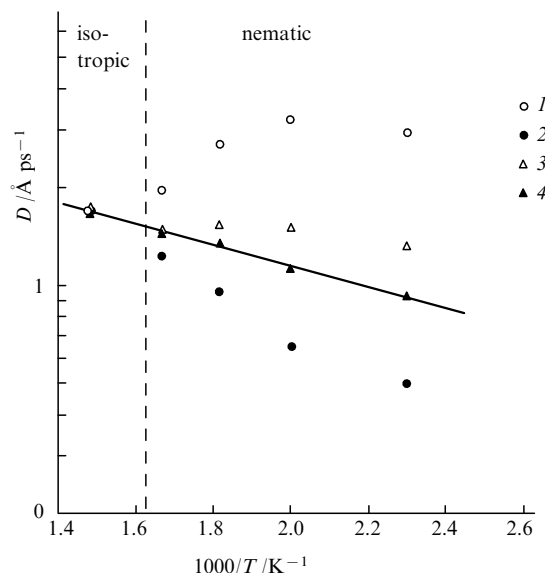


Figure 6. The temperature dependences of the diffusion tensor components and their averages as obtained from MD simulation.¹⁶⁴ (1) $D_{\parallel}$, (2) $D_{\perp}$, (3) $\langle D \rangle_a$, (4) $\langle D \rangle_g$.

Calculations of mean-square displacements were performed in a system of soft-core spherocylinders (cylinders with hemispherical caps) interacting by an inverse-power pair potential.¹⁵⁴ The obtained data showed that, in the smectic A phase, diffusion takes place exclusively along the layer. In an MD simulation of a Gay-Berne mesogen,¹⁶³ $D_{\parallel}$ was shown to change abruptly for the phase sequence isotropic–smectic A, which is characteristic of a first-order phase transition, and $D_{\parallel} < D_{\perp}$. However, if the system also exhibits an extended nematic phase, starting from $D_{\parallel}(\text{smec A}) \approx D_{\parallel}(\text{nem})$ in the vicinity of nematic–smectic A transition, the $D_{\parallel} > D_{\perp}$ nematic property permeates the smectic A phase and may become inverted at lower temperatures. The coefficient $D_{\perp}$ essentially follows the same temperature trend well described by the Arrhenius law over the whole range of smectic and nematic phases. This type of diffusion was observed experimentally in liquid crystals of 8CB.⁵⁵

MD simulation has been performed in the columnar phase of the discotic molecules of hexakis(pentyloxy)triphenylene.¹⁶⁵ The diffusion process exhibited a solid-like jump behaviour in the plane perpendicular to the columnar axis. The translational dynamics of the molecules along the axis was described by the model of column sliding.

IV. Experimental studies of diffusion in thermotropic liquid crystals

Early NMR diffusion experiments in thermotropic nematic^{8, 72, 74, 75, 77, 88, 166} and smectic systems^{8, 73, 76, 79, 80} often merely recorded the fact that the diffusion is anisotropic. The experimental accuracy, reproducibility and the range toward slow diffusion were limited, as has been demonstrated recently

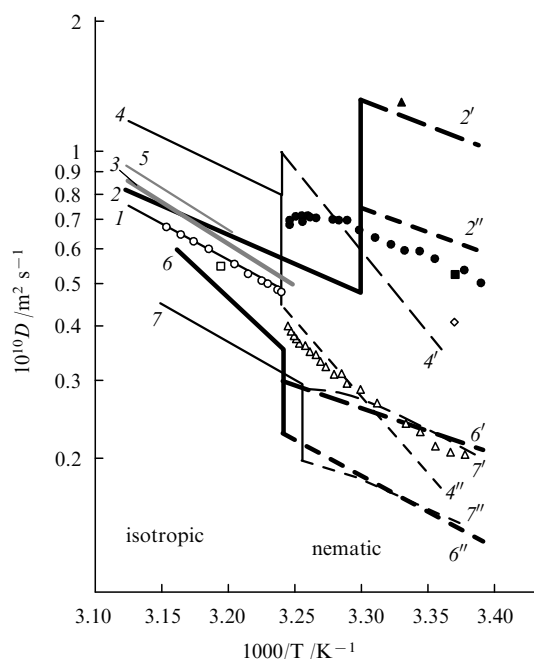


Figure 7. Data on anisotropic diffusion in 5CB as obtained by spin-decoupling-based NMR diffusion experiments ($\circ$ — D_{iso} , $\bullet$ — $D_{\parallel}$, Δ — $D_{\perp}$),⁵² in comparison with the results obtained by other techniques: PGSE NMR [(1) D_{iso} ,¹⁶⁷ [(2) D_{iso} , (2') $D_{\parallel}$, (2'') $D_{\perp}$];¹⁶⁸ fringe-field NMR (3) D_{iso} ,¹⁶⁹ field cycling NMR [(4) D_{iso} , (4') $D_{\parallel}$, (4'') $D_{\perp}$];⁴⁶ PGSE NMR with the sample reorienting in the electric field [(5) D_{iso} , $\blacktriangle$ — $D_{\parallel}$];⁷⁸ forced rayleigh scattering [(6) D_{iso} , (6') $D_{\parallel}$, (6'') $D_{\perp}$];²⁷ [(7) D_{iso} , (7') $D_{\parallel}$, (7'') $D_{\perp}$];³⁵ QENS ($\square$ — D_{iso} , $\blacksquare$ — $D_{\parallel}$, $\diamond$ — $D_{\perp}$).¹⁹

(Fig. 7).⁵² The early works performed up to 1982 have been comprehensively reviewed by Krüger,⁸ and hence are only briefly recalled here.

A parameter that can be measured with the acceptable accuracy is the activation energy, since it may be obtained from the strong temperature dependence of the diffusion coefficient. The values of the activation energies $E_{a\parallel} \approx E_{a\perp}$ that have been obtained in nematic liquid crystals were comparable to those in isotropic phases. In smectics, the relationships $E_{a\parallel} > E_{a\perp}$ and $E_{a\perp}(\text{smec}) \approx E_{a\perp}(\text{nem})$ have generally been observed, which is consistent with the model of in-layer continuous diffusion in liquids and a jump process between the layers typical of solids.

The diffusion anisotropy $D_{\parallel}/D_{\perp}$ in nematic phase ranges between 1.2 and 4. Within the experimental accuracy, the values of the majority of average diffusion coefficients $\langle D \rangle_a$ in the nematic phase at the clearing point determined earlier were close to the isotropic diffusion coefficients. The ratio $D_{\parallel}/D_{\perp}$ in smectics was found to vary in a wider range from $D_{\parallel}/D_{\perp} \geq 1$ to $D_{\parallel}/D_{\perp} \ll 1$.

1. Diffusion in nematic and cholesteric phases

Nematic phases were frequently chosen for testing new techniques for the determination of diffusion coefficients in liquid crystals, the nematic phase of 5CB being the most popular model compound. Recently, the diffusion coefficients in 5CB obtained by different methods have been compared (see Fig. 7).⁵² While earlier results strongly disagree, obviously due to methodological problems, more recent studies by advanced NMR techniques, including multiple-pulse-decoupling PGSTE,^{52,55} fringe-field-gradient stimulated echo⁴⁷ and spectral-slice-selection PGSTE⁸³ demonstrate a good agreement.

The most accurate values of the diffusion tensor components in 5CB over a wide temperature range (Fig. 8) have been obtained by multiple-pulse-decoupling PGSTE NMR.^{52,55} The temperature dependence of the diffusion coefficient D_{iso} in the isotropic

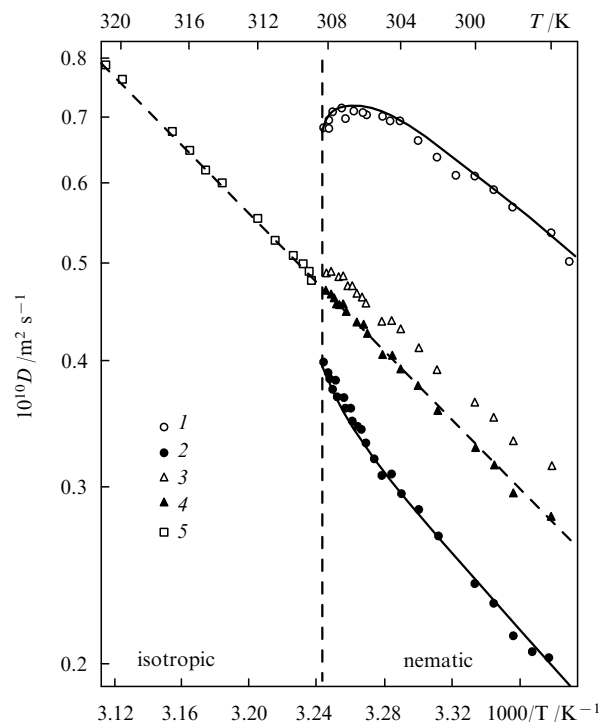


Figure 8. Values of $D_{\parallel}$ (1), $D_{\perp}$ (2), $\langle D \rangle_a$ (3), $\langle D \rangle_g$ (4) and D_{iso} (5) in 5CB obtained by multiple-pulse spin-decoupling-based NMR experiment.⁵² Solid lines are the fits by the affine transformation model.¹⁴⁷

phase is described with high accuracy by the Arrhenius equation. Although the temperature dependence of both $D_{\parallel}$ and $D_{\perp}$ in the nematic phase at the points far from the nematic–isotropic phase transition can be approximated by the Arrhenius-type relationship (with the activation energies $E_{a\parallel} < E_{a(\text{iso})} < E_{a\perp}$), the two curves $D_{\parallel}(T)$ and $D_{\perp}(T)$ converge fast toward the isotropic value closer to the phase transition. This suggests that the anisotropy of the translational diffusion reflects the orientational ordering of the molecules, which decreases sharply on approaching the isotropic phase. The temperature dependence of the isotropic average $\langle D \rangle_a$ [see Eqn (3)] also deviates from the simple Arrhenius relationship in the vicinity of the phase transition. At the phase transition, there is an appreciable discontinuity between D_{iso} and $\langle D \rangle_a$. This behaviour contradicts that predicted from a model of a momentum time-autocorrelation function used for the diffusion coefficient calculations.¹⁴⁶ In contrast, calculations using the affine transformation model¹⁴⁷ are consistent with experimental results. In particular, the values of the geometric average $\langle D \rangle_g$ [see Eqn (4)] are on the line extrapolated from the isotropic phase. An analogous behaviour was observed in the nematic phases of 8CB (Refs 53, 55) and *N*-(4-ethoxybenzylidene)-4'-butylaniline (EBBA)⁵⁵ where the same types of multiple pulse techniques were employed.

Diffusion measurements have been performed in 4-(*n*-octyl-oxy)-4'-cyanobiphenyl (8OCB) and 4,4'-di-(*n*-octyl)azoxybenzene (OAB) using fringe-field-gradient NMR.^{59,60} The temperature dependences of $D_{\parallel}$ in the nematic phase and at the isotropic–nematic phase transition resemble that in 5CB and 8CB. Since the temperature dependences of the $D_{\perp}$ component of the diffusion tensor were not measured and since the nematic phase in OAB exists in a limited temperature range, no comparison with the theoretical models was performed.

The temperature dependences of the principal components of the diffusion tensor were reported for homologous series of di(alkyl)azoxybenzenes and (alkoxy)cyanobiphenyls^{46,82} using the field-cycling technique. A characteristic alternation of diffusion coefficients and activation energies as functions of the chain

length, *i.e.*, the familiar odd-even effect, has been observed. Unexpectedly, it was found⁸² that both $D_{\parallel}$ and $D_{\perp}$ were larger than D_{iso} , which is probably due to systematic errors caused by methodological problems.

An anomalous temperature dependence[†] of the components of the diffusion tensor was also found in nematic 4-pentylphenyl 2-chloro-4-(4-pentylbenzoyloxy)benzoate.¹⁰⁰ This behaviour is most probably an artefact due to interference between the heteronuclear decoupling and the field gradient as discussed in Ref. 50.

Conventional PGSTE NMR has been applied for studying the diffusion behaviour in a cholesteric phase formed by 5CB doped with an optically active chiral component, *viz.*, 4-cyano-4'-(2-methyl)butylbiphenyl (CB15).¹⁶⁸ The orientation of molecules in a cholesteric phase corresponds to that in the nematic phase with the director helically twisted in space. The pitch axis of the twisted structure is aligned perpendicular to the direction of the magnetic field of a spectrometer. This experiment demonstrates the existence of the translational diffusion anisotropy (ratio $D_{\parallel}/D_{\perp} \approx 1.7$) with the diffusion coefficients dependent on the diffusion time.

In a number of diffusion studies in cholesteric phases, NMR spectral shape analysis has been used, which allowed measurement of only $D_{\perp}$, *i.e.*, diffusion along the pitch axis. It was shown that $D_{\perp}$ increases with pitch length and depends on the diffusion time.^{128–130} The Arrhenius-type temperature dependence was commonly observed with apparent activation energies close to those in nematic phases and with relationship $D_{\perp} < D_{\text{iso}}$ at the clearing temperature (Fig. 9).^{128, 131}

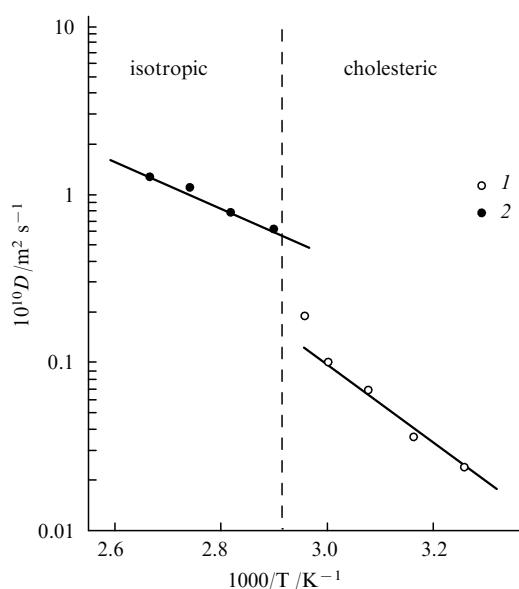


Figure 9. The temperature dependence of the diffusion coefficients in the isotropic and cholesteric phases of a mixture of substituted phenylbenzoates and chiral dopants.¹³¹ (1) $D_{\perp}$, (2) D_{iso} .

While diffusion coefficients in the isotropic phases of liquid-crystalline compounds commonly display simple Arrhenius-type temperature dependences,^{47, 52, 55, 167, 169–174} accurate measurements performed in the vicinity of the isotropic–nematic phase transition on the isotropic side indicated a noticeable deviation from this conventional behaviour.^{106, 175} This effect has been attributed to the formation of locally ordered nematic clusters (cybotactic groups) in isotropic surroundings.

[†] The experimental values of the activation energies in this nematics were related as $E_{\parallel} > E_{\perp}$, which is not typical of nematics.

2. Smectic phases

Smectics A exhibit high molecular mobility within the layers comparable to that in conventional liquids. Diffusion anisotropy in smectics typically becomes $D_{\parallel}/D_{\perp} < 1$,^{8, 57, 76, 79} as opposed to that in nematics. At the nematic–smectic phase transition, $D_{\perp}$ changes nearly continuously, while $D_{\parallel}$ and its apparent activation energy change abruptly as a result of molecular jumps between adjacent smectic layers.^{8, 55, 60} However, smectic A materials that exhibit a broad temperature range of the nematic phase display a different behaviour (Fig. 10): for them, the nematic-like relationship $D_{\parallel}/D_{\perp} > 1$ is typically found in the vicinity of the phase transition point.^{55, 56, 58, 59, 81} Upon cooling deeper into the smectic phase, the diffusion ratio may change to the opposite, more common for smectics.^{59, 73} As concerning the activation energies, the relation $E_{\parallel} \geq E_{\perp}$ is always fulfilled.

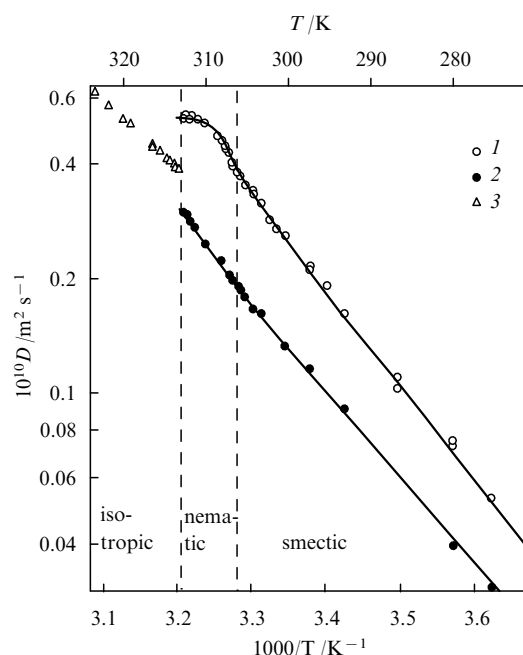


Figure 10. The temperature dependences of the diffusion coefficients in isotropic, nematic and smectic A phases of 8CB.⁵⁵ Lines are fits by the affine transformation model¹⁴⁷ in the nematic phase and by a model with a temperature-dependent periodic potential in the smectic A phase.^{55, 150} (1) $D_{\parallel}$, (2) $D_{\perp}$, (3) D_{iso} .

Fringe-field-gradient stimulated echo has been applied¹¹⁴ to measure the diffusion coefficients in different smectic A, C* and C_A* phases[‡] of the liquid crystal of 1-methylheptyl 4'-[4-(n-decyl-oxy)benzoyloxy]biphenyl-4-carboxylate. A continuous decrease in the diffusion coefficient in the direction of the layer normal was observed in smectic A and C* phases, while an abrupt decrease by nearly two orders of magnitude was found on the transition to C_A* phase. Similarly, slow interlayer diffusion in smectic C_A* phase compared to phase C* has been detected using ²H NMR spectral shape analysis.^{137, 176} This finding was explained by steric effects arising from the anticlinical molecular arrangement in adjacent layers, which hinder the interlayer diffusion.

Experimental results obtained in smectic A phases^{55, 59, 60} have been compared to the available theoretical models. Some results⁵⁹ were consistent with the model developed by Volino *et al.*,^{150, 151} which predicts an abrupt decrease in $D_{\parallel}$ at the transition from nematic or isotropic phases to smectic A phases (Fig. 11).

[‡] C* and C_A* are chiral smectic phases C with synclinically and anticlinically ordered molecules, respectively.

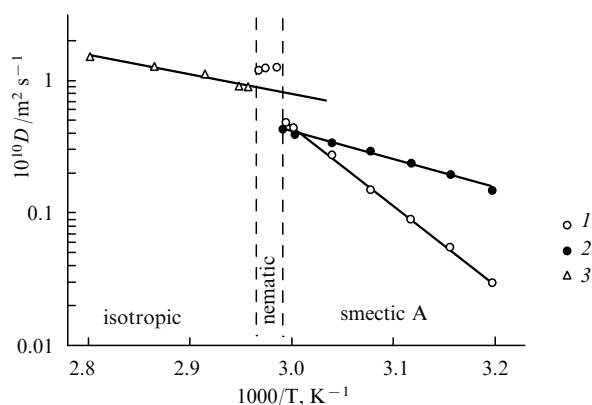


Figure 11. Diffusion coefficients of OAB obtained in the isotropic, nematic and smectic A phases.⁵⁹ (1) $D_{\parallel}$, (2) $D_{\perp}$, (3) D_{iso} .

However, for systems with a weak second-order nematic-to-smectic phase transition, a model with the temperature-dependent potential (see Eqn 7 and Fig. 10) should be assumed for the analysis of the experimental data. The behaviour of 8CB⁵⁵ and 8OCB⁶⁰ was correctly described in that way.

3. Columnar phases of discotic molecules

In contrast to conventional thermotropics built by rod-like mesogenic units, columnar phases are formed by discotic flat molecules.¹⁷⁷ For the columnar hexagonal phase of a discotic thermotropic hexapentylxytriphenylene, it was shown that the diffusion is very slow⁵⁴ in contrast to early indications.¹⁷⁸ The diffusion in the direction perpendicular to the columnar axes was measured by ^2H PGSTE NMR. A low magnitude of the diffusion coefficient [$D_{\perp} = (1-4) \times 10^{-14} \text{ m}^2 \text{ s}^{-1}$] and a high activation energy ($E_{\perp} = 115 \text{ kJ mol}^{-1}$) suggested solid-like or, perhaps, collective diffusion mechanisms in discotics.⁵⁴

4. Polymeric liquid crystals

Anisotropic diffusion with the relationship $D_{\parallel} > D_{\perp}$ relative to the α -helical chain axis and with apparent activation energies dependent on the main-chain length has been observed in LC phases formed by rod-like polypeptides.¹⁷⁹⁻¹⁸¹ In the polymeric LC phase formed by flexible poly(diethylsiloxane) molecules, the diffusion was found to be faster than that in the isotropic phase.¹⁸² This was attributed to a decrease in the degree of entanglement between the polymer chains that become orientationally correlated in the anisotropic phase.¹⁸²

5. Liquid crystals confined in porous media

The effect of confinement on the diffusion properties of LC embedded in porous glass matrices (with the pore size varied from 7.5 to 140 nm) was studied for the nematic 5CB as an example.⁴⁷ A strong decrease in the diffusion coefficient with the decrease in the pore size was observed. The PGSE NMR measurement of self-diffusion in nematic EBBA confined in porous glasses was used to estimate the size of the nematic clusters in the isotropic pre-transition region adjacent to the nematic phase.¹⁰⁶

6. Diffusion of small solute molecules in mesophases

Due to their low orientational order, small organic molecules dissolved in liquid crystals exhibit long decays of spin coherences. Therefore, conventional PSGE or PGSTE experiments can be used to assess their diffusion coefficients.^{8, 14, 72, 86, 87, 183-189} In nematic phases, the solute diffusion is fast and the diffusion anisotropy is small, as compared to the diffusion of molecules forming a mesophase.^{8, 9} This contrasts the strong translational diffusion anisotropy $D_{\parallel}/D_{\perp} \ll 1$ observed in smectic phases.⁸

Recently, the diffusional behaviour of xenon in liquid crystals has been studied in detail.¹⁹⁰⁻¹⁹⁴ PGSE ^{129}Xe NMR has been used to probe diffusion of xenon dissolved in nematic^{190, 191, 194} and smectic (A and C*) phases.¹⁹²⁻¹⁹⁴ No diffusion anisotropy and very weak anisotropy ($D_{\parallel}/D_{\perp} > 1$) were observed in the nematic phases of ZLI-1132¹⁹⁰ and EBBA/ZLI-1167,¹⁹¹ respectively. In contrast, significant anisotropy was found in smectic phases of ferroelectric liquid crystals, where $D_{\parallel}/D_{\perp} \ll 1$.^{192, 193}

V. Conclusion

A number of new diffusion techniques applicable to liquid crystals have been developed during the past decade. In contrast to techniques applied for isotropic liquids, these advanced approaches with various degrees of sophistication have not yet become routine tools. However, when applied with insight, the new techniques provide much higher accuracy and significantly extend the range of the accessible diffusion coefficients.

Self-diffusion data provide detailed and easily interpreted information on the molecular organisation and dynamics in mesophases. The anisotropic diffusion tensor and the activation energy in liquid crystals are very sensitive to structural changes at the phase transitions. Observing the changes in components of the diffusion tensor at the phase transitions allow a thorough evaluation of, and discrimination among, the theoretical models as well as the assessment of the computer simulation data. For conventional thermotropic phases, such as nematics and smectics A, the accurate diffusion data obtained with advanced NMR methods are well understood in terms of available theoretical models. For other systems, including highly ordered columnar and smectic phases generally exhibiting slow diffusion, only limited data are available as yet.

This work was supported by the Russian Foundation for Basic Research (Project Nos 04-03-32639 and 05-08-50280) and by the Swedish Research Council VR.

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^a — *Colloid. J. (Engl. Transl.)*

Metal derivatives of tetrazoles

P N Gaponik, S V Voitekhovich, O A Ivashkevich

Contents

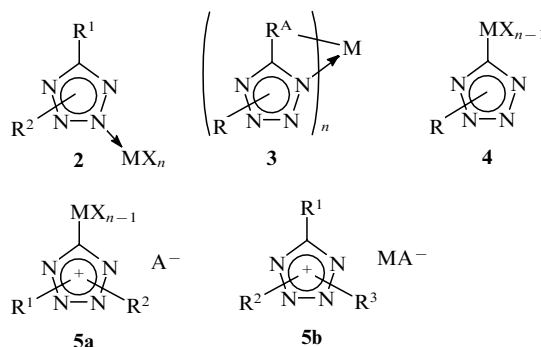
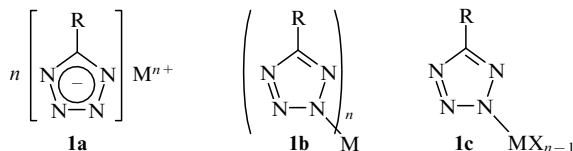
I. Introduction	507
II. Metal derivatives of unsubstituted and 5-substituted tetrazoles	508
III. Metal derivatives of neutral <i>N</i> -substituted tetrazoles	520
IV. Metal derivatives of <i>C,N</i> -substituted tetrazoles generating anionic centres in the substituent	525
V. Applications of metal tetrazole derivatives	531
VI. Conclusion	533

Abstract. Published data on the synthesis, structure, properties and applications of metal derivatives of tetrazoles are generalised and described systematically. Compounds based on the anionic and neutral tetrazole forms, *C*- and *N*-mono- and *C,N*-disubstituted tetrazoles are considered. The bibliography includes 464 references.

I. Introduction

In recent years a new direction has been developed in the tetrazole chemistry, which has appeared at the border with inorganic chemistry and is related to the synthesis and studies into the structure and properties of metal tetrazole derivatives (MT). This is due to the practical and theoretical significance of these unique compounds and diversity of their properties, depending on both the nature of the metal atom and the functional groups attached to the tetrazole ring.

Tetrazoles are a peculiar class of heterocyclic compounds exhibiting properties of both acids and bases.^{1–3} Therefore, they can exist in neutral, anionic and cationic forms. The metal atom (M) in MT can be bound to the heterocycle by a covalent, ionic or coordination bond or can be incorporated into a neutral molecule, anion or cation. When considering the enormous array of existing data in terms of these peculiar features, one can distinguish several main types of MT (**1**–**5**) (R^A is the substituent generating the anionic centre, X is an inorganic or organic ligand, A is the anion, MA is the metal-containing anion).



Compounds **1a,b** are formed upon deprotonation of 5-substituted tetrazoles and, in the case of alkali and alkaline earth metals, are mainly ionic (**1a**). For other metals, a more or less covalent bond of the type **1b** is formed; this also occurs for mixed-ligand complexes (**1c**). Compounds **2** are π -complexes in which neutral mono- and disubstituted tetrazoles are present as ligands. A separate type of MT is represented by chelates **3** formed by *C*- and *N*-substituted tetrazoles in which substituents generate the anionic centre. The metal atom in MT **4** and **5a** is directly linked to the carbon atom of the tetrazole ring, while in tetrazolium salts **5b**, the metal is a part of the anion.

Owing to the availability and good prospects for the practical use, derivatives of types **1**–**3** are most studied. And only in the last decade, more than 300 relevant papers were published. However, numerous data on the synthesis, structures and properties of these compounds have not been described systematically as yet. Data on transition metal compounds of tetrazoles and tetrazolate anions published before 1987 have been surveyed.⁴ Two reviews devoted to complexes of 1,5-disubstituted tetrazoles⁵ and thermo- and photochromic iron(II) complexes with 1-alkyltetrazoles⁶ have been published. In addition, a recent review⁷ devoted to organo-metallic complexes of azoles contains some data on the tetrazole derivatives.

The purpose of the present review is to describe systematically and generalise the existing data on the synthesis, structure, properties and applications of MT of types **1**–**3** prepared using anionic and neutral forms of unsubstituted and *N*-substituted tetrazoles. Organometallic compounds **4** and tetrazolium compounds **5**, which are somewhat different and much less studied, are beyond the scope of the review. However, judging from the latest publications, the attention to these derivatives increased owing to

P N Gaponik, S V Voitekhovich, O A Ivashkevich Research Institute for Physical Chemical Problems of the Belarusian State University, ul. Leningradskaya 14, 220050 Minsk, Belarus. Fax (37-517) 226 46 96, tel. (37-517) 209 51 91, e-mail: gaponik@bsu.by (P N Gaponik), tel. (37-517) 209 51 98, e-mail: azole@tut.by (S V Voitekhovich), tel. (37-517) 209 52 54, e-mail: fhp@bsu.by (O A Ivashkevich)

Received 6 September 2005

Uspekhi Khimii 75 (6) 569–603 (2000); translated by Z P Bobkova

the prospects of their use in organic synthesis⁸ and analytical chemistry.^{3,9}

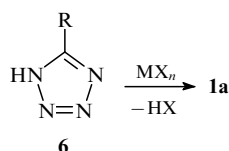
The information is systematised according to the type of tetrazole that forms MT, because the structure of the tetrazole derivative, *i.e.*, the presence, positions and the nature of substituents in the ring, determines the formation of metal–tetrazole bonds of different nature and, hence, dictates the methods used to synthesise the MT. The attention is focused on the synthetic aspects and applications of MT. Structural features and properties of MT are also discussed.

II. Metal derivatives of unsubstituted and 5-substituted tetrazoles

5-Substituted tetrazoles are the most readily available tetrazole derivatives.^{1–3,10} This accounts for the considerable interest in them as the starting compounds in the synthesis of MT. Due to their unique structures and properties, tetrazoles of this type form diverse metal derivatives; the methods of their synthesis can be divided into two groups. The first one includes the reactions of 5-substituted tetrazoles with bases, metal salts or other metal-containing compounds and transformations of the MT formed. Due to acidic properties of 5-substituted tetrazoles, the pK_a of which ranges from -0.8 to 6 depending on the nature of substituent R ,^{1–3,11,12} it is possible to prepare salts **1a** and similar metal derivatives **1b,c**. In some cases, tetrazoles are not deprotonated, complexes **2** ($R^2 = H$) being formed with involvement of the lone pair of the tetrazole nitrogen. The second group of methods comprises heterocyclisations of linear polynitrogen structures with metal salts or complexes; this gives metal derivatives **1a–c**.

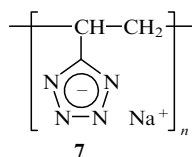
1. Synthesis of metal derivatives from tetrazoles

The reactions of 5-substituted tetrazoles **6** with bases (alkali and alkaline earth metal hydroxides,^{13–18} alkoxides^{19–25} or hydrides^{16,26}) afford tetrazolates **1a**. In most cases, the reaction is carried out in water, ethanol or acetonitrile, and the resulting salts are often used for subsequent transformations without isolation from the reaction medium.

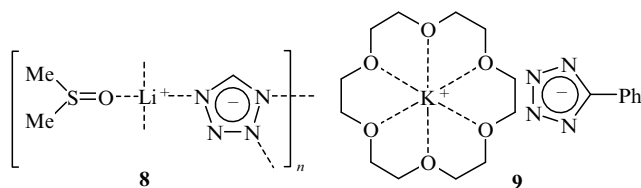


M is alkali or alkaline earth metal; $X = H, OH, OAlk$.

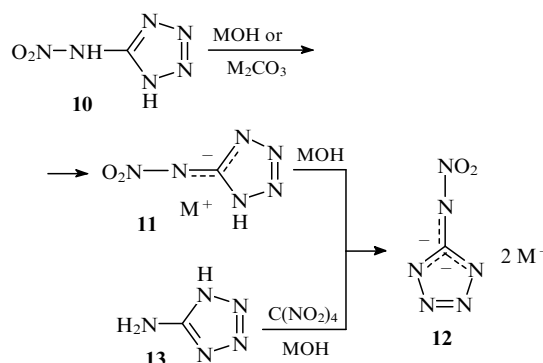
This reaction is also suitable for the synthesis of poly(5-vinyl-tetrazole) (PVT) salts. However, the reaction in water or ethanol does not proceed to completion despite an excess of the base.²⁷ In other organic solvents, sodium poly(5-vinyltetrazolate) (**7**) with a metal content of 99.9% of the stoichiometric amount was obtained.²⁸



In the presence of complex-forming compounds, this reaction may give salts with a more intricate composition. In particular, the reaction of tetrazole with lithium hydroxide in DMSO afforded lithium tetrazolate **8**, incorporating a DMSO molecule, in 33% yield.²⁹ Treatment of 5-phenyltetrazole with potassium hydride and 18-crown-6 in THF at room temperature gave 5-phenyltetrazolate of the potassium complex with 18-crown-6 (**9**) in 94% yield.²⁶ The structures of compounds **8** and **9** were determined by X-ray diffraction analysis.

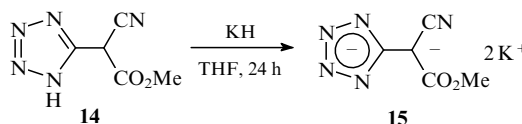


The substituent at the heterocycle carbon atom can also exhibit acidic properties; in this case, the tetrazole forms salts of different types. For instance, 5-nitraminetetrazole (**10**) is converted into salts **11** and **12** containing singly and doubly charged tetrazole anions, respectively.^{30–33} According to X-ray diffraction data, in caesium³¹ and lithium (hydrate)³³ salts **11**, the negative charge is delocalised over the anion. Salts **12** are often prepared using more readily available 5-aminotetrazole (**13**) instead of tetrazole **10**. Upon nitration with polynitro compounds in the presence of an alkali, compound **13** is converted into 5-nitraminetetrazolate(2–) salts (**12**) (yields 68%–91%).³⁰

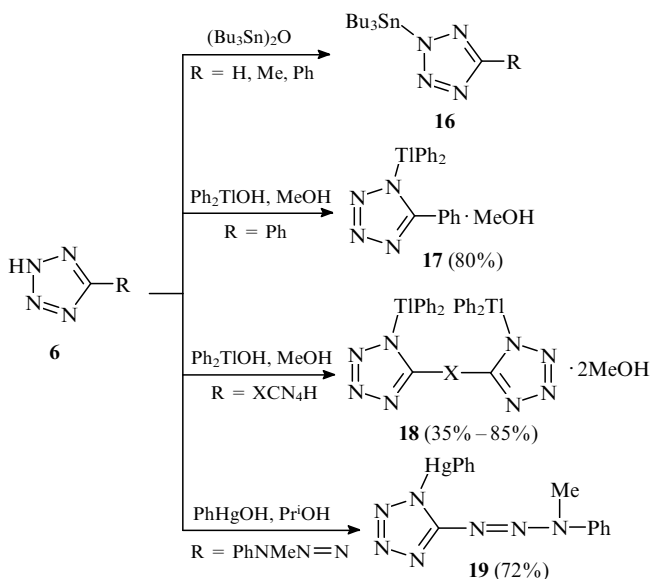


$M = Li, Na, K, Rb, Cs$.

5-Substituted tetrazole **14** reacts with potassium hydride as a dibasic acid to give dipotassium salt **15** in a quantitative yield.³⁴



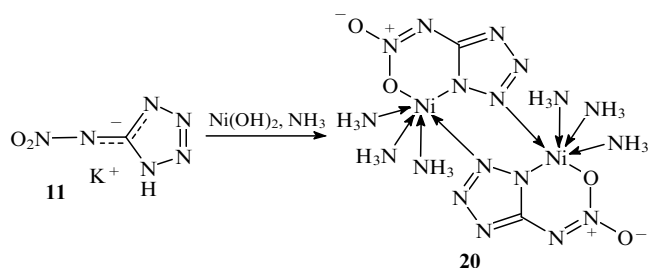
A series of MT **1c** have been prepared by the reaction of 5-substituted tetrazoles **6** with organometallic bases and oxides, in particular, tributyltin oxide^{1,2} and diphenylthallium²¹ and phenylmercury¹ hydroxides dissolved in lower alcohols. MT **16–19**



$X = 1,3-C_6H_4, (CH_2)_n$ ($n = 1, 2, 4$).

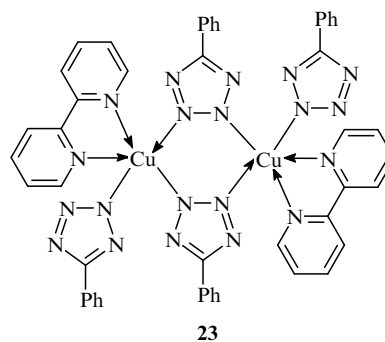
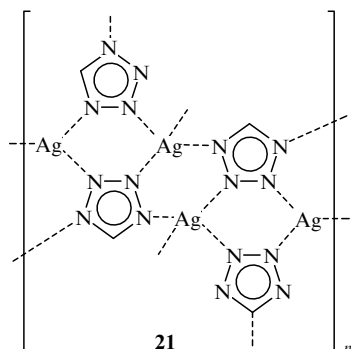
obtained in this way may have more complex structures in the crystalline state due to the additional coordination of the metal atom to the tetrazole ring. According to X-ray diffraction data, compound **17** is a dimer formed through the N(1),N(2)-binding of the tetrazole ring to the metal atom, and MT **18** [$X = (CH_2)_4$] is polymeric owing to the tridentate coordination of the heterocycle by the N(1), N(2), N(3) atoms to different metal atoms.²¹

The use of the methods to prepare compounds **1b**, where M is a transition metal, is virtually unexplored. The reaction of 5,5'-bitetrazole with copper(II) oxide or copper(II) basic carbonate gave³⁵ copper(II) bitetrazolate. These reactions proceed more smoothly in the presence of ammonia or ethylenediamine, which are incorporated into the final product.^{35–37} Thus the reaction of potassium 5-nitraminotetrazolate (**11**, $M = K$) with nickel(II) hydroxide in aqueous ammonia furnished triammine(5-nitraminotetrazolato)nickel(II) (yield 80%) having dimeric structure **20** according to X-ray diffraction data.³⁷

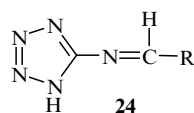


The reaction of tetrazoles **6** with metal chlorides, sulfates, acetates and other salts is a convenient method for the preparation of MT **1b**. Due to poor solubility, the target compounds are formed on mixing aqueous or aqueous ethanolic solutions of reactants at room temperature. This procedure was used to prepare silver (**21**)³⁸ and copper(II) tetrazolates³⁹ and nickel(II) and copper(II) 5-vinyltetrazolates⁴⁰ having a stoichiometric composition. Due to the possibility of inclusion of a reagent into the final product, the composition of the resulting salt depends on the starting reactant ratio. In particular, tetrazole reacted with excess silver nitrate to give the double salt $2 Ag(HCN_4) \cdot AgNO_3$ (**22**).³⁸

According to X-ray diffraction, the structure of tetrazolate **21** is a 3D network of three- and four-coordinate silver ions linked by tri- and tetradentate tetrazolate ligands. In salt **22**, the silver atoms are two- and three-coordinate, while the tetrazole ring is linked to the metal atoms through four nitrogen atoms. The Ag–N bond lengths in these compounds are in the range of 2.197(4)–2.410(4) Å.³⁸ Note that participation of all four nitrogen atoms of the tetrazole ring in metal coordination is a rare case. This coordination mode has also been found recently by X-ray diffraction analysis in the structure of copper(I) 5-methyltetrazolate.⁴¹ More often, the tetrazolate anion acts as a bidentate bridging ligand or a monodentate ligand. According to X-ray diffraction data, both types of coordination exist in the mixed-ligand copper(II) complex **23**, prepared by the reaction of 5-phenyltetrazole with copper acetate in aqueous ethanol in the presence of 2,2'-bipyridine.⁴²

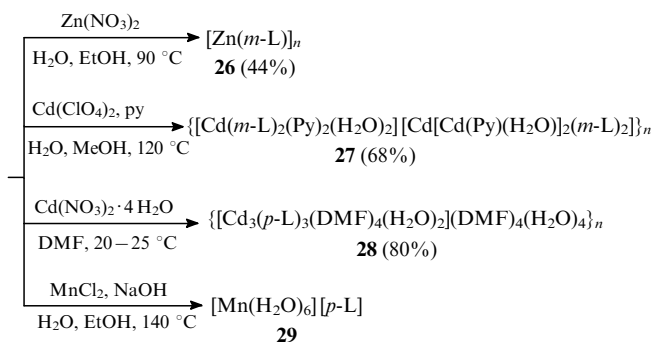
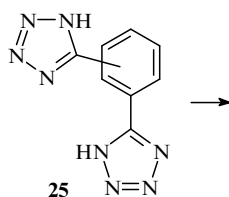


The reaction of salts MX_2 ($M = Cu, Cd, Zn$; $X = Cl, OAc$) with Schiff bases **24** in methanol resulted in the complexes $M(HL)_2(MX_2)_n$, where $n = 0–2$, HL is the singly deprotonated ligand, and the complexes ML, where L is the doubly deprotonated ligand. The diversity of compositions of the complexes obtained is due to the ability of metal atoms to substitute the hydrogen atoms in the tetrazole ring and the hydroxy group, polydentate nature of the heterocycle and participation of the azomethine group in the coordination, as indicated by IR spectroscopic data.⁴³



$R = 2,4\text{-Cl}_2\text{C}_6\text{H}_3, 2\text{-MeO-}3,5\text{-Cl}_2\text{C}_6\text{H}_2, 2,4\text{-(MeO)}_2\text{C}_6\text{H}_3, 4\text{-Me}_2\text{NC}_6\text{H}_4, 2\text{-HOC}_6\text{H}_4, 2\text{-HO-}5\text{-BrC}_6\text{H}_3, 2\text{-HO-}5\text{-NO}_2\text{C}_6\text{H}_3.$

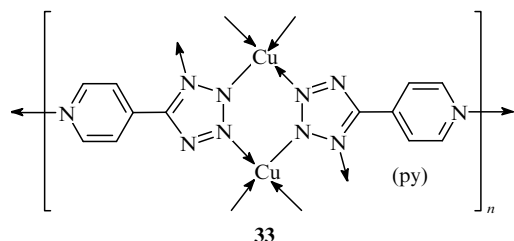
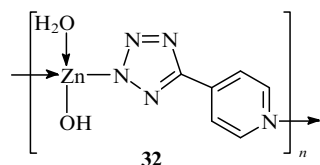
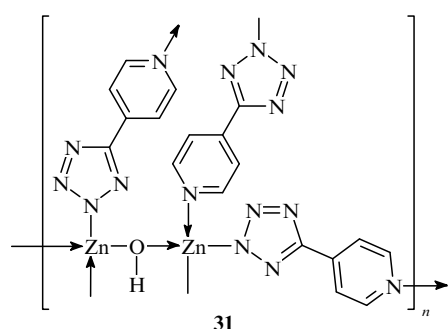
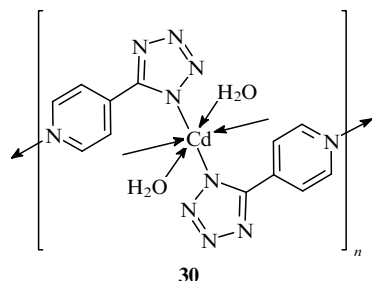
Depending on the reaction conditions, *meta*- and *para*-5,5'-phenyleneditetrazoles **25** react with Cd, Zn and Mn(II) salts to give essentially different, as regards both composition and structure, complexes **26**, **27**,⁴⁴ **28**,⁴⁵ **29**.⁴⁶ The structures of compounds **26–29** were determined by X-ray diffraction. Compounds **26–28** in which the doubly charged anions derived from tetrazole **25** function as bridges are two- and three-dimensional coordination polymers. Conversely, compound **29** is a mononuclear aqua complex containing no metal–tetrazole coordination bond. In the structure of complex **28**, one-dimensional channels were found which occupy up to 35% of the void volume and encapsulate tetrameric cyclic water clusters and DMF molecules. On heating to 150 °C, water and DMF are removed from the channels, which accounts for the interest of researchers in this type of compound for the preparation of inclusion compounds and sorbents. A coordination polymer with a composition similar to complex



$L = N_4CC_6H_4CN_4.$

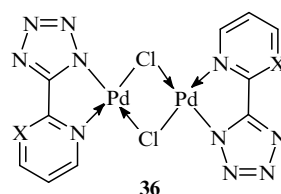
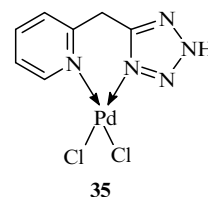
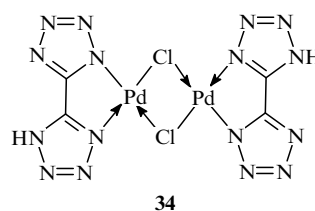
26 is formed upon the reaction of 3-(tetrazol-5-yl)benzoic acid with zinc chloride under hydrothermal conditions.⁴⁷

The 5-(4-pyridyl)tetrazole anion also acts as a bridging ligand forming two-dimensional coordination polymers **30–32** upon the reaction with Cd⁴⁸ and Zn⁴⁹ ions under hydrothermal conditions. The products were characterised by X-ray diffraction. Under the same conditions, Cu(II) ions are reduced and the process ends in the formation of Cu(I) complex **33**, having a 3D structure.⁴⁹



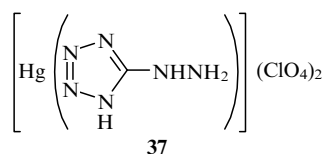
The high thermal stability, insolubility in most of solvents and photophysical properties of complexes **28** and **30–33** induce interest in these compounds as promising fluorescent materials.^{45, 48, 49}

Not only derivatives of tetrazolate anions **1b** can be isolated as the reaction products of 5-monosubstituted tetrazoles with transition metal salts, but also complexes **2** containing the molecular form of tetrazoles. This is true first of all for palladium salts. Unlike copper(II) and nickel(II) chlorides, palladium(II) chloride reacts with 5-vinyltetrazole in water⁴⁰ or chloroform⁵⁰ to give the molecular complex Pd(CH₂=CH–CN₄H)₂Cl₂. However, 5,5'-bitetrazole and 5-monosubstituted tetrazoles containing a pyridyl or pyrimidyl group react under the same conditions to give complexes **34–36** in which the tetrazole ring occurs in the anionic or neutral form.⁵¹

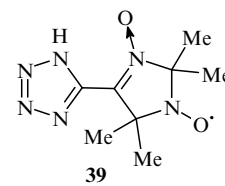
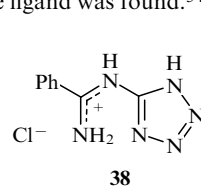


X = CH, N.

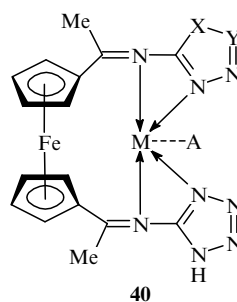
The preparation of nv-complexes of neutral 5-substituted tetrazoles with other metal salts has been reported. In particular, the synthesis of compound **37** by the reaction of mercury(II) salts or oxide with 5-hydrazinotetrazole in aqueous perchloric acid has been described.⁵²



A complex of *N*-(tetrazol-5-yl)benzamidine hydrochloride (**38**), viz., CoLCl₂ (L is ligand **38**),⁵³ and complexes of 2,2,5,5-tetramethyl-4-(tetrazol-5-yl)-3-imidazole-1-oxyl 3-oxide (**39**),⁵⁴ viz., NiLCl₂(H₂O) and CuLCl₂ (L is ligand **39**), have been prepared. According to IR spectroscopy, diffuse reflectance spectroscopy and magnetochemical measurements, neutral ligands in these complexes are coordinated in the bidentate mode, namely, by a nitrogen atom of the tetrazole ring and either the amidine nitrogen atom (compound **38**) or the oxygen atom of the N→O group (compound **39**). In the complexes of tetrazole **39**, weak interaction between the unpaired electrons of the metal and the ligand was found.⁵⁴

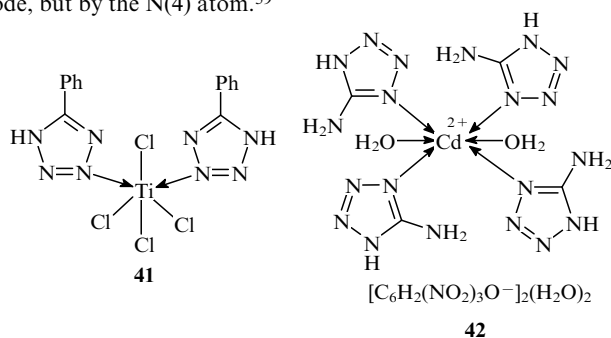


Refluxing in ethanol of divalent metal salts with Schiff bases prepared from 1,1'-diacetylferrocene, 5-aminotetrazole or some other azoles gives rise to MT having apparently chelate structure **40** in which the metal atom can be additionally coordinated by the anion.^{55–57}



X–Y = SCH, NHCH, NHN; M = Co, Cu, Ni, Zn;
A = NO₃, SO₄, C₂O₄.

Note that in the studies cited above,^{40, 50–57} involvement of the molecular form of 5-substituted tetrazoles in the coordination was proposed relying on the results of spectroscopic studies and chemical analysis. X-Ray diffraction data confirming the existence of complexes of neutral tetrazoles have been obtained only for compounds **41**⁵⁸ and **42**.⁵⁹ Complex **41** in which 5-phenyl-tetrazole is coordinated by the metal ion through the N(3) atom has been prepared in 94% yield by the reaction of the ligand with titanium(IV) chloride at room temperature. Studies of the mass spectra of this complex and its behaviour in a THF solution indicate that the tetrazole ligand is bound rather weakly to the metal ion; this restricts the suggested use of compound **41** for the synthesis of titanium nitride.⁵⁸ In complex **42** obtained by the reaction of 5-aminotetrazole with cadmium picrate on heating in water, neutral tetrazole is also coordinated in the monodentate mode, but by the N(4) atom.⁵⁹



Poly(5-vinyltetrazole) behaves with respect to metal salts like monomeric 5-substituted tetrazoles. It reacts with nickel(II) and copper(II) chlorides in water to give the salts $[M\{\text{CH}_2\text{CH}(\text{CN}_4)\}_2]_n$, while with palladium chloride, molecular complexes $[\text{Pd}\{\text{CH}_2\text{CH}(\text{CN}_4\text{H})\}_3\text{Cl}_2]_n$ are formed.⁴⁰ The reaction of poly(5-vinyltetrazole) with excess copper(II) nitrate is accompanied by a decrease in the solution pH to give a water-insoluble complex containing three tetrazole fragments per metal ion.⁶⁰ A specific feature of the complexation of PVT with copper(II) ions is the formation of complexes, under certain conditions, with a high local concentration of copper stabilised by both coordination bonds and hydrogen bonds between the tetrazole units. The mutual strengthening of these bonds results in the cooperative stabilisation of the whole system.⁶¹ The reaction of PVT with chromium(III) chloride is accompanied by a slight decrease in pH; this gives soluble complexes in which the chromium atom coordinates both the tetrazole ring and water molecules.⁶² A method for the synthesis of iron poly(5-vinyltetrazole) complex from the monomer has been reported.⁶³ Some of the Fe^{2+} ions arising upon electrochemical dissolution of an iron electrode (with potassium

peroxydisulfate as the electrolyte) form a redox system, $\text{Fe}^{2+} - \text{S}_2\text{O}_8^{2-}$, which initiates the radical polymerisation of 5-vinyltetrazole; other Fe^{2+} ions interact with the tetrazole ring as complex-forming agents. This yields the polymer $[\text{Fe}\{\text{CH}_2\text{CH}(\text{CN}_4)\}_2]_n$ insoluble in water or organic solvents.

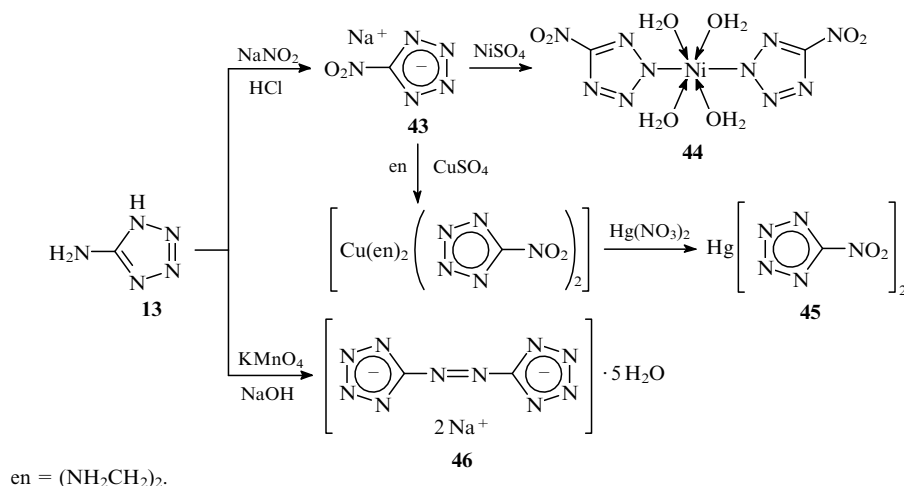
The replacement of neutral tetrazole in the reactions with transition metal salts by water-soluble ammonium and alkali or alkaline earth metal tetrazolates rules out the possibility of formation of complexes **2** and is used successfully for the synthesis of MT **1b**. This method was employed to prepare silver 5-nitroaminotetrazolate (**12**, $\text{M} = \text{Ag}$),⁶⁴ a number of fluorine-containing silver tetrazolates $\text{Ag}(\text{RCN}_4)$, where $\text{R} = \text{CF}_3$, NF_2CF_2 , NF_2CFCl , and transition metal tetrazolates $\text{Ni}(\text{RCN}_4)_2 \cdot 2\text{MeOH}$, $\text{Cu}(\text{RCN}_4)_2 \cdot 2.5\text{MeOH}$ and $[\text{Fe}(\text{RCN}_4)\text{Cl}] \cdot \text{MeOH}$, where $\text{R} = \text{NF}_2\text{CF}_2$.⁶⁵ The transformation of 5-aminotetrazole (**13**) via sodium salts **43** or copper salts and the 5-nitrotetrazolate anion afforded nickel(II) (**44**)⁶⁶ and mercuric (**45**)⁶⁷ 5-nitrotetrazolates (Scheme 1). The presence of inner-sphere water and the monodentate mode of coordination of the tetrazolate anion in complex **44** were established by X-ray diffraction analysis.

Sodium 5,5'-azoditetrazolate pentahydrate (**46**),⁶⁸ which is also readily prepared from tetrazole **13**, serves as a convenient starting compound for the synthesis of other 5,5'-azoditetrazolates. Recently, a large group of 5,5'-azoditetrazolates of other alkali and alkaline earth metals, aluminium, yttrium, some lanthanides (La, Ce, Nd, Gd),⁶⁹ and thallium(I)²¹ have been synthesised by this method (as hydrates) and characterised by X-ray diffraction analysis. It is noteworthy that these compounds easily eliminate water even at room temperature. This makes the salts sensitive to friction or impact; therefore, handling these salts requires special care.⁶⁹

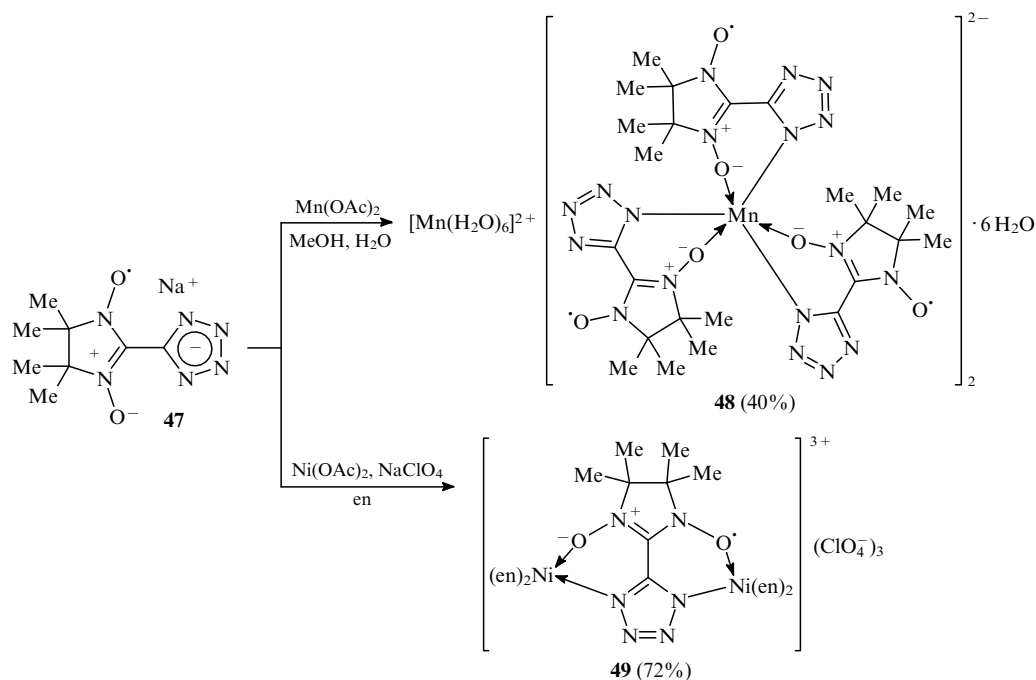
The reaction of sodium salt of 2-(tetrazol-5-yl)-4,4,5,5-tetramethyl-4,5-dihydroimidazol-1-oxyl 3-oxide (**47**) with manganese(II) and nickel(II) acetates gave ionic complexes **48** and **49** (Scheme 2) in which (according to X-ray diffraction data) the paramagnetic tetrazolate anion acts as a bidentate chelating or bridging ligand. Due to intermolecular hydrogen bonds, these complexes form high-dimensional heterospin structures whose magnetic properties are of obvious interest.⁷⁰

A number of neutral water-soluble highly stable gadolinium(III) **50**, **51** and zinc **52** complexes with 5-(2-pyridyl)- and 5-(2-pyridyl 1-oxide)tetrazoles have been prepared by the reactions of metal salts with potassium or barium tetrazolates obtained *in situ* from tetrazoles and the corresponding carbonates in water. Compounds **50–52** were prepared in 48%–76% yields. According to X-ray diffraction data, in these complexes tetrazoles are bidentate ligands forming stable five- and six-membered chelate rings. In gadolinium compounds **50**, **51**, the second coordination sphere includes additional water molecules, which

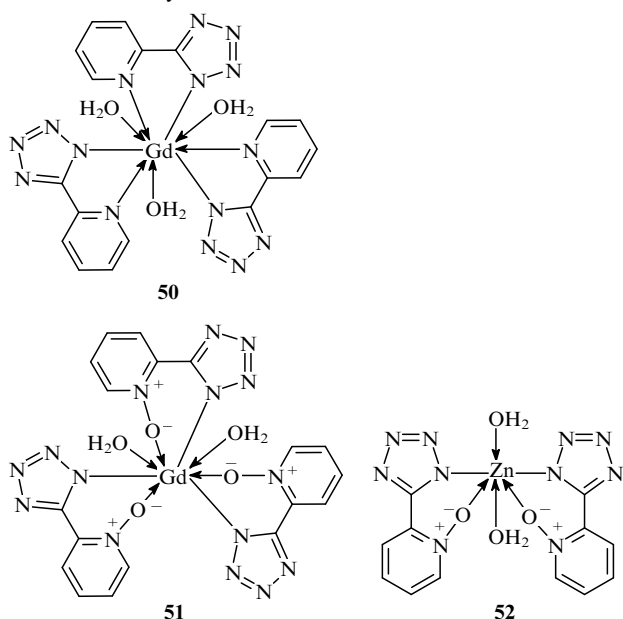
Scheme 1



Scheme 2

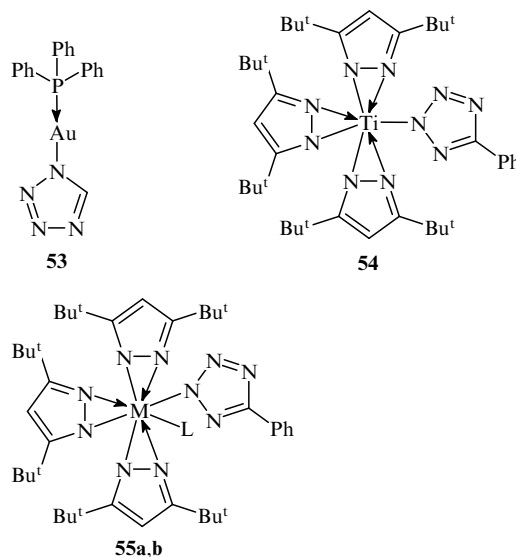


makes the complexes readily soluble and provides high proton relaxation ability.⁷¹



Synthesis of MT by the reaction of 5-R-tetrazolates with transition metal salts is of interest due to the fact that the resulting compounds are capable of subsequent transformations involving the initial tetrazolate. In particular, cobalt(II) and nickel(II) nitrates react with sodium 5-R-tetrazolates in aqueous solutions to give metal tetrazolates as the solid phase, which is gradually dissolved on treatment with excess 5-R-tetrazolate anion. The dissolution is accompanied by an increase in the solution viscosity and gives rise to water-soluble polymers. The rate of dissolution depends substantially on the nature of substituent R; in particular, it increases in the order $\text{NH}_2 < 4\text{-MeC}_6\text{H}_4 < \text{CH}=\text{CH}_2 < \text{Ph} < \text{H} < \text{Bu} < \text{Et} < \text{Me}$. In the case of $\text{R} = \text{NO}_2$, CF_3 , the process stops after the formation of solid products insoluble in an excess of the ligand. Presumably, polymeric complexes are formed in the case of azoles with $\text{p}K_{\text{a}}$ and $\text{p}K_{\text{BH}^+}$ values in the 3.5 to 12 and -4 to 5 ranges, respectively.⁷²

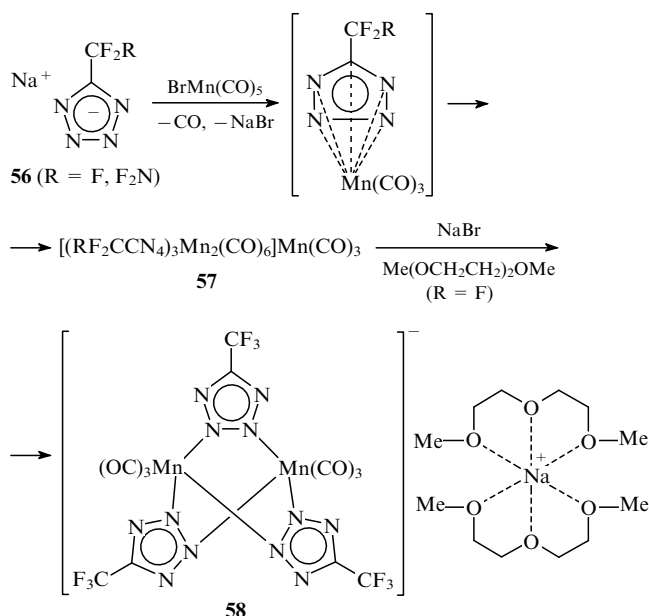
The tetrazolate anion has a fairly high nucleophilicity and can replace some groups in coordination compounds; this is used for the synthesis of mixed-ligand complexes. In these processes, the tetrazolate anion is introduced in the reaction as alkali metal tetrazolates or is generated *in situ* from 5-R-tetrazole and a base. The ligand being replaced is, most often, a halogen atom. The reaction of complex $[\text{AuCl}(\text{PPh}_3)]$ and tetrazole in the presence of sodium hydroxide in acetone according to this synthetic protocol gave complex 53 in 52% yield.⁷³ The reaction of chlorotris(3,5-di-*tert*-butylpyrazolato)titanium(IV) with sodium 5-phenyltetrazolate in THF (23°C , 48 h, 74%) resulted in tris(3,5-di-*tert*-butylpyrazolato)-5-phenyltetrazolatotitanium(IV) (54). The replacement of two chlorine atoms in analogous niobium(V) and tantalum(V) dichloride complexes requires more drastic conditions (refluxing), and in the latter case, only one chlorine atom is substituted despite the use of excess tetrazolate.⁷⁴ According to X-ray diffraction data, the tetrazole ring in the resulting complexes 53–55 is coordinated as a monodentate ligand.



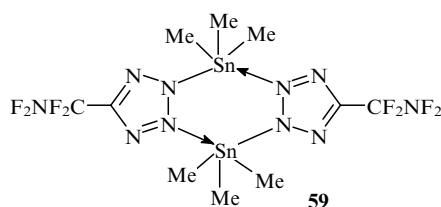
$\text{M} = \text{Nb}$, $\text{L} = 2\text{-(5-phenyltetrazolato)}$ (a); $\text{M} = \text{Ta}$, $\text{L} = \text{Cl}$ (b).

When sodium 5-perfluoroalkyltetrazolates 56 react with (pentacarbonyl)bromomanganese, the bromide ion and some of the

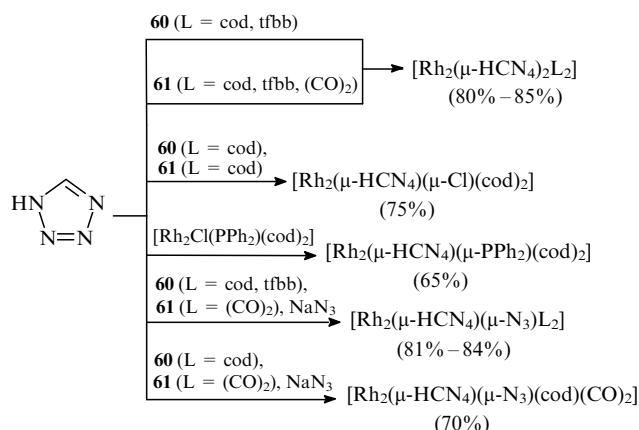
carbon monoxide molecules are substituted. On the basis of IR spectroscopic data, it was assumed that the tetrazolate anion forms a π -complex in solution, which is transformed into σ -complex **57** upon removal of the solvent. Attempts to grow single crystals of the obtained compounds from a diglyme solution in the presence of sodium bromide resulted in ionic complex **58** (for $R = F$) with the N(2),N(3)-bridging bidentate coordination of the heterocycle (X-ray diffraction data).⁷⁵



A similar bridging bidentate coordination of the tetrazole ring has been proposed on the basis of mass spectrometry and ^{19}F and ^1H NMR spectroscopy for complex **59** synthesised by the reaction of silver 5-(difluoroamino)difluoromethyltetrazolate with Me_3SnCl in THF.⁶⁵



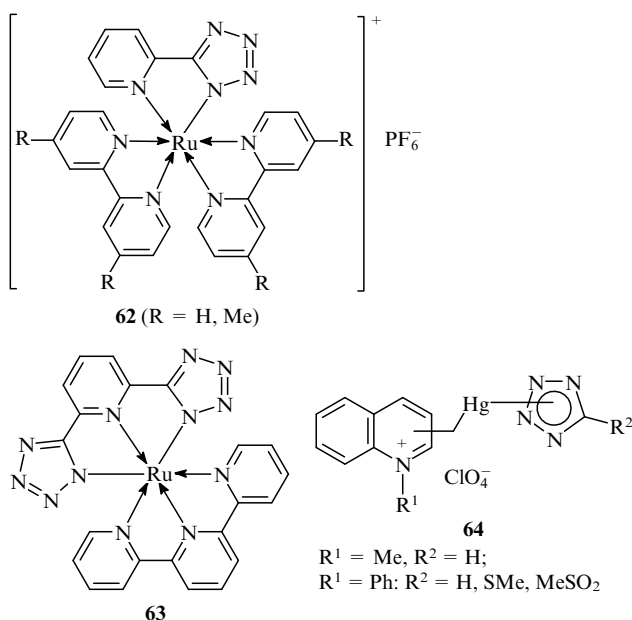
A series of homo- and heterobridged rhodium complexes with the tetrazolate anion and other ligands have been prepared by replacement of the chloride ions or acetylacetonate molecules in rhodium diene compounds $[\text{RhCl}_2\text{L}_2]$ (**60**), $[\text{Rh}(\text{acac})\text{L}]$ (**61**), *et al.*^{76,77}



cod is cycloocta-1,5-diene; tfbb is tetrafluorobenzo[5,6]bicyclo[2.2.2]octa-2,5,7-triene.

These reactions of tetrazole with rhodium compounds readily proceed at room temperature in the presence of triethylamine, and in the case of rhodium acetylacetonate, no base is required. However, in the synthesis of the complex with a bridging diphenylphosphide group, the best results are attained with lithium tetrazolate. The resulting compounds are of interest for the synthesis of trinuclear complexes, for example, $[\text{Rh}_3(\mu_3\text{-HCN}_4)(\mu\text{-Cl})\text{Cl(CO)}_6]$, which represent (according to X-ray diffraction data) unusual examples of metal–metal interaction; the tetrazolate anions in these complexes are bound in the tridentate bridging mode.⁷⁶

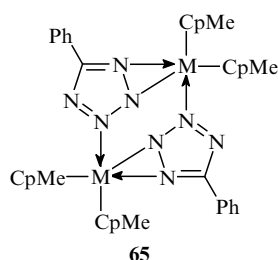
Similarly, the substitution of 5-(2-pyridyl)tetrazole and 2,6-bis(tetrazol-5-yl)pyridine for chlorine in the complexes RuL_2Cl_2 (L is 2,2'-bipyridine, 4,4'-dimethyl-2,2'-bipyridine)⁵¹ and $\text{Ru}(\text{tpy})\text{Cl}_3$ (tpy is 2,2':6',2''-terpyridine)⁷⁸ gave ruthenium-containing tetrazoles **62** and **63** in 55%–84% yields. The UV-spectroscopic and electrochemical studies have shown that the introduction of a tetrazolyl group having strong σ -donor properties into the $\text{Ru}(\text{tpy})\text{Cl}_3$ complex results in destabilisation of the ground energy state and decreases the metal oxidation potential.



This is also accompanied by a decrease in the emission energy and an increase in the luminescence time from 1 to 80 ns.⁷⁸

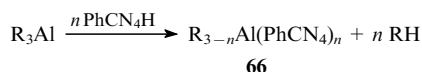
The 5- R -tetrazolate anion replaces the acetoxy group in 2- and 4-mercuriomethylquinolinium salts. The ^1H NMR characteristics of compounds **64** prepared in this way in 76%–96% yields indicate that only one N -isomer is formed in each case; however, the available data are insufficient for assigning the reaction products to either N(1)- or N(2)-isomeric tetrazoles.²⁴

The presence of an active hydrogen atom in 5-substituted tetrazoles accounts for their ability to replace the alkyl and cyclopentadienyl groups in organometallic compounds susceptible to hydrolytic decomposition. For example, 5-phenyltetrazole replaces one methylcyclopentadienyl ligand in $(\text{CpMe})_3\text{M}$, where $\text{CpMe} = \eta\text{-C}_5\text{H}_4\text{Me}$, $\text{M} = \text{Yb, Er}$, at room temperature to give binuclear complexes **65** in 60%–78% yields. According to X-ray diffraction data, the phenyltetrazolate anion in these complexes is coordinated by three nitrogen atoms as a bridging and chelating ligand.⁷⁹ Attempts to prepare a similar praseodymium complex failed: complete substitution took place to give the salt $\text{Pr(PhCN}_4)_3$. For $\text{M} = \text{Dy or Gd}$, the reaction gave crystals of complexes containing, apart from the methylcyclopentadienyl ligand, a cyclopentadienyl ligand, the formation of which was attributed to the presence of a small amount of cyclopentadiene in the starting methylcyclopentadiene.



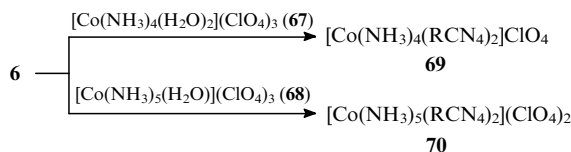
M = Yb, Er.

In the case of trialkylaluminium, the reaction smoothly proceeds in toluene and, depending on the reactant ratio, may give the substitution products of the 5-phenyltetrazolate anion for one, two or three alkyl groups, *viz.*, compounds **66**.⁸⁰



R = Me, $n = 1-3$; R = Et, Buⁱ, $n = 1$.

Yet another possibility of MT synthesis is provided by displacement of neutral ligands (water, THF, ammonia) from various complexes. Water present as a ligand in cobalt(III) ammine complexes **67** and **68** is bound weaker to the central atom than the ammonia molecules and can be easily replaced by the tetrazolate anion. This underlies the preparation of cobalt(III) tetra- (**69**) and pentaammine (**70**) complexes, which contain a metal-coordinated 5-substituted tetrazole ring.⁸¹⁻⁸⁷

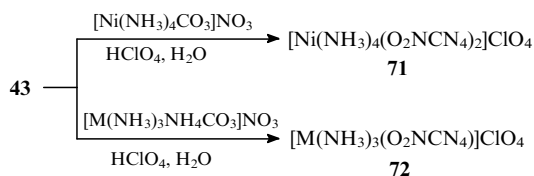


R = H, Me, NH₂, NO₂, CH₂N₃, C(NO₂)₃, (NNO₂⁺)(NH₄⁺), Ph,

3-NO₂C₆H₄, [X = NH₂, NO₂, N₃, (NNO₂⁺)(NH₄⁺)].

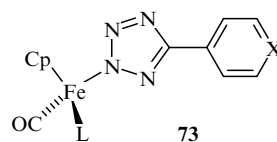
In the case of 5-phenyl-⁸² and 5-(3-nitrophenyl)tetrazoles,⁸⁵ compounds [Co₂(NH₃)₈(RCN₄)(H₂O)₂](ClO₄)₅ · n H₂O, where R = Ph, 3-NO₂C₆H₄, were isolated in addition to the expected complexes **69**. With microwave heating, 5-phenyltetrazole replaces not only water in complex **67**, but also the ammonia molecule to give compound [Co(NH₃)₃(PhCN₄)₃].⁸² More readily available precursors of cobalt(III) aqua ammine complexes, *viz.*, tetraamminecarbonatocobalt salts,^{81, 83, 84, 86} are often used in these syntheses instead of the Co(III) complexes themselves.

Compounds **71** and **72** [M = Cu(II), Zn(II)] potentially useful as initiating explosives were prepared from similar ammine complexes of other metals.⁸⁸



M = Cu, Zn.

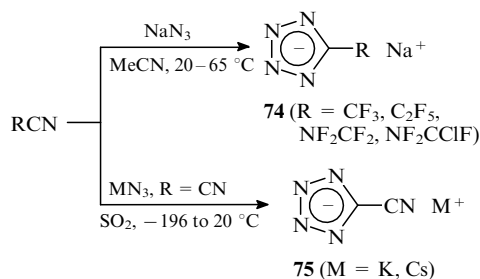
5-(4-Pyridyl)tetrazole⁸⁹ and 5-(4-cyanophenyl)tetrazole⁹⁰ react with the complexes [CpFe(CO)L(THF)]CF₃SO₃ in the presence of triethylamine. They replace the coordinated THF molecule to give compounds **73** containing, according to ¹H and ¹³C NMR spectroscopy, a Fe—N(2) σ-bond.



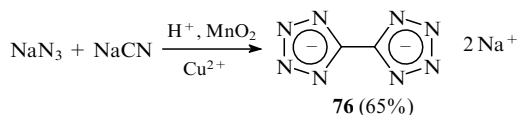
L = CO, PPh₃, P(OMe)₃; X = N, CCN; Cp = η-C₅H₅.

2. Synthesis of metal derivatives of tetrazoles by heterocyclisation

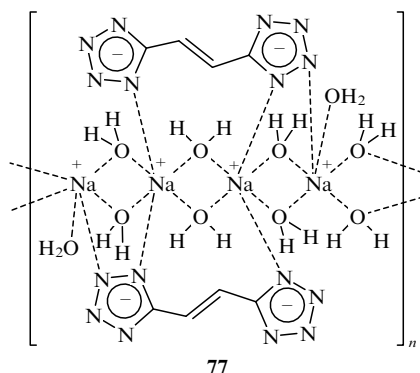
Among heterocyclisation reactions, [3 + 2]-cycloaddition of azides to systems containing C≡N bonds is most significant for the synthesis of tetrazoles.^{1-3, 10} This method allows one to prepare both 5-substituted tetrazoles and their metal derivatives.⁹¹ The starting compounds include nitriles and organic or inorganic azides, in particular, sodium or ammonium azide prepared *in situ*. Sodium azide, like other alkali metal azides, is less reactive than ammonium azide and reacts only with activated nitriles containing electron-withdrawing substituents. The reaction occurs smoothly at room temperature or on moderate heating to give 5-R-tetrazolates **74**^{65, 75, 92} and **75**⁹³ in quantitative yields.



Salt **47** containing a paramagnetic anion has been obtained in a somewhat lower yield (77%) by treatment of the appropriate nitrile with a mixture of sodium azide and ammonium chloride in DMF.⁷⁰ An attempt to prepare caesium 5,5'-bitetrazolate from dicyanogen and excess caesium azide was unsuccessful.⁹³ 5,5'-Bitetrazole salts, in particular, sodium salt **76**, can be synthesised by the reaction of sodium cyanide and azide with manganese dioxide in the presence of copper(II) salts.¹³

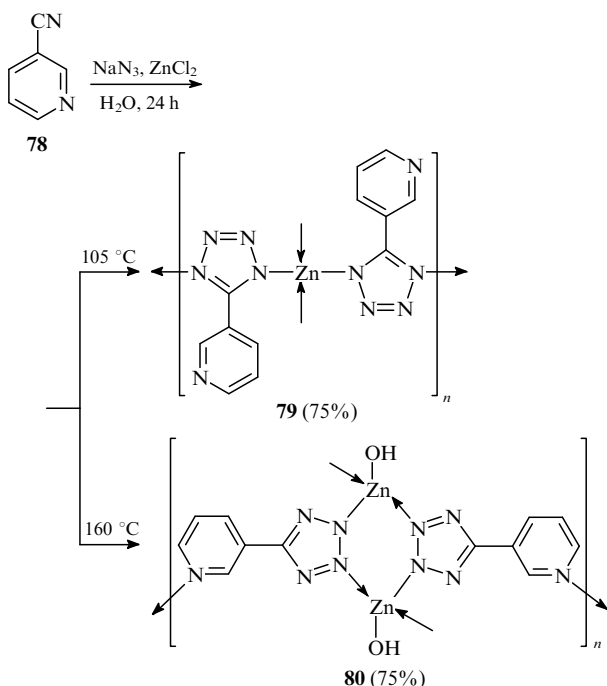


Under hydrothermal conditions (water, 130 °C), dicyanoethylene reacts with sodium azide in the presence of zinc chloride and sodium hydroxide⁹⁴ to give the sodium salt of *trans*-1,2-di(tetrazol-5-yl)ethylene (**77**) (yield 35%). According to X-ray diffraction, salt **77** is a one-dimensional coordination polymer in the crystalline state.



In this synthesis, zinc chloride acts as a catalyst of cycloaddition, which is typical of Lewis acids. This route is suitable for the preparation of complexes of some other metals.^{95–107}

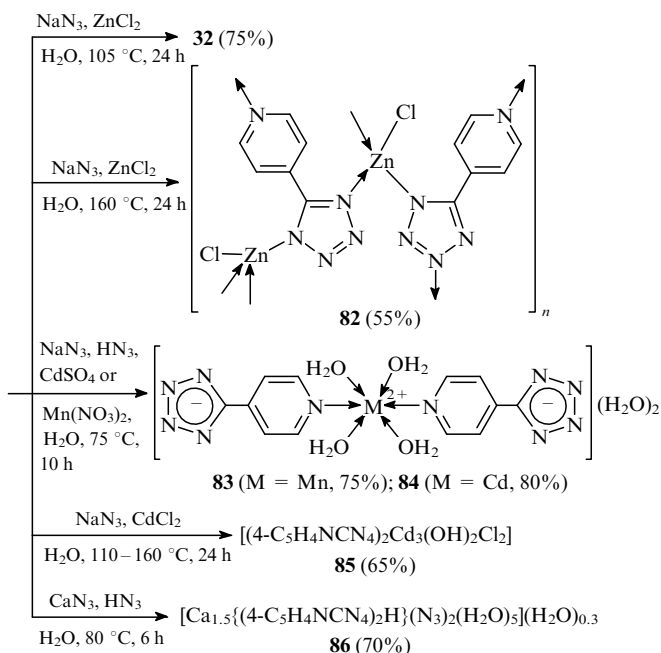
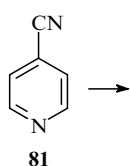
The synthesis of MT from cyanopyridine isomers has been studied rather comprehensively. Depending on the temperature of the reaction carried out in the presence of zinc chloride, 3-cyanopyridine (**78**) forms zinc 5-(3-pyridyl)tetrazolate (**79**)⁹⁵ or hydroxy complex **80**,⁹⁶ which are polymeric (according to X-ray diffraction data).



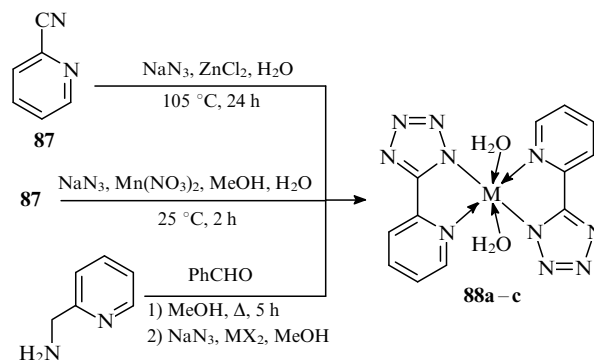
The complex $(3\text{-C}_5\text{H}_4\text{NCN}_4)\text{CdN}_3$ was isolated in 55% yield upon the reaction of nitrile **78** with sodium azide and cadmium chloride in water at 120 °C. According to X-ray diffraction data, the metal atoms in this compound are linked by bidentate azide and tetradentate pyridyltetrazolate [N(1), N(2), N(4) and N(Py) atoms] bridges to form an intricate 3D structure.⁹⁶

According to this procedure, nitrile **81** was converted into 5-(4-pyridyl)tetrazolate complexes of zinc **32**⁹⁵ and **82**,⁹⁶ manganese **83**,⁹⁷ cadmium **84**⁹⁷ and **85**⁴⁸ and calcium **86**.⁹⁷ Recently, it has been shown in relation to the synthesis of complex **83** that cycloaddition can also be accomplished at room temperature.⁹⁸ After a 2-h reaction of 4-cyanopyridine with manganese nitrate and sodium azide in a water–methanol mixture, the yield of complex **83** was 48%.

Complex **85** is a three-dimensional coordination polymer in which each cadmium cation has a nearly square planar environment composed of four anions (two *trans*- Cl^- and two *trans*- HO^-); the other two *trans*-positions are occupied by the nitrogen atoms of two tetrazole ligands. The latter function as tridentate ligands, being coordinated through the N(2), N(3) and N(Py) atoms. This complex has high thermal stability (stable up to 450 °C) and is attractive as a material with light-blue fluorescence and phosphorescence.⁴⁸



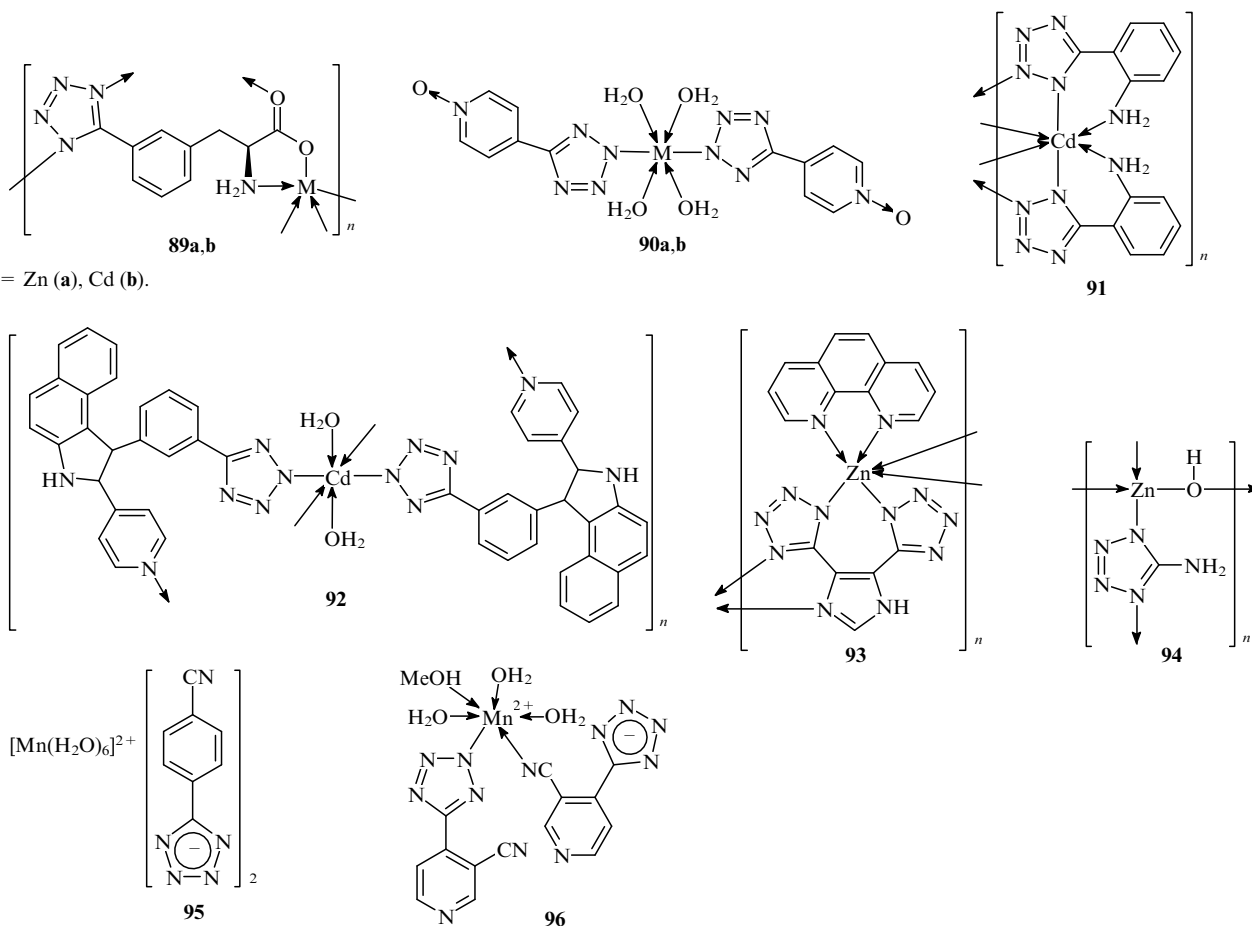
Similarly, 2-cyanopyridine (**87**) has been converted into zinc (**88a**)⁹⁵ and manganese (**88b**)⁹⁵ 5-(2-pyridyl)tetrazolate dihydrate. Complex **88b** was prepared [like a similar copper(II) derivative **88c**] using a somewhat unusual protocol, *viz.*, by refluxing a methanolic solution of 2-aminomethylpyridine and benzaldehyde with subsequent addition of sodium azide and the corresponding metal salts followed by slow evaporation (the yield was 20%). The mononuclear blocks of complexes **88** are linked to one another by hydrogen bonds to form a 2D framework.⁹⁹



M = Zn (**a**, 85%), Mn (**b**, 54%; 20%), Cu (**c**, 15%); X = ClO_4 , BF_4 .

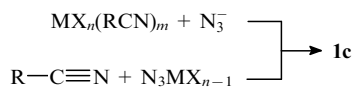
Tetrazolates **89**,¹⁰⁰ **90a**,¹⁰¹ **90b**,¹⁰² **91**¹⁰³ and **92**¹⁰⁴ have been prepared from the appropriate nitriles and metal salts; all these compounds were studied by X-ray diffraction. Complexes **90** are smoothly formed at room temperature in high yields (81%–84%), which is apparently due to good solubility of the starting nitrile in water and the electron-withdrawing properties of the substituent attached to the cyano group. Complex **92** has a high thermal stability (stable up to 345 °C) and is a second harmonics generator 80 times as active as urea.¹⁰⁴

Dinitriles react with sodium azide in water in different ways. Indeed, in the presence of zinc chloride and 1,10-phenanthroline, 4,5-dicyanoimidazole is converted after 24 h at 160 °C into crystals of one-dimensional polymeric complex of 4,5-di(tetrazol-5-yl)imidazole **93** (yield 53%).¹⁰⁵ Similar treatment of 1,2-



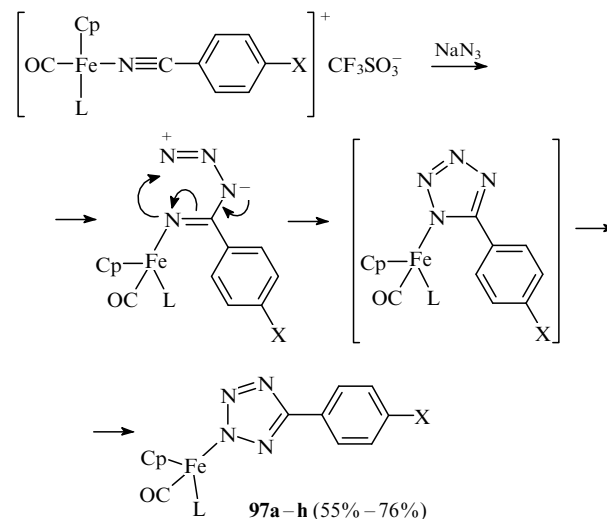
dicyanohydrazine is accompanied by cleavage of the N–N bond to give (5-aminotetrazolato)hydroxyzinc (**94**).¹⁰⁶ In the case of terephthalonitrile and 3,4-dicyanopyridine, the reaction in the presence of manganese salts is limited to azidation of only one cyano group to give complexes **95**¹⁰⁷ and **96**⁹⁸ in which the tetrazolate anion is not involved in coordination (X-ray diffraction data). A similar structure has been found for some other tetrazole-containing manganese aqua complexes.^{46,97}

Other methods based on cycloaddition of azides to nitriles require introducing the metal into the reaction as a nitrile or azide complex, which somewhat restricts their synthetic scope. However, these approaches are quite efficient in the synthesis of different-ligand metal complexes **1c** in which one of the ligands is represented by 5-substituted tetrazole.^{108,109}



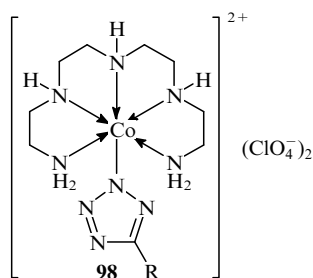
A series of iron(II) complexes of this type **97a–h** have been synthesised; high yields are attained at room temperature for several hours.^{90,110} Presumably, the process starts with a nucleophilic attack by the azide ion on the nitrile carbon atom to give the N(1) derivative, which is rapidly converted in the N(2)-isomer.¹¹⁰ Despite the excess of sodium azide, in the case of binuclear nitrile complexes, the reaction stops after the formation of monotetrazole derivatives **97f–h**.⁹⁰ The coordination to the N(2) atom of the tetrazole ring in these products was confirmed by X-ray diffraction data for complex **97c** and by similarity of the spectro-

scopic (¹H and ¹³C NMR) characteristics to those of other complexes **97**.¹¹⁰



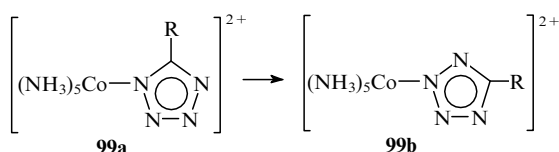
X = CN: L = CO (**a**), PPh₃ (**b**), P(OMe)₃ (**c**), 2,6-Me₂C₆H₃CN (**d**);
X = NO₂: L = P(OMe)₃ (**e**); X = CNFeCp(L)(CO)⁺CF₃SO₃[−]:
L = CO (**f**), PPh₃ (**g**), P(OMe)₃ (**h**).

On the basis of kinetic studies, a similar mechanism has been proposed also for the formation of cobalt(III) complexes **98** from the nitrile complexes and sodium azide.¹¹¹



R = Me, Ph.

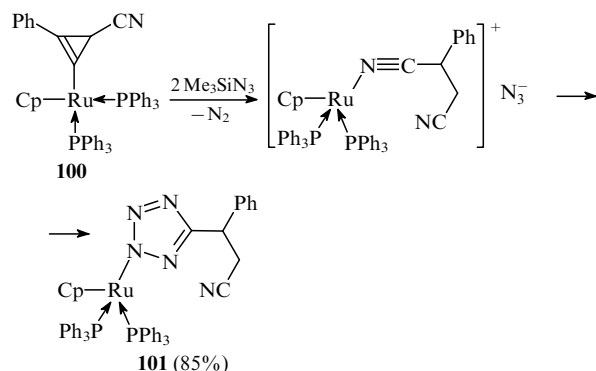
The kinetics and mechanism of isomerisation have been studied in substantial detail for *N*-coordinated pentaamminocobalt(III) 5-*R*-tetrazolates **99a,b**.^{112–115} The isomerisation is due to higher thermodynamic stability of N(2)-coordinated complexes compared to the 1-isomers. This is indicated, in particular, by quantum chemical calculations for silver(I) 5-chlorotetrazolate complexes.¹¹⁶



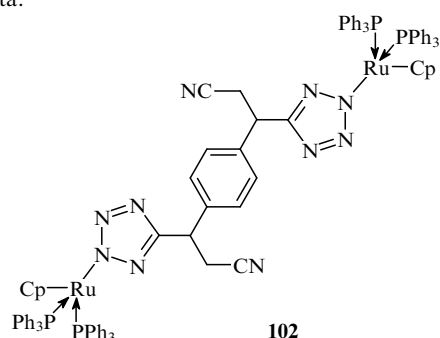
R = Me, Ar.

The cycloaddition of the azide ion to nitrile complexes prepared by N-cyanation of histidine has been used to introduce Mn(II)-,¹¹⁷ Fe(II)-¹¹⁸ and Fe(III)-coordinated¹¹⁹ tetrazolyl group into myoglobin derivatives.

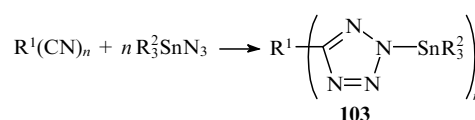
Complex-type tetrazolates can be synthesised not only from coordinated nitriles, but also from their synthetic precursors. Recently, it has been found^{120,121} that the reaction of cyclopropenyl complex **100** with an excess of trimethylsilyl azide yields ruthenium(II) tetrazolate complex **101**. A ruthenium nitrile complex is formed as an intermediate in this reaction.



Bis-tetrazolate complex **102** was prepared in a similar way from the corresponding binuclear ruthenium complex.¹²² Coordination by the N(2) atom of the tetrazole ring has been proposed for compounds **101** and **102** on the basis of X-ray diffraction data.¹²¹

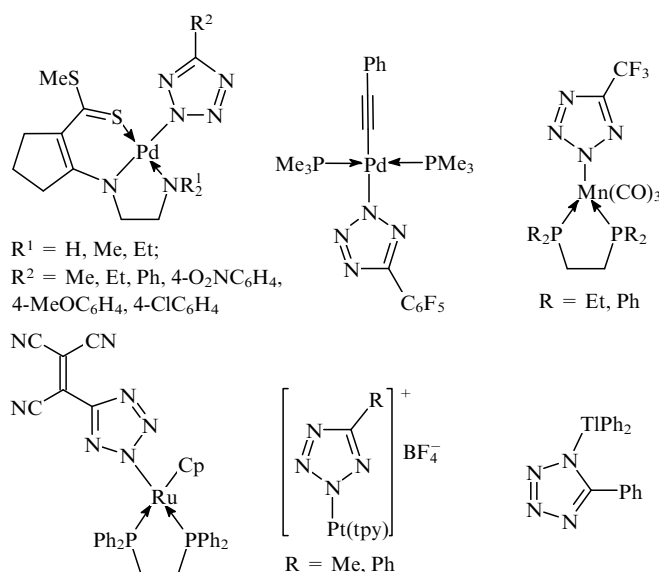


Reactions of metal azide complexes are often used for the synthesis of MT. In recent years, the addition of organic derivatives of stannyl azides to nitriles, resulting in tetrazoles with an organotin substituent at N(2), has been studied in detail. Researchers focused the attention on the use of this reaction for the synthesis of bis-, tris- and tetrakis- and functionally substituted 2-(trialkylstannyl)tetrazoles **103**.^{58, 123–130} Note that the compounds synthesised have a fairly complex structure in the crystalline state due to coordination of different nitrogen atoms of the heterocycle to the metal, as followed from X-ray diffraction data for compounds of this series.^{58, 126–130}



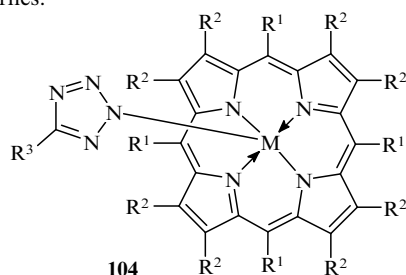
R ¹	R ²	<i>n</i>	Yield (%)	Ref.
Ph ₂ P(CH ₂) _m (<i>m</i> = 3, 4, 7)	Bu	1	—	123
Ph ₃ Sn(CH ₂) _m (<i>m</i> = 2, 3)	Bu	1	97–100	124
Ph	Bu	1	80	125
2-MeC ₆ H ₄	Bu	1	100	58
2-Ph ₂ PC ₆ H ₄	Et, Bu	1	—	123
1 <i>H</i> -Indol-3-yl	Bu	1	60	125
1 <i>H</i> -Indol-3-yl(phenyl)-methyl	Bu	1	60	125
2-, 3-, 4-Py	Et, Bu	1	47–88	126
CH ₂	Me, Pr ⁱ , Bu	2	22–45	127
(CH ₂) _m (<i>m</i> = 2, 4, 5, 6)	Bu	2	13–65	127
(CH ₂) ₄	Et	2	62	127
1,2-C ₆ H ₄	Me, Pr ⁱ , Bu	2	48–63	128
1,3-C ₆ H ₄	Et, Bu	2	68–77	128
1,4-C ₆ H ₄	Pr ⁱ , Bu	2	33–70	128
[2-C ₆ H ₄ O(CH ₂) ₂] ₂ O	Bu	2	98	126
O ₂ NC(CH ₂ CH ₂) ₃	Me, Et, Bu	3	42–63	129
1,3,5-C ₆ H ₃	Me, Et, Bu	3	52–70	129
CHCH ₂ CH	Et, Bu	4	24–80	129
C(CH ₂ CH ₂) ₂	Et, Bu	4	68–70	130
1,2,4,5-C ₆ H ₂	Et, Bu	4	30–56	130

The same method was used to prepare complex palladium(II),^{131–133} manganese(II),¹³⁴ ruthenium(II),¹³⁵ platinum(II)¹³⁶ and thallium(III)²¹ 5-*R*-tetrazolates shown below.



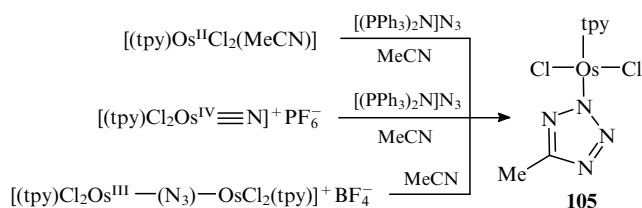
Mixed tetrazolate complexes **104** with 2,3,7,8,12,13,17,18-octaethyl- and 5,10,15,20-tetraarylporphyrin anions as ligands

have been prepared by cycloaddition of azide complexes to nitriles.

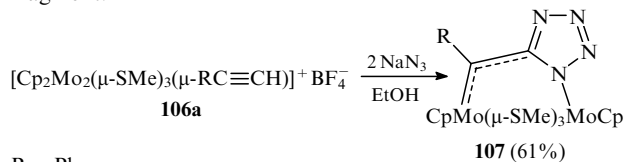


M	R ¹	R ²	R ³	Yield (%)	Ref.
Mn	Ph	H	Et, Ph, CH=CH ₂ , CH=CH-CN	31–77	137
Fe	H	Et	Me, Et, Ph, 3-MeC ₆ H ₄ , 4-MeC ₆ H ₄	46–75	138
Fe	2,4,6-Me ₃ C ₆ H ₂	H	Me, Ph	55–60	138
In	H	Et	Me, Et, Ph, 4-O ₂ NC ₆ H ₄	55–88	139
In	Ph, 4-CF ₃ C ₆ H ₄	H	Me, Et, Ph, 4-O ₂ NC ₆ H ₄	32–65	139

The first Os(III) tetrazolate complex **105** was prepared from terpyridine-stabilised complexes of osmium in different oxidation states using three methods. X-Ray diffraction data confirm the *trans*-geometry of the complex compound, the N(2)-coordination of the 5-methyltetrazolate anion and coplanarity of the tetrazole ring and terpyridine.^{140–142}



Organometallic compounds containing alkyne and vinylidene fragments can also be used as the starting compounds in the synthesis of tetrazolate complexes by cycloaddition. On treatment of molybdenum complexes **106a,b** with sodium azide at room temperature, complexes **107** were isolated as the major products. Presumably, the reaction proceeds through the intermediate coordination of azides and nitriles to the metal and intramolecular 1,3-dipolar cycloaddition. According to X-ray diffraction data, complex **107** (R = Ph) contains two cluster molybdenum atoms [the Mo–Mo bond length is 2.7913(6) Å], one being bonded to the heterocycle N(1) atom, while the other, to the α-carbon atom; substantial electron delocalisation occurs in the Mo–C–C(5) fragment.¹⁴³



R = Ph;



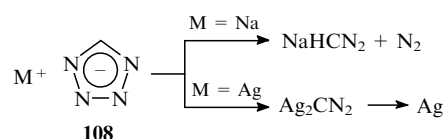
R = Pr, C(Me)=CH₂, Ph, MeC₆H₄.

3. Physicochemical properties and chemical transformations

Salts of 5-substituted tetrazoles are rather stable compounds; however, some of them are known to be sensitive to mechanical impact or heating. The sensitivity of these salts is mainly determined by the nature of the substituent at C(5) in the tetrazole ring and the nature of the cation. Electron-withdrawing substituents

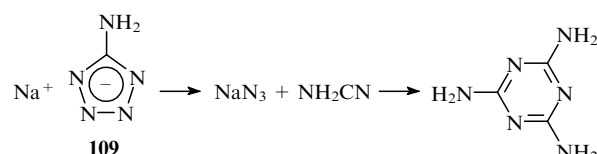
increase the N(1)–N(2) bond polarity and hence decrease the thermal stability of the heterocycle.¹⁴⁴ Tetrazole salts with alkali and alkaline earth metal cations are rather stable. Lithium tetrazolate melts at 318 °C, and sodium and potassium tetrazolates melt at 284 and 228 °C, respectively. Calcium tetrazolate melts at 282 °C, whereas analogous strontium and barium salts explode (before melting) at 374 and 344 °C, respectively.²⁰ Metal tetrazole derivatives stable up to 400–450 °C are also known.¹⁰⁰

Sodium tetrazolate monohydrate undergoes a polymorphic transformation after dehydration at 192 °C, melts at 284 °C and decomposes with explosion above 323 °C. Decomposition is accompanied by nitrogen evolution to give sodium hydrocyanamide.¹⁷ Silver tetrazolate (**108**, M = Ag) decomposes at 224 °C with heat evolution to give silver cyanamide, which also decomposes at 600 °C to give metallic silver.³⁸



Study of the combustion of mixtures of tetrazole with alkali and alkaline earth metal tetrazolates resulted in the discovery of new types of combustion, *viz.*, liquid-flame^{19, 145–147} and layer-by-layer combustion,¹⁴⁷ which are distinguished by a high self-organisation level and a number of specific features. This opens up prospects for the design of new types of non-expendable gas generants and for the development of self-propagating high-temperature synthesis techniques in combustion waves.

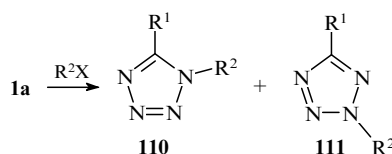
A different fragmentation pathway is observed for 5-substituted tetrazole salts. For example, sodium 5-aminotetrazolate (**109**) decomposes to give sodium azide and cyanamide in the first stage (290–460 °C). Secondary reactions include decomposition of sodium azide with nitrogen evolution and cyclotrimerisation of cyanamide to give melamine and its condensation products.²² A similar mechanism is observed in the first stage of thermal decomposition of PVT sodium salt (**7**), which takes place at 340–400 °C with heat evolution and gives rise to polyacrylonitrile and sodium azide.²⁸



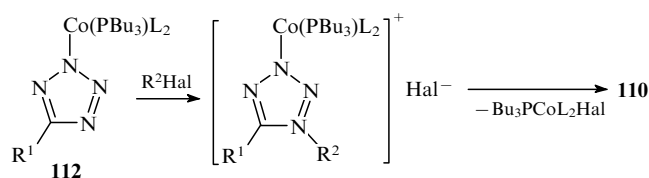
Complex tetrazolates and some salts of 5-substituted tetrazoles are promising as initiating explosives (IE) and serve as components of gas generating compositions (see Section V); therefore, their thermal transformations have been studied rather comprehensively. The mechanism of thermal decomposition giving condensed or gaseous products depends appreciably on the conditions of thermolysis, the nature of the metal and the reactivity of gaseous products.^{31, 32, 37, 69, 86, 88, 148}

Among the chemical transformations of metal derivatives of 5-substituted tetrazoles, N-alkylation reactions have a high practical value, because they underlie the most facile and general method for the synthesis of *N*-substituted tetrazoles.^{1–3} The use of 5-substituted tetrazole salts in the synthesis of *N*-mono- and *C,N*-disubstituted tetrazoles by alkylation is more expedient than the use of neutral 5-substituted tetrazoles. This is due to higher nucleophilicity of the tetrazole ring in tetrazole salts resulting from their ionic structure. The mainly ionic type of the metal–tetrazole bond follows from X-ray diffraction data obtained in recent years for alkali and alkaline earth metal tetrazolates.^{29, 69, 70, 93, 149–152} A distinctive feature of the structure of these salts is a symmetric structure of the tetrazole ring in which the C–N(1) and N(1)–N(2) bond lengths are equal to C–N(4) and N(3)–N(4) bond lengths, respectively. This structure of the

heterocycle accounts for the high aromaticity of the tetrazolate anion (which is the highest among the tetrazoles); therefore, the nature of the cation has an insignificant influence on the selectivity of alkylation of metal tetrazolates and, in most cases, a mixture of 1- and 2-substituted tetrazoles **110** and **111** is formed. The product ratio is mainly determined by the electronic and spatial structure of the R^1 substituent at the C atom.

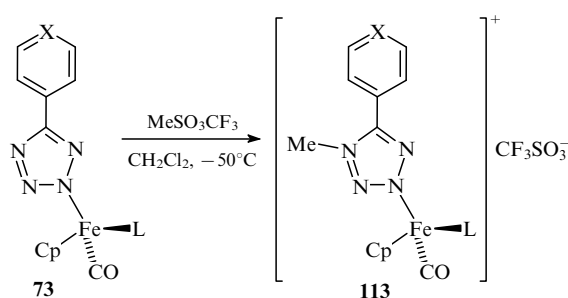


A more pronounced influence of the nature of the metal should be expected for salts and complexes of p- or d-elements with a covalent bond between the metal and the ring nitrogen atom. Indeed, the selectivity of alkylation of cobalt(III) 5-R-tetrazolate complexes **112** in which the tetrazole ring is bound to the metal through the N(2) atom (X-ray diffraction data) differs sharply from the selectivity of alkylation of alkali metal tetrazolates. In the former case, only 1,5-disubstituted tetrazoles **110** without any isomeric tetrazoles **111** were found among the reaction products with alkyl halides in chloroform and nitrobenzene at 36–57 °C. A ^1H NMR study of the alkylation kinetics has shown that the reaction occurs in two stages *via* a 1,5-disubstituted tetrazole complex.¹⁵³



$R^1 = Me, PhCH_2, Ph, CF_3, 4-FC_6H_4, 3-FC_6H_4$; $R^2 = Me, PhCH_2$;
 $L = HONC(Me) = C(Me)NO$.

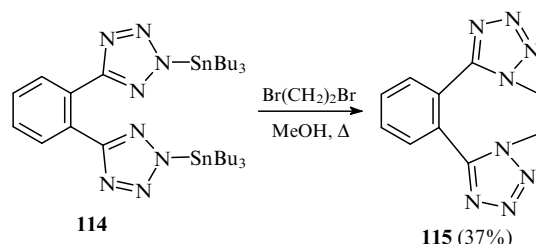
The alkylation of iron(II) complexes **73** also proceeds selectively. At lower temperatures, the process ends in the formation of complexes of 1,5-disubstituted tetrazoles **113** isolated from the reaction mixture in high yields (67%–98%).^{89, 90, 110}



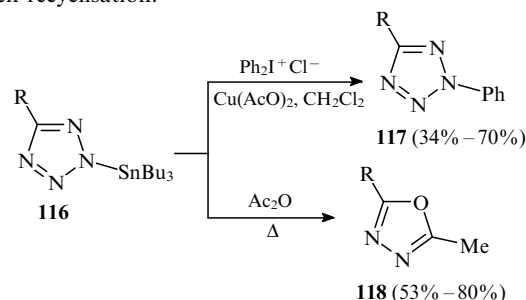
$X = CCN$: $L = CO, PPh_3, P(OMe)_3$; $X = N$, $L = CO$;
 $X = CCNFeCpL(CO)^+ CF_3SO_3^-$: $L = PPh_3, P(OMe)_3$.

Several examples of alkylation of complex tetrazolates used for the synthesis of *N*-substituted tetrazoles has been described.^{69, 121} However, the selectivity of these reactions has not been discussed. The alkylation of 5-substituted 2-(tributylstannyl)tetrazoles has been studied in more detail. Methylation of these compounds with some reagents is selective and gives 1,5-disubstituted tetrazoles.^{1, 2} However, in the case of other alkylating reagents, mixtures of 1- and 2-substituted tetrazoles have been obtained. This behaviour of stannyl derivatives is attributed to different degrees of their association in solutions. In recent years, alkylation of stannyltetrazoles has been employed for the syn-

thesis of poorly accessible disubstituted tetrazoles. Thus the reaction of *o*-phenylenedi(2-tributylstannyltetrazole) (**114**) with an excess of 1,2-dibromoethane in methanol resulted in cyclophane **115**.¹⁵⁴ In dibromoethane, alkylation of tetrazole **114** is accompanied by dehydrohalogenation to give *N*-vinyltetrazoles.¹⁵⁵



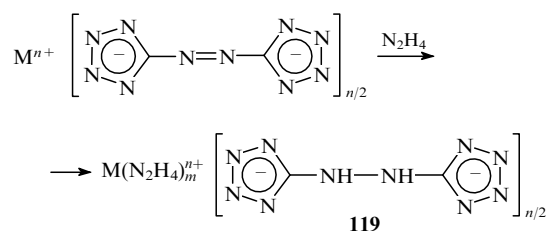
Arylation of 2-tributylstannyltetrazoles **116** with diphenyliodonium chloride at room temperature afforded 5-aryl- and 5-hetaryl-2-phenyltetrazoles **117**.¹⁵⁶ The reaction was selective unlike a similar reaction of sodium 5-phenyltetrazolate in which approximately equal amounts of 1,5- and 2,5-diphenyltetrazoles are formed.²³ On refluxing with acetic anhydride, tetrazoles **116** are converted into 2-R-5-methyl-1,3,4-oxadiazoles **118**. The reaction proceeds apparently with formation of *N*-acyltetrazoles and their recyclicalisation.¹²⁵



117: $R = Ph, 4-MeC_6H_4, 4-BrC_6H_4, 1H-indol-3-yl, 1H-indol-3-ylmethyl$;
118: $R = Ph, 1-acetylindol-3-yl, 1H-indol-3-yl(phenyl)methyl$.

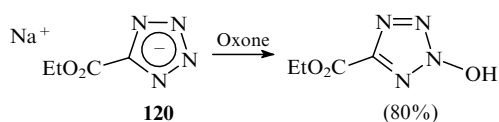
Most complexes and salts of 5-substituted tetrazoles are sensitive to the action of acids. Upon the reaction with an equimolar amount of acids under mild conditions, N(2)-coordinated ruthenium(II) **100**¹²¹ and iron(II) **73**^{89, 90, 110} complexes are protonated at the N(4) atom of the heterocycle. Under more drastic conditions, this type of compounds are destroyed to give tetrazoles **6**, which is used for the synthesis of the latter.^{1-3, 10, 98, 157-162}

The behaviour of MT towards oxidising and reducing agents has not been systematically studied. However, the tetrazolate anion is known to be stable against these reagents, only substituents being affected. Thus upon dissolution in hydrazine, alkali and alkaline earth metal 5,5'-azoditrazolates are reduced to give 5,5'-hydrazoditrazolates **119**.¹⁵²

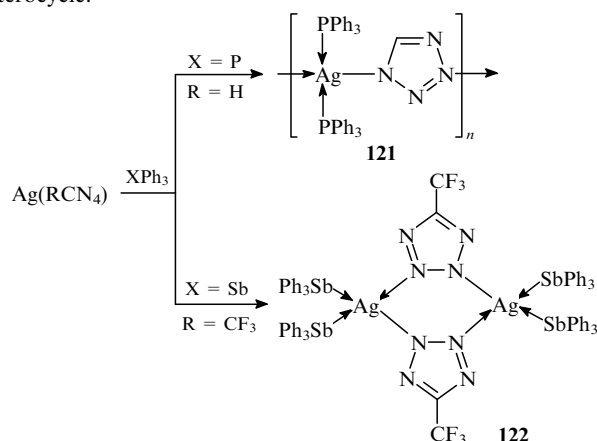


$M = Li, Na, Ba$; $n = 1, 2$.

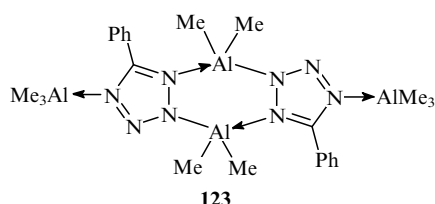
The action of oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) on sodium 5-(ethoxycarbonyl)tetrazole **120** allows a hydroxyl group to be introduced into the heterocycle at N(2) position.¹⁶³



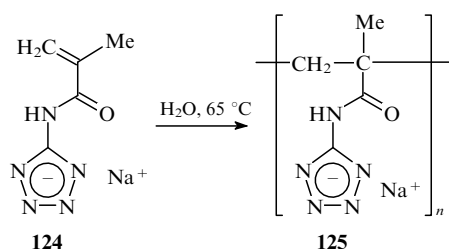
Other known transformations of this type of MT have been used to prepare bi- and polynuclear metal-containing tetrazoles the structures of which were determined by X-ray diffraction analysis. Silver tetrazolates react with triphenylphosphine in dichloromethane to give polymeric complex **121** through bridging N(1),N(3)-coordination of the heterocycle.⁷³ Silver 5-trifluoromethyltetrazolate reacts with triphenylantimony in acetone to give binuclear complex **122** with the N(2),N(3)-coordination of the heterocycle.⁶⁵



Mono- and dimethylaluminium 5-phenyltetrazolates **66** (R = Me; $n = 1, 2$) react with trimethylaluminium to give bi- and tetranuclear complexes $[(\text{PhCN}_4)_2\text{AlMe} - \text{AlMe}_3]$ and compounds **123**, respectively.⁸⁰



Worthy of note is also radical polymerisation of sodium 5-(methacrylamido)tetrazole (**124**) to give polymer **125**. Copolymerisation of this salt with 0.08 mol.% of *N,N'*-methylenebis(acrylamide) affords a polymeric gel absorbing up to 200 g of water per gram.¹⁸



III. Metal derivatives of neutral *N*-substituted tetrazoles

The introduction of an *N*-substituent into the tetrazole ring, instead of the hydrogen atom capable of migration (prototropy) and dissociation, gives rise to two isomeric *N*-substituted tetrazoles **110** and **111**,¹⁻³ which behave as weak bases ($-\text{p}K_{\text{BH}^+} = 2-4$); note that 1-substituted tetrazoles are much more basic than the 2-isomers.¹⁶⁴ In these compounds, the N(4)

atom is the most basic; however, the sequences of variation of the proton affinity (according to quantum-chemical calculations) are different: $\text{N}(4) > \text{N}(3) > \text{N}(2) > \text{N}(1)$ for 1-substituted tetrazoles; $\text{N}(4) > \text{N}(1) > \text{N}(3) > \text{N}(2)$ for 2-isomers.^{165, 166}

In early studies, complexes of 1-substituted tetrazoles have been prepared by procedures based on the use of non-aqueous solvents and forced removal of water from the starting salt hydrates.^{4,5} Only in the 1980s, did publications appear (see, for example, Ref. 4) describing the synthesis of transition metal complexes with *N*-substituted tetrazoles directly from metal salt hydrates in organic solvents, their mixtures with water and even in water. The solvent is selected considering its electron-donating activity, the ability to dissolve the reactants and precipitate or function as a crystallisation medium for the final product. Most often, the complex is isolated by partial concentration of the reaction mixture, its storage for a certain period of time or cooling. In most cases, the reactions of 1-substituted tetrazoles in weakly coordinating solvents (alcohols, acetone, diethyl ether, acetonitrile, *etc.*) smoothly proceed at room temperature to give solid complexes.

2-Substituted tetrazoles are more sensitive to the conditions under which the complex formation is carried out, in particular, to the presence of water in the reaction mixture.^{167, 168} In addition, the formation of solid complexes of 2-substituted tetrazoles is prevented by their high solubility. Therefore, high concentrations of components and dry solvents are required to obtain such complexes (although in some cases, the presence of a minor amount of water is allowed). In some cases, the reaction mixture must be heated and then concentrated. Many *N*-substituted tetrazoles are liquids, which allows preparing complex-type compounds by the reaction of the starting components without a solvent.

Complexes of 1-substituted tetrazoles **110** ($\text{R}^1 = \text{H}$) have been studied in most detail, first of all, due to the discovery, for these derivatives, of spin transitions accompanied by thermo- and photochromism (Fe^{2+} complexes) and ferromagnetic ordering of the electron spins (Cu^{2+} compounds). More than a hundred complex-type compounds have been prepared and characterised; their compositions vary over a broad range, being mainly dependent on the nature of the metal cation and the counter-ion (Table 1). In some cases, the compositions of the complexes formed are affected by the starting reactant ratio, the solvent, and the nature and the size of the substituent in 1-substituted tetrazole. For example, metal (Cu^{2+} , Co^{2+} , Ni^{2+}) chlorides and 1-alkyl-, 1-vinyl- and 1-allyltetrazoles form the ML_2Cl_2 complexes irrespective of the reactant ratio. Copper(II) bromide and thiocyanate behave in a similar way. In the case of weakly coordinating anions (BF_4^- , ClO_4^- , PF_6^- , *etc.*), the greatest number of coordinated ligands corresponds to the formula ML_6X_2 ($\text{M} = \text{Zn}, \text{Fe}, \text{Cu}, \text{Co}, \text{Ni}$). Metal nitrates occupy an intermediate position, being capable of forming compounds with a $\text{MX}_n:\text{L}$ ratio of 1:2, 1:3, 1:4 and 1:6. For 1-substituted tetrazoles containing bulky substituents (Bu^t , Ph, Mes, 3-Cl-4- FC_6H_3), complexes with a smaller number of coordinated tetrazoles, in particular, equimolar complexes, CuLCl_2 , $\text{CuL}(\text{BF}_4)_2$, have been isolated. In some cases (for $\text{L} = 1\text{-propyl-}$, 1-chloroethyl- or 1-phenyltetrazole), during the growth of single crystals, additional uncoordinated tetrazole molecules were incorporated in the crystals.

2-Substituted tetrazoles **111** ($\text{R}^1 = \text{H}$) behave in complexation reactions in a different way. It has been shown in relation to 2-alkyltetrazoles and copper(II) chloride that, depending on the reactant ratio, the resulting complexes may be described as CuLCl_2 , CuL_2Cl_2 or $\text{Cu}_3\text{L}_4\text{Cl}_6$ (Table 2), the last-mentioned complexes being also formed during recrystallisation of CuL_2Cl_2 or during their synthesis with low reactant concentrations. The greatest number of coordinated 2-substituted tetrazole molecules is four in the case of copper(II) tetrafluoroborate or two with the nitrate.

Table 1. Complexes ML_nX_2 prepared by the reaction of 1-R-tetrazoles (L) with metal salts MX_2 .

R	Complex composition	Ref.	R	Complex composition	Ref.
$n-C_nH_{2n+1}$ ($n = 1-10, 12, 16, 18$)	$FeL_6(BF_4)_2$	169, 170	$CH_2=CH-CH_2$	$ML_6(NO_3)_2(H_2O)$ ($M = Co, Ni$) CuL_2Cl_2	195 167, 195,
$n-C_nH_{2n+1}$ ($n = 1-4, 6, 8$)	CuL_2X_2 ($X = Cl, NCS$)	167			198
Me	$FeL_6(BF_4)_2$	171-173		$CuL_2(NCS)_2$	167
	$FeL_6(CIO_4)_2$	172		$CuL_2(NO_3)_2, CuL_6(NO_3)_2,$	199
	$FeL_6(PF_6)_2$	174	CH_2CH_2Y	$CuL_6(CIO_4)_2$	
	$FeL_6(CF_3SO_3)_2$	175, 176	($Y = F, Cl, Br, I$)	$FeL_6(BF_4)_2$	169
	$NiL_6(CF_3SO_3)_2$	176	CH_2CH_2Y	FeL_6X_2 ($X = BF_4, CIO_4$)	200
	CuL_2Cl_2	177, 178	($Y = F, Br, I$)		
	CuL_2Br_2	179	CH_2CH_2Cl	FeL_6X_2 ($X = BF_4, CIO_4, PF_6$)	201
	$ML_6(BF_4)_2$ ($M = Cu, Zn$)	180		CuL_2X_2 ($X = Cl, Br$)	202
Et	$FeL_6(BF_4)_2$	181		CuL_6X_2L ($X = BF_4, CIO_4$)	203
	$ML_2Cl_2(H_2O)$ ($M = Co, Ni$)	182		$CuL_2(NO_3)_2$	204
	$CoL_6(NO_3)_2, NiL_6(NO_3)_2,$	183		$(CuL_5)_2(CuL_6)[PMO_{12}O_{40}]_2(H_2O)_2$	205
	$CdL_3(NO_3)_2(H_2O)_2$		CH_2CH_2OMe	$\alpha-CuL_2Br_2, \beta-CuL_2Br_2$	206
	CuL_2Cl_2	182, 184	$CH_2CH_2N_3$	CuL_2Cl_2	207
	CuL_2Br_2	185	CH_2CH_2Y	CuL_2Cl_2	177
	$CuL_2(NO_3)_2$	186	($Y = CN, Ac$)		
	$CuL_3(NO_3)_2$	187	CH_2CO_2Et	CuL_2Cl_2	177
Pr	$FeL_6(BF_4)_2$	172, 188,	$CH_2CONHNH_2$	$ML_2(CIO_4)_2$ ($M = Co, Ni, Cu$),	208
		189		$NiL_3(CIO_4)_2$	
	$FeL_6(CIO_4)_2$	190		ML_2X_2 ($M = Zn, Cd$);	209
	$FeL_6(PF_6)_2$	191		$X = NO_3, CIO_4$	
	$FeL_6(CF_3SO_3)_2L_2$	173		PbL_2X_2 ($X = NO_3, CIO_4$)	210
	$ZnL_6(BF_4)_2$	189	cyclo- C_3H_7	$ML_6(BF_4)_2$ ($M = Ni, Cu$)	211
$n-C_6H_{13}$	CuL_2Br_2	185	Ph	$ML_2Cl_2(H_2O)_{0.5}$ ($M = Co, Ni$)	182
$n-C_nH_{2n+1}$ ($n = 8, 12, 18$)	$FeL_6(BF_4)_2$	192		$CuLCl_2, CuL_nX_2$ ($X = Cl, Br$)	182
Bu ^t	$CuLCl_2, CuL_4(BF_4)_2, CuL_6(BF_4)_2$	193		$CuL_2Cl_2L_{0.5}$	212
	CuL_2Cl_2	193, 194		$CuL_2(NO_3)_2(H_2O)_2$	182, 213
$CH_2=CH$	$CoL_2Cl_2, CuL_4(NO_3)_2(H_2O)$	195		$CuL_n(BF_4)_2$ ($n = 2-5$)	214
	ML_2Cl_2 ($M = Cu, Ni$)	40, 195	Mes	$CuL_5(BF_4)_2$	215
$CH_2=CH$	$CuL_2(NCS)_2$	167		CuL_2Cl_2	214, 216
$CH_2=CH-CH_2$	CoL_2Cl_2	195-197	$3-Cl-4-FC_6H_2$	$CuLCl_2, CuL_n(BF_4)_2$ ($n = 1, 2$)	214
	$NiL_2Cl_2(H_2O), CuL_2Br_2$	195	$2-PyCH_2$	$CuLCl_2, CuL_n(BF_4)_2$ ($n = 4, 5$)	214
				$PdLCl_2(H_2O)_2$	51

Some syntheses of copper(II) chloride complexes with 2-alkyltetrazoles were accompanied²²³ by the formation of tetra-

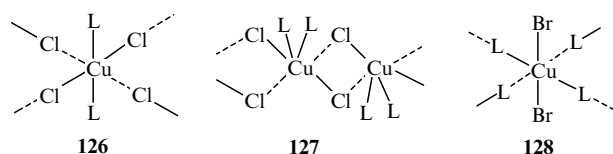
Table 2. Complexes ML_nX_2 prepared by the reaction of 2-R-tetrazoles (L) with metal salts MX_2 .

R	Complex composition	Ref.
$n-C_nH_{2n+1}$ ($n = 1-4, 6$)	CuL_2X_2 ($X = Cl, NCS$)	167
$n-C_nH_{2n+1}$ ($n = 1-3, 6$); Bu ^t	$CuLCl_2$	167
Me, Et	$Cu_3L_4Cl_6$	167
Me	CuL_2Cl_2	217
Et	CuL_2Cl_2	218
	$CuL_2(NO_3)_2$	183, 187
	$CuL_4(BF_4)_2$	187
	$ML_2(NO_3)_2(H_2O)_n$ ($M = Co, Ni$; $n = 4$; $M = Cd$; $n = 2$)	183
Pr	CuL_2Cl_2	219
Bu ^t	CuL_nCl_2 ($n = 1, 2$); $CuL_4(BF_4)_2$	193
	$CuLCl_2$	220
$n-C_6H_{13}$	$CuLCl_2$	221
$CH_2=CH-CH_2$	$Cu_3L_4Cl_6$	222
	CuL_2Cl_2	219
$2-PyCH_2$	$PdLCl_2$	51

nuclear oxychloride $Cu_4OL_4Cl_6$ complexes, as a result of hydrolysis of copper chloride and due to high thermodynamic stability of this type of cluster. Such a transformation has also been observed²²⁴ on attempted synthesis of the 1-ethyltetrazole complex with copper(II) bromide carried out by slow concentration of a solution of the reactants in 96% ethanol, which gave single crystals of the $Cu_4OL_4Br_6$ complex.

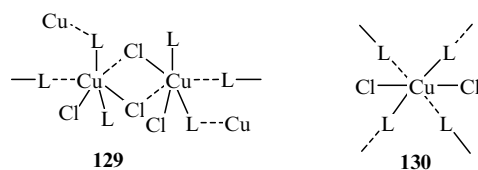
The structures of complexes of *N*-substituted tetrazoles have been studied by spectroscopic techniques and by X-ray diffraction analysis. Most often, 1-substituted tetrazoles are monodentate ligands, complex formation involving the N(4) atom. Hence, the environment of the copper atom in the halide complexes CuL_2X_2 , where $X = Cl, Br$; L is 1-R-tetrazole ($R = Me$; Et; $CH_2=CHCH_2$; CH_2CHY , $Y = Cl, Br, N_3$), is completed to a square bipyramid due to contacts with halogen atoms coordinated to the neighbouring copper atom,^{179, 182, 184, 185, 195, 202, 207} i.e., halide ions are bridges connecting the CuL_2X_2 fragments into layers (structure **126**). The *trans*-coordinated tetrazole ligands occur in the interlayer space; the size of the substituent in the ligand determines the interlayer spacing. All complexes of copper(II) halides with 1-monosubstituted tetrazoles having such structure are low-temperature ferromagnets.^{185, 198, 199, 202, 225} According to electronic and IR spectroscopy, this type of a layered polymeric structure is also characteristic of cobalt(II) and nickel(II) chloride complexes with 1-ethyl-¹⁸² and 1-allyltetrazoles¹⁹⁵, ML_2X_2 . Recently,¹⁹⁶ this has been confirmed by X-ray diffraction analysis carried for cobalt 1-allyltetrazole complex.

The key difference between the structures of these copper(II) and cobalt(II) complexes is that in the latter compound, the bridging bonds have the same length (2.54 Å), whereas in the copper complex these bonds are markedly dissimilar due to the Jahn–Teller effect (2.30 and 2.99 Å). It was found, however, that the cobalt complex is a weak ferromagnet with $T_N = 102 \pm 1$ K having spontaneous magnetisation of $\sigma_s(5 \text{ K}) = 710 \pm 5 \text{ G cm}^3 \text{ mol}^{-1}$. In the case of bulky substituents ($R = \text{Bu}^t, \text{Ph}, \text{Mes}$), the CuL_2Cl_2 complex exists as linear polymeric structure **127** due to chloride bridges, while the tetrazole ligands are coordinated in the *cis*-position.^{194, 212, 216}

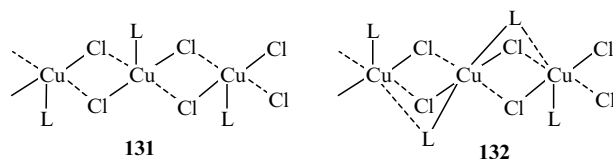


1-(2-Methoxyethyl)tetrazole (**110**, $R^1 = \text{H}$, $R^2 = \text{CH}_2\text{OMe}$) shows an unusual ligand behaviour compared to other 1-alkyltetrazoles. It reacts with copper(II) bromide in methanol or ethanol to give two isomeric complexes, α - and β - CuL_2Br_2 , which differ substantially in physicochemical properties and structure.²⁰⁶ The α -form obtained from methanol is a 2D structure **128** in which the copper ions are connected by the N(4),N(2)-bridging tetrazole ligands and the bromide ion is monodentate. In this species, no magnetic interaction occurs between the copper ions. Conversely, the β -form, which crystallises from ethanol, exhibits ferromagnetic properties ($C = 0.41 \text{ cm}^3 \text{ K mol}^{-1}$, $J/k_B = 16.4 \text{ K}$, $\theta = 30.5 \text{ K}$) and has structure **126**.

A substantial influence of the substituent on the structure of the complex is also observed for 2-substituted tetrazoles. Indeed, complexes $\text{Cu}(2\text{-R-tetrazole})_2\text{Cl}_2$ ($R = \text{Me}, \text{Et}$) have a layered polymeric structure **129** joined by bridges formed by some of the chlorine atoms and tetrazole ligands coordinated through the N(4) and N(1) atoms. The second tetrazole ligand is coordinated in the monodentate mode through the N(4) atom.^{217, 218} As the substituent bulk increases ($R = \text{Pr}, \text{CH}_2 = \text{CHCH}_2$), both tetrazole ligands become bridging and are coordinated by the N(4) and N(1) atoms (structure **130**).²¹⁹

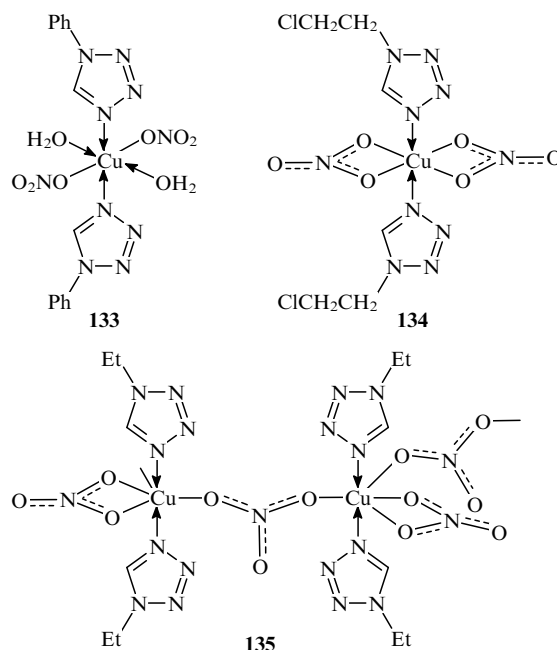


Note that complexes **128**–**130** are the first examples of layered polymeric structures formed by *N*-substituted tetrazoles through two nitrogen atoms of the heterocycle. The complexes CuLCl_2 and $\text{Cu}_3\text{L}_4\text{Cl}_6$ are polymeric chains **131** and **132**, respectively, formed owing to the bridging coordination of chlorine atoms;^{220–222} in **132**, the neighbouring copper atoms are additionally linked by the tetrazole ring [N(3), N(4) atoms]; hence, a half of the tetrazole ligands in the structure are bridging.²²²



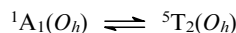
The main feature of the metal nitrate complexes is related to different coordination modes of nitrate anions even in compounds with similar compositions. According to X-ray diffraction data, in three copper(II) complexes, **133**,²¹³ **134**,²⁰⁴ **135**,¹⁸⁶ in which 1-substituted tetrazole ligands are coordinated through the N(4) atom and occupy *trans*-positions, the nitrate anions are coordinated as

monodentate, bidentate and bridging ligands. Moreover, compound **135** is a 2D coordination polymer. The linear chain packing of mononuclear complexes **134** gives rise to a weak ferromagnetism ($\theta = 0.30 \text{ K}$ and $C = 0.44 \text{ cm}^3 \text{ K mol}^{-1}$).



No structural data for the thiocyanate or chloride complexes $\text{CuL}_2(\text{NCS})_2$ and CuLCl_2 (L is 1-substituted tetrazoles) have been reported. The IR and EPR data indicate a bridging type of the $\text{Cu}–\text{NCS}–\text{Cu}$ bond, while in the case of CuLCl_2 , a bridging coordination of 1-substituted tetrazoles through the N(3) and N(4) atoms is assumed.¹⁶⁷ The salts of bivalent metals ($\text{Fe}, \text{Ni}, \text{Cu}, \text{Zn}$) with weakly coordinated anions (BF_4^- , ClO_4^-) react with an excess of 1-substituted tetrazole to give mononuclear complexes containing MN_6 coordination octahedra. The coordination involves the N(4) atom of the ring. In compounds with fewer coordinated tetrazole molecules, the copper coordination sphere contains anions (according to IR spectroscopic and X-ray diffraction data).^{215, 226}

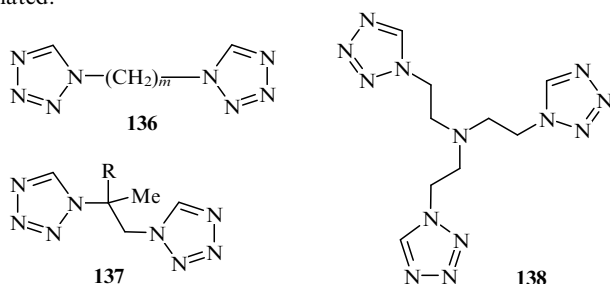
The structures and properties of six-coordinate iron(II) complexes FeL_6X_2 (see Table 1) have been studied in most detail; these compounds possess unique properties related to the extremely high sensitivity of their electronic characteristics to relatively weak impact of temperature, pressure or light with a definite wavelength. This induces easy reversible spin transitions (ST)



between the ground diamagnetic low-spin ($\text{LS}, S = 0$) and paramagnetic high-spin ($\text{HS}, S = 2$) states the nature of which for iron(II) complexes has been studied in fair detail and considered in reviews^{6, 227, 228} and references cited therein. Characteristics of the ST (a broad range of temperatures, 45–200 K, the character and sharpness of transitions, the presence of hysteresis and the width of the hysteresis loop) are determined by structural features of the complexes. Numerous publications describe X-ray diffraction, magnetochemistry, and Mössbauer, EXAFS, photoelectron, FT IR and Raman spectroscopic studies of the structures, physicochemical properties and their variation in the series of related iron(II) complexes and those diluted over broad ranges with isomorphous zinc^{229–232} and nickel²³³ complexes (Refs 169–176, 181, 188–192, 199, 200, 234–250). It was found that the ST may be accompanied by a structural phase transition, which results in shortening of the $\text{Fe}–\text{N}$ bond in the coordination polyhedron by $\sim 0.2 \text{ Å}$ and distortion of the polyhedron symmetry.^{6, 228, 249, 251} Therefore, ST characteristics may be sensitive to the external pressure.^{6, 191, 251}

The obtained data suggest that the change in the magnetic and optical properties upon spin transitions in Fe(II) complexes with 1-substituted tetrazoles is largely related to the cooperative mechanism of transfer of the electronic effects and is determined by the efficiency of intermolecular contacts, including hydrogen bonds, π - π and other interatomic interactions between the structural fragments of the compounds. Recent theoretical descriptions of spin transitions for a series of iron(II) complexes with 1-(2-haloethyl)tetrazoles in terms of physical²⁵² and quasi-chemical²⁵³ models of the intermolecular interactions are in fairly good agreement with experimental data.

These results have stimulated the research aimed at the development of methods for the synthesis and study of the properties of iron(II) complexes with binuclear monosubstituted tetrazoles, the structure of which could ensure effective cooperative interactions through bridging ligands. A number of recent publications have been devoted to the iron(II) complexes FeL_3X_2 , where L is di(tetrazol-1-yl)alkanes **136** ($m = 2$, $\text{X} = \text{BF}_4$;²⁵⁴ $m = 4$: $\text{X} = \text{ClO}_4$,²⁵⁵ PF_6 ²⁵⁶) and **137** ($\text{R} = \text{H}$, $\text{X} = \text{ClO}_4$;²⁵⁷ $\text{R} = \text{Me}$, $\text{X} = \text{BF}_4$).²⁵⁸ A broader set of these compounds based on tetrazoles **136** ($m = 1-8, 10, 12$) have been described in dissertations.^{169, 259} However, it was noted¹⁶⁹ that for $m = 6, 8, 12$, complexes $\text{FeL}_3(\text{BF}_4)_2$ with a sufficient purity could not be isolated.

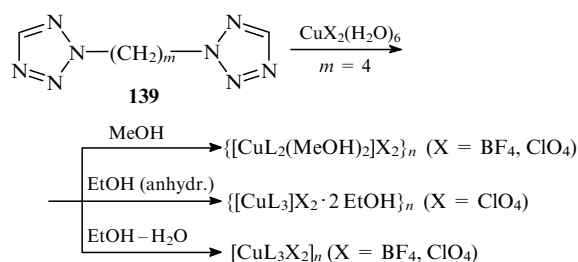


An important feature of iron(II) complexes with bistetrazoles is that they form one-^{254, 257} and three-dimensional^{255, 256, 259, 260} polymeric structures. This stimulated further investigations into the self-assembly of supramolecular structures and self-organisation of molecules through coordination to transition metal ions. Of special note is the structural, chemical and functional diversity of the resulting objects. A series of 2D polymeric complexes based on tetrazolylamine **138** described as ML_2X_2 ($\text{M} = \text{Fe}, \text{Cu}, \text{Co}, \text{Zn}$; $\text{X} = \text{BF}_4^-$ and $\text{M} = \text{Fe}, \text{Zn}$; $\text{X} = \text{ClO}_4^-$) and a series of double compounds $[\text{Cu}_{0.01}\text{M}_{0.99}\text{L}_2](\text{BF}_4)_2$ ($\text{M} = \text{Zn}, \text{Fe}$); $[\text{Fe}_x\text{Zn}_{(1-x)}\text{L}_2](\text{BF}_4)_2$ ($x = 0.0062-0.970$)²⁵⁹ have been synthesised and studied. Research into the formation of this type of supramolecular structures is needed to study systematically the mechanism of transfer of electronic effects.^{252, 259}

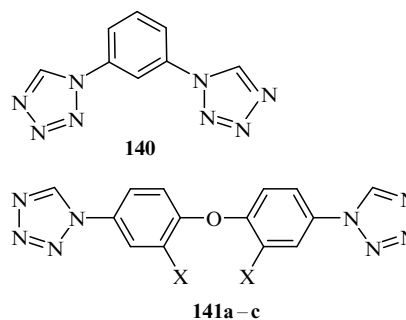
It has been noted^{6, 259} that spin transition characteristics depend essentially (apart from the nature of the ligand and counter-ion) on the formation conditions of the crystals of complexes. The investigation of compounds such as $\text{FeL}_6(\text{CF}_3\text{SO}_3)_2 \cdot \text{L}_2$ (L is 1-propyltetrazole),¹⁷³ $\text{FeL}_3(\text{PF}_6)_2 \cdot \text{Solv}$ [L is **136** ($m = 4$), Solv is 0.5 MeOH or H_2O],²⁵⁶ $\text{FeL}_3\text{X}_2 \cdot \text{MeCN}$ [L is **136** ($m = 5$), $\text{X} = \text{BF}_4, \text{PF}_6$]²⁵⁹ has shown that inclusion of uncoordinated tetrazole or solvent molecules into the structure changes substantially the characteristics of spin transitions.

The structures and physicochemical properties of several complexes of other transition metals with bis-tetrazoles similar in composition to iron(II) complexes have been studied, in particular, the complex $\text{CuL}_3(\text{ClO}_4)_2$ [L is **136** ($m = 2$)],²⁶¹ the Ni(II) and Cu(II) complexes with 1,4-di(tetrazol-1-yl)butane (**136**, $m = 4$).²⁵⁵ The first representatives of coordination polymers based on 2-substituted bis-tetrazoles **139** have been prepared and characterised: one-dimensional $\text{ZnL}_3(\text{ClO}_4)_2$ complex [L is **139** ($m = 2$)],¹⁶⁸ one- and three-dimensional polymers, $\text{CuL}_3(\text{ClO}_4)_2$ and $\text{ZnL}_3(\text{ClO}_4)_2 \cdot 2\text{EtOH}$ [L is **139** ($m = 3$)],²⁶² and five copper complexes with 1,4-di(tetrazol-2-yl)butane (**139**, $m = 4$).²⁶³ The

synthesis of the last-mentioned compounds shows an essential dependence of the composition and structure of MT on the nature of the solvent used.

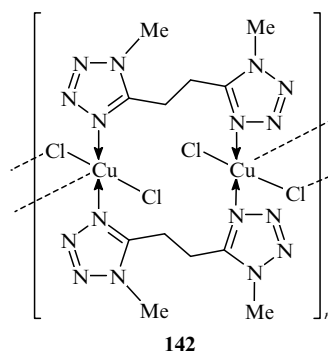


Generally, binuclear tetrazoles function most often as bridging ligands and give coordination compounds containing fewer ligands than in the case of mononuclear *N*-substituted tetrazoles. Apart from those mentioned above, a number of such compounds with 1,1'-*m*-phenyleneditetrazole (**140**) have been obtained, in particular, ML_2X_2 , where $\text{M} = \text{Ni}, \text{Co}, \text{Cu}$; $\text{X} = \text{NO}_3, \text{ClO}_4$;¹⁹⁹ CuL_2X_2 , where $\text{X} = \text{NO}_3, \text{BF}_4$, and CuLCl_2 .²⁶⁴ An equimolar ratio has also been found for copper(II) chloride complexes with *para*- and *ortho*-isomers of compound **140**²⁶⁴ and with bis-tetrazoles based on diphenyl ethers **141a-c**.²⁶⁵



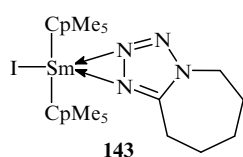
$\text{X} = \text{H}$ (a), NO_2 (b), tetrazol-1-yl (c).

Bis-tetrazole **141c** reacts with copper(II) chloride to give compounds $\text{CuL}_{0.5-0.75}\text{Cl}_2$ with composition depending on the reactant ratio.²⁶⁵ It was shown by X-ray diffraction that 1,2-bis(1-methyltetrazol-5-yl)ethane functioning as a bridging ligand with respect to copper(II) chloride forms polymeric complex **142** containing both monodentate and bridging chlorine atoms.²⁶⁶

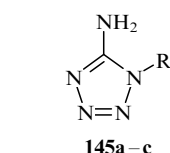
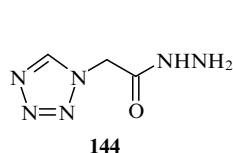


The presence of second substituent in the tetrazole ring (tetrazoles **110, 111**) and a substituent capable of complexation has a pronounced influence on the compositions and structures of the coordination compounds. Unlike 1-monosubstituted tetrazoles, which form the complexes CuL_2Cl_2 and CuL_6X_2 ($\text{X} = \text{BF}_4, \text{ClO}_4$) (see Table 1), 1,5-disubstituted tetrazoles form compounds CuLCl_2 (see Ref. 177) and CuL_4X_2 (see Ref. 267) under the same conditions. For 1:1 complexes, a bidentate bridging tetrazole coordination is assumed, which is in line with the results of quantum-chemical calculations of the proton affinity¹⁶⁵ and

with experimental data on quaternisation,²⁶⁸ indicating that 1,5-disubstituted tetrazoles contain two clear-cut nucleophilic centres [N(4) and N(3)], coordination through these atoms being energetically favourable.²⁶⁹ According to X-ray diffraction data,⁵ the ligand in $\text{Ag}_2\text{L}_4(\text{NO}_3)_2$, where L is perhydroazepino[1,2-*e*]tetrazole, is coordinated in the bidentate bridging mode, two ligand molecules being coordinated through the N(3) and N(4) atoms, while the other two ligand molecules, through N(4). However, in the polymeric-chain complex CuLCl_2 , where L is 5,5-dimethyl-5,6-dihydro-tetrazolo[5,1-*a*]isoquinoline,²⁷⁰ as well as in palladium(II) chloride complexes with isomeric 5-vinyl-1(2)-methyl-tetrazoles,^{271, 272} only the N(4) atom of the tetrazole ring is involved in coordination (X-ray diffraction data). In the case of steric restrictions (aryl substituent in position 5), palladium chloride forms a bond with the N(3) atom.²⁷³ X-Ray diffraction data have been obtained, indicating that perhydroazepino[1,2-*e*]tetrazole can also function as a bidentate ligand giving formally nine-coordinate complex of samarium(III) **143**.²⁷⁴



N-Substituted tetrazole **144** containing an acetohydrazide group, which can act as a chelating ligand, forms complexes ML_2X_2 with metal nitrates and perchlorates; various types of coordination of this tetrazole to the metal are encountered in the complexes. According to X-ray diffraction data, coordination through the N and O atoms of the acetohydrazide group and the N(4) atom of the tetrazole ring giving linear polymeric chains is found in copper(II)²⁰⁸ and cadmium(II)²⁰⁹ perchlorate complexes. IR data indicate that the same coordination mode is also characteristic of zinc(II),²⁰⁹ nickel(II) and cobalt(II)²⁰⁸ coordination compounds. In the case of lead(II)²¹⁰ and nickel(III)²⁰⁸ complexes, the interaction occurs only through the hydrazide fragment. It was shown by X-ray diffraction analysis²¹⁰ that polymeric chains of the lead nitrate complex are formed due to the tridentate chelating-and-bridging coordination of the nitrate group.

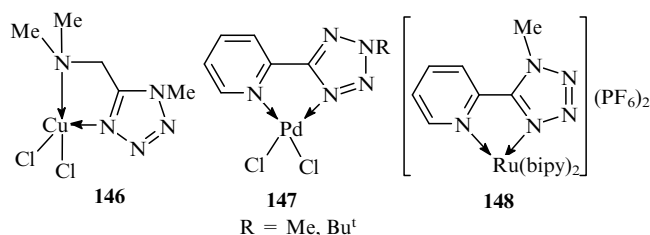


R = NH_2 (a), Me (b), $\text{CH}=\text{CH}$ (c).

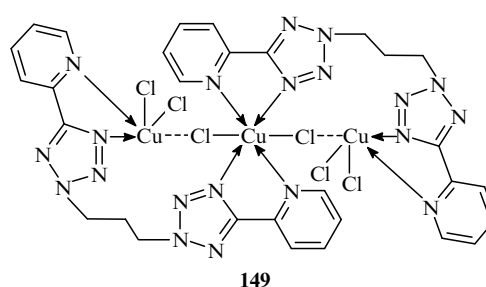
The amino groups of 1-*R*-5-aminotetrazoles **145a-c** can also coordinate the metal atom. A number of complexes of these ligands with transition metals have been prepared and studied.^{40, 84, 88, 275} It was found²⁷⁵ that in the compound $\text{NiL}_2\text{Cl}_2(\text{H}_2\text{O})_{0.5}$, where L is tetrazole **145a**, the exchange interaction between the unpaired electrons of the Ni^{2+} ion is ferromagnetic. According to X-ray diffraction data,²⁷⁶ the complex CuL_2Cl_2 is a 2D coordination polymer in which 1,5-diamino-tetrazole functions as a bridging ligand coordinated by the N(4) atom of the ring and the nitrogen atom of the 1-amino group. It is also worth noting that in the octahedral complex $[\text{Co}(\text{NH}_3)_4\text{L}_2] \cdot (\text{ClO}_4)_3$ (L is tetrazole **145b**), the monodentate tetrazole ligands are coordinated in different ways, namely, by the N(3) or N(4) atom.²⁷⁷ Several compounds of this type, viz. $[\text{Co}(\text{NH}_3)_4\text{L}_2] \cdot (\text{ClO}_4)_3$ and $[\text{Co}(\text{NH}_3)_5\text{L}](\text{ClO}_4)_3$ (L are ligands **145a, b**^{88, 278} or perhydroazepino[1,2-*e*]tetrazole),²⁷⁹ prepared from cobalt ammine complexes **69**, have been reported (see Section II). Their physicochemical properties were studied in detail.^{84, 88, 278, 279}

It was shown by X-ray diffraction²⁸⁰ that 1-methyl-5-dimethylaminotetrazole reacts with copper(II) chloride as a bidentate

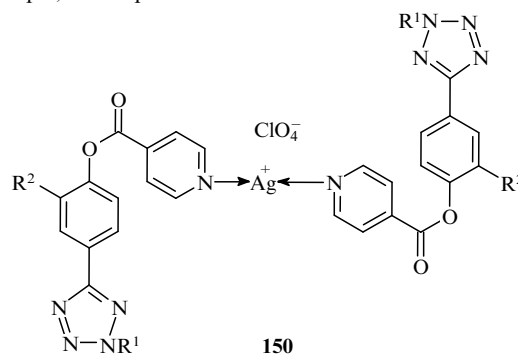
chelating ligand to give complex **146**. 2-Pyridyltetrazole ligands are also coordinated in the bidentate mode when react (in 1 : 1 ratio) with palladium and ruthenium chlorides to give five-membered metallacycles **147** and **148**, respectively.⁵¹



A compound with two pyridyltetrazole fragments and copper(II) chloride form a trinuclear linear complex **149** (X-ray diffraction data) in which the ligand occupies a bridging position between two neighbouring copper atoms.²⁸¹



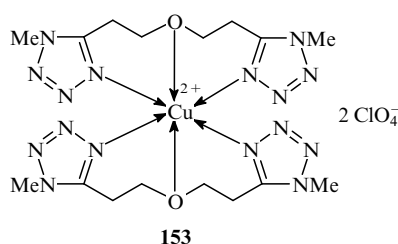
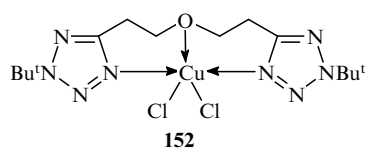
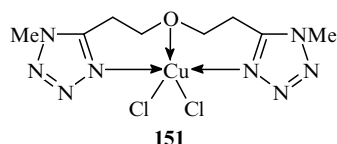
In a search for new metal-containing mesogens, complexes of long-chain 2-alkyltetrazoles containing additionally a 4-pyridyl fragment have been synthesised. The coordination in these complexes was found²⁸² to involve the pyridine nitrogen atom, as for example, in compounds **150**.



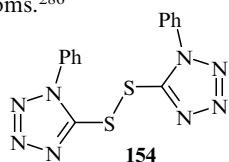
$\text{R}^1 = \text{Alk}$; $\text{R}^2 = \text{H}, \text{OMe}$.

It was shown²⁸² that only silver complexes **150** ($\text{R}^1 = n\text{-C}_9\text{H}_{19}, n\text{-C}_{14}\text{H}_{29}$; $\text{R}^2 = \text{H}$) exhibit mesomorphic properties, smectic S_A phases arising in the temperature range of 174–204 °C. It is noteworthy that analogous ligands containing no pyridine rings are coordinated through the tetrazole N(4) atom and form palladium(II) complexes giving no liquid-crystalline phases.²⁸³

According to X-ray diffraction data,^{284, 285} in copper(II) complexes **151–153**, the exocyclic oxygen atom also participates in the coordination of the metal ion to binuclear tetrazoles. Note that 1,5-bis(1-methyltetrazol-5-yl)-3-oxapentane isolated as perchlorate reacts with copper(II) chloride to yield complex **151** or **153**, depending on the nature of the solvent. In complex **151**, the intermolecular interactions of the $\text{C}-\text{H}\cdots\text{Cl}$ and $\text{C}-\text{H}\cdots\text{N}$ types are responsible for the formation of infinite one-dimensional chains.²⁸⁵



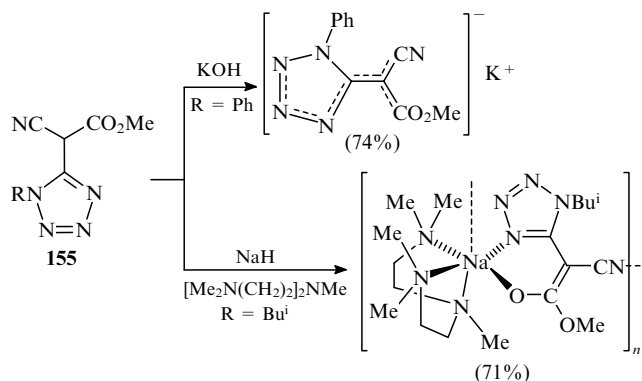
On the basis of IR spectra of disulfide **154** and the complexes $\text{MO}_2\text{L}_2\text{Cl}_2$ ($\text{M} = \text{Mo}, \text{W}$; L is compound **154**), it was concluded that the ligands are coordinated through one of the sulfur atoms.²⁸⁶



The complex formation of the tetrazole analogues of peptides deltorphin,²⁸⁷ β -casomorphin,²⁸⁸ enkephalin²⁸⁹ and tetraalanine²⁹⁰ has been studied by potentiometric and spectroscopic methods. The stability constants of the copper(II) complexes formed in aqueous solutions were determined; it was shown that the introduction of a 1,5-tetrazolyl fragment, which mimics the *cis*-amide group, into the peptide gives rise to peptide agents that efficiently chelate copper(II) ions under physiological conditions. The site of introduction of the tetrazolyl fragment into the amino acid residues has a crucial influence on the coordinating ability of the compounds. The obtained data may underlie the simulation of the peptide–metal binding sites.

IV. Metal derivatives of *C,N*-substituted tetrazoles generating anionic centres in the substituent

N-Substituted tetrazoles containing electron-withdrawing proton-containing substituents in the 5-position of the ring are capable of tautomeric transformations. They can be deprotonated to give various anionic forms that react with metal cations to give, as a rule, chelate complexes **3**. In recent years, the ways of synthesis of MT of various dimensions based on tetrazole-containing cyanoacetates **155** have been studied in detail. Depending on the nature of reactants and synthesis conditions, these tetrazoles react with alkali metal compounds to give (according to X-ray diffraction data) salts or complexes.^{291,292}



The reactions of these ligands or enol forms of compounds **156** with transition metal salts occur in different ways. By varying the nature of substituents and using metal ions with appropriate coordination properties, one can obtain mono- and binuclear complexes and also polymeric structures of different dimensionality. The composition and dimensionality of the ML_m complexes are presented in Table 3.

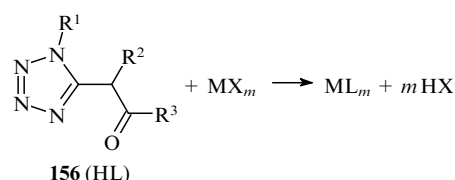
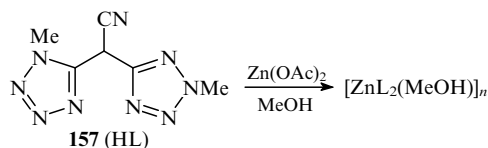


Table 3. Composition and dimensionality of the complexes ML_m derived from ligand **156**.

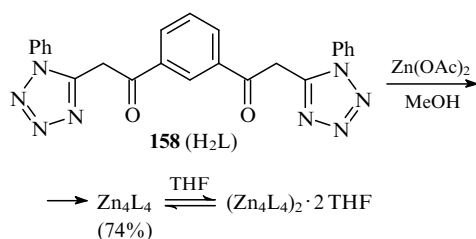
R^1	R^3	MX_m	Complex ML_m			Yield (%)	Ref.
			composition	dimensionality	polyhedron		
Et	Ph	FeCl_3	FeL_3^a		FeN_3O_3	60–90	293
Bu^t	Ph	FeCl_3	FeL_3^a		FeN_3O_3	84–89	294
Bu^i	OMe	FeCl_3	FeL_3		FeN_3O_3	84–89	294
Bu^t	OMe	$\text{Cu}(\text{OAc})_2$	$[\text{CuL}_2]_n$	1	CuN_4O_2	71	295
Bu^t	Bu^t	$\text{Cu}(\text{OAc})_2$	$[\text{CuL}_2]_n$	2	CuN_4O_2	86	296
Bu^t	Bu^t	$\text{Cu}(\text{OAc})_2$	$[\text{CuL}_2]_n$	3	CuN_4O_2	90	297
neo- C_5H_{11}	OMe	FeCl_3	FeL_3		FeN_3O_3	—	293
neo- C_5H_{11}	OMe	FeSO_4	$[\text{FeL}_2]_n$	3	FeN_4O_2	—	293
neo- C_5H_{11}	OMe	$\text{Cu}(\text{OAc})_2$	$[\text{CuL}_2]_2$		CuN_3O_2	—	295
Bn	OMe	FeCl_3	FeL_3		FeN_3O_3	84–89	293
Bn	OMe	FeSO_4	$[\text{FeL}_2]_n$	3	FeN_4O_2	—	293
Ph	Me	$\text{Cu}(\text{OAc})_2$	$[\text{CuL}_2]_n$	2	CuN_4O_2	82	296
Ph	Me	$\text{Zn}(\text{OAc})_2$	$\text{ZnL}_2(\text{MeOH})_2$		ZnN_2O_4	65	296
Ph	OMe	$\text{Cu}(\text{OAc})_2$	CuL_2		CuN_2O_2	95	296
4- MeC_6H_4	Bu^t	$\text{Cu}(\text{OAc})_2$	$[\text{CuL}_2(\text{MeOH})_2]_n$	1	CuN_2O_4	88	295
4- EtC_6H_4	OMe	FeCl_3	FeL_3		FeN_3O_3	84–89	293
4- EtC_6H_4	OMe	FeSO_4	$[\text{FeL}_2]_n$	3	FeN_4O_2	—	293

^a In these cases, $\text{R}^2 = \text{H}$, in other cases, $\text{R}^2 = \text{CN}$.

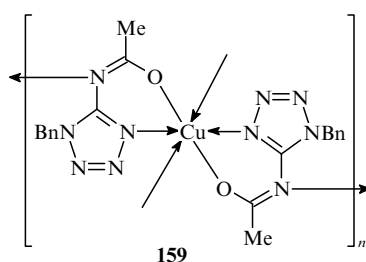
The second tetrazole ring can also act as an electron-withdrawing substituent in the carbon chain. Thus, bistetrazole **157** reacts with zinc acetate in methanol to give a complex (in 78% yield), representing, according to X-ray diffraction data, a one-dimensional coordination polymer with rather short (2.257 Å) intermolecular $\text{Zn} \cdots \text{N} \equiv \text{C}$ bonds.²⁹⁸



Bis(tetrazolylmethyl ketone) **158** undergoes double deprotonation in the reaction with zinc acetate to give the tetranuclear chelate Zn_4L_4 , which crystallises from THF as cryptatoclathrate (according to X-ray diffraction data); this dissociates in solution.²⁹⁹ In the 3D structure of this compound, each zinc ion is connected to three ligands, and the coordination sphere is a distorted trigonal bipyramid. When made to react with iron(III) chloride in the presence of triethylamine, compound **158** forms the complex Fe_2L_3 with D_3 symmetry and the (Δ, Δ) – (Λ, Λ) –*fac*-configuration of the Fe(III) coordination polyhedron (octahedron), and the *p*-phenylene ligand of this type forms a tetranuclear adamantane-like chelate complex.²⁹⁹



The reactions of acyl derivatives of *N*-alkyl-5-aminotetrazoles with metal salts proceed in a similar way, the amide group being deprotonated. For example, 5-acetylamino-1-benzyltetrazole reacts with copper(II) acetate to give complex **159** (in 74% yield), which is self-assembled into a stair-like one-dimensional supramolecular structure owing to the intermolecular interaction between the coordinatively unsaturated copper(II) ion and the nitrogen atom of the amide group. The copper(II) environment in this complex is a tetragonal bipyramid.²⁹⁵



The introduction of an α -pyridyl group into these ligands changes considerably their coordination properties. *N*-(2-Alkyl-tetrazol-5-yl)pyridine-2-carboxamides and -thioamides **160** were shown^{300, 301} to react with copper(II), zinc(II), cobalt(II) and nickel(II) acetates at 20 °C to give a series of mono-, bi- and tetranuclear complexes differing appreciably in the structure of the coordination unit, which decompose only at temperatures above 250 °C [note that during the synthesis Co(II) was oxidised to Co(III)]. For the Ni_4L_8 complexes and their solvates with metal–metal distances of 5.56–5.57 Å, a weak intramolecular ferromagnetic interaction has been found^{300, 302}

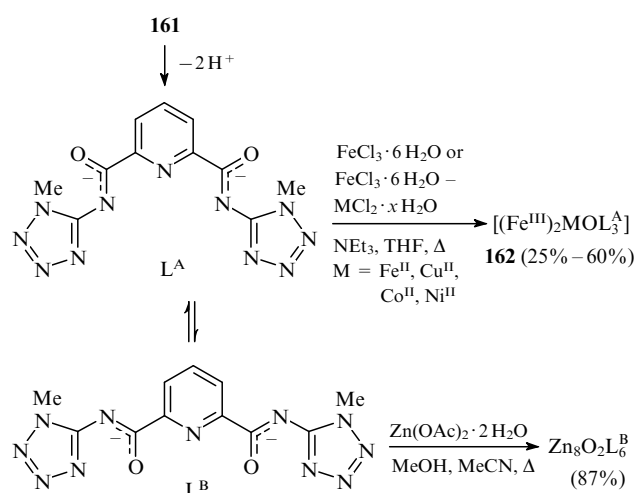
$\xrightarrow[\text{MeOH}]{\text{M(OAc)}_2}$

ML_3
 M_2L_4
 M_4L_8

160 (HL)

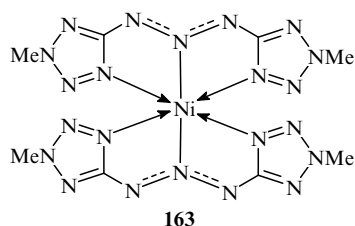
X	R	M	Complex composition	Coordination polyhedron	Yield (%)	Ref.
O	Me	Zn	Zn_4L_8	ZnN_5O	86	300
O	Me	Co(II)	Co(III)L_3	CoN_6	85	301
O	Et	Cu	Cu_2L_4	CuN_5	82	301
O	Et	Ni	Ni_4L_8	NiN_5O	85	300
S	Et	Ni	Ni_4L_8	NiN_5S	79	301
S	Et	Cu	Cu_2L_4	CuN_3S_2	51	301

A ditetrazole derivative of this type, *N*(2),*N*(6)-bis(1-methyl-tetrazol-5-yl)pyridine-2,6-dicarboxamide (**161**), has been used^{303, 304} for the synthesis of transition metal oxo complexes. This compound undergoes double deprotonation, and the doubly charged anion exists in solution as two rotamers, L^{A} and L^{B} ; these species selectively form oxo complexes of two different types, Fe_2MOL_3 [$\text{M} = \text{Fe(II)}, \text{Cu(II)}, \text{Co(II)}, \text{Ni(II)}$] and $\text{Zn}_8\text{O}_2\text{L}_6$. These complexes are considered as models of metalloproteins and promising oxidation catalysts.

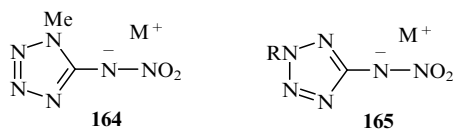


The structures and properties of trinuclear oxo-centred complexes have been studied in most detail using a variety of spectroscopic, electrochemical and spectroelectrochemical methods and X-ray diffraction analysis. In these compounds, the ligand acquires the shape of a helix and binds all three metal atoms by five electron-donating nitrogen atoms, giving rise to complexes stable in solution and in the solid state (m.p. > 250 °C with decomposition). These complexes show unusual electronic properties of the central $\text{Fe}_2^{\text{III}}\text{M}^{\text{II}}\text{O}$ core, which imply the possibility of fine tuning of the parameters of the reversible electron transitions $\text{Fe}^{\text{III}} \rightleftharpoons \text{M}^{\text{II}}$ by external action. According to X-ray diffraction data, compounds **162** ($\text{M} = \text{Fe}, \text{Ni}, \text{Cu}$) correspond to the D_3 point group of symmetry, three metal ions being indistinguishable in these structures. The metal–metal distances (3.267–3.287 Å) are somewhat shorter than those in similar complexes with carboxylate bridges (3.306–3.308 Å). Mixed-valence iron complex **162** can be easily converted into $[\text{Fe}_3^{\text{III}}\text{OL}_3]$ by treatment with cerium(IV) nitrate; the reaction of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ with the ligand under consideration in the presence of triethylamine at room temperature affords the ionic complex $(\text{HNEt}_3)[\text{Fe}^{\text{III}}\text{L}_2]$ (yield 87%).³⁰⁴

The triazene ligand $\text{RNHN}=\text{NR}$ (R is 2-methyltetrazol-5-yl) is also easily deprotonated in the reaction with nickel chloride. The resulting dark red crystals of mononuclear complex **163** are thermally stable despite the high content of nitrogen, and undergo no changes below 250°C .³⁰⁵

**163**

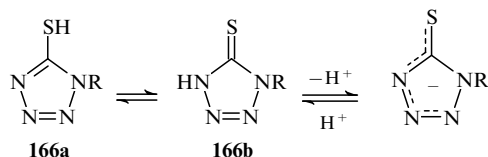
Like the initial 5-aminotetrazole (**13**), its 1- and 2-methyl derivatives react with tetranitromethane in alkaline media to give 5-nitraminotetrazole salts **164**, **165** (yields 65%–85%), which vigorously decompose at temperatures of $248\text{--}325^\circ\text{C}$. In the case of *N*-cyanoethyl derivatives, this reaction occurs smoothly only for the 2-isomer. The nitration of 5-amino-1-cyanoethyltetrazole is accompanied by dealkylation to give salts **12**.³⁰⁶

**164****165**

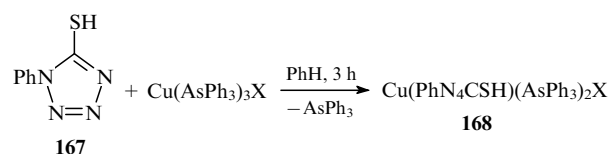
M = Li, Na, K, Rb, Cs (**164**); R = Me, $\text{CH}_2\text{CH}_2\text{CN}$; M = Na, K (**165**).

Silver(I) complexes based on *N*-nitraminotetrazole anions **110** ($\text{R}^1 = \text{H}$, $\text{R}^2 = \text{NHNO}_2$) and **111** ($\text{R}^1 = \text{H}$, $\text{R}^2 = \text{NHNO}_2$; $\text{R}^1 = \text{NHNO}_2$, $\text{R}^2 = \text{Me}$) have also been reported.⁶⁴ These 1:1 complexes were prepared in almost quantitative yields from ammonium salts of tetrazoles and silver nitrate in water; they are stable under ambient conditions and susceptible to explosive decomposition on heating; their decomposition temperatures lie in the range of $180\text{--}275^\circ\text{C}$.

Of substantial value for MT synthesis are *N*-substituted 5-mercaptotetrazoles **166**, which may exist in thiol **166a** and thione **166b** tautomeric forms, form **166b** predominating in the condensed state.³⁰⁷ These compounds are readily deprotonated to give tetrazolethiolate anion, which is a stable 6π -electron cyclic system.

**166a****166b**

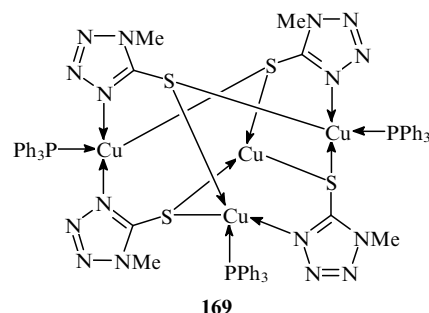
Depending on the reagents and reaction conditions, 5-mercaptotetrazoles **166** (R = Ph, 4-MeC₆H₄, 3-MeC₆H₄, 4-ClC₆H₄) form complexes involving both deprotonated (L) and neutral (HL) forms, for example, $\text{Bi}(\text{HL})_2\text{Cl}_3$, $\text{Bi}(\text{HL})(\text{H}_2\text{O})\text{Cl}_3$,³⁰⁸ $\text{VO}_2(\text{HL})_2\text{Cl}(\text{H}_2\text{O})$, $\text{NbL}_2(\text{H}_2\text{O})\text{Cl}_3$ and $\text{TaL}_5(\text{H}_2\text{O})$.³⁰⁹ Complexes with a neutral form of the ligand are prepared by reactions of tetrazoles **166** with a metal salt in ethanol or aqueous ethanol solution with heating and with maintaining of the required pH. The nature of the substituent R and metal cation also influence the composition of the complex and the form of existence of the ligand in the complex. The data from IR, electronic and ^1H NMR spectroscopy provided the conclusion³¹⁰ that neutral 1-substituted mercaptotetrazoles are coordinated in the thione form **166b**. It was also shown that 5-mercapto-1-phenyltetrazole (**167**) displaces triphenylarsine from copper(I) triphenylarsine complexes to give complexes **168** involving the neutral form of the tetrazole ligand, which is coordinated in the thione form through the sulfur atom.³¹⁰

**167****168**

X = Cl, Br, I.

However, no structural data are still available for this type of complexes. In some cases,^{308,311} data on the composition and properties of complexes have been improperly interpreted.

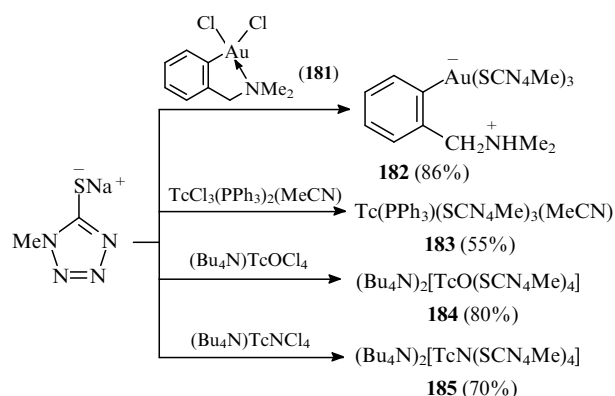
Complexes with mercaptotetrazole anions are mainly prepared by substitution of an appropriate thiolate anion (taken as the ammonium or sodium salt) for a halide ion. They can also be prepared by the reaction of the metal salt with a neutral ligand in the presence of an amine. A number of neutral and ionic complexes of 1-methyl- and 1-phenyltetrazole-5-thiones have been prepared by this method; their molecular structures have been studied by X-ray diffraction: $(\text{Ph}_3\text{P})_3\text{Cu}_4(\text{MeN}_4\text{CS})_4 \cdot \text{CH}_2\text{Cl}_2$ (**169**), $[\text{Ph}_3\text{PAu}(\text{MeN}_4\text{CS})]_2$ (**170**), $\text{Ph}_3\text{PAu}(\text{PhN}_4\text{CS})$ (**171**), $(\text{Ph}_3\text{P})_2\text{Ag}(\text{PhN}_4\text{CS}) \cdot \text{CH}_2\text{Cl}_2$ (**172**), $(\text{Ph}_3\text{P})_2\text{Hg}(\text{MeN}_4\text{CS})_2$ (**173**), $(\text{AsPh}_4)_2[\text{Hg}(\text{MeN}_4\text{CS})_4]$ (**174**), $(\text{AsPh}_4)_2[\text{Pd}(\text{MeN}_4\text{CS})_4]$ (**175**), $\text{AsPh}_4[\text{Au}(\text{PhN}_4\text{CS})_2]$ (**176**), $\text{AsPh}_4[\text{Au}(\text{PhN}_4\text{CS})_4]$ (**177**),³¹² $\text{NEt}_4[\text{Au}(\text{MeN}_4\text{CS})_4]$ (**178**),³¹³ $\text{PPh}_4[\text{Au}(\text{MeN}_4\text{CS})_4] \cdot 0.5 \text{H}_2\text{O}$ (**179**),³¹⁴ $(\text{Ph}_3\text{P})_2\text{Ag}(\text{PhN}_4\text{CS}) \cdot \text{MeOH}$ (**180**).³¹⁵ Note that tetranuclear complex **169** is formed upon crystallisation of the dimeric compounds $[\text{Ph}_3\text{PCu}(\text{MeN}_4\text{CS})]_2$ existing in solution and has an unusual asymmetric structure. One copper atom not bound to triphenylphosphine is coordinated only by three sulfur atoms and the other three copper atoms are tetracoordinated by the P, N and S atoms.

**169**

In complexes **170–180**, 1-R-5-mercaptotetrazoles are coordinated to the metal atom in the monodentate mode through the sulfur atom. Complex **170** is a dimer owing to the intermolecular Au–S bonds, while the other compounds are monomers. Unexpectedly, the M–P bonds in all triphenylphosphine complexes were found to be shorter than the M–S bonds. On the basis of Raman spectra and quantum-chemical calculations for tetrazole **167**, its sodium salt and the complex $\text{Ag}(\text{PhN}_4\text{CS})$, one can conclude that in the absence of other ligands, this tetrazole is bound to silver(I) by two donor atoms, S and N(4).³¹⁶

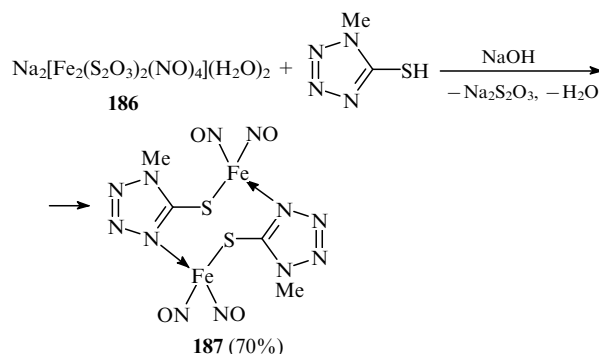
The substitution reaction in gold(III) complex **181** on treatment with sodium 1-methyltetrazole-5-thiolate was found³¹³ to involve Au–N bond cleavage, protonation of the dimethylamino group and the formation of zwitter-ion complex **182** in which the gold atom (X-ray diffraction data) has a distorted square planar environment (AuCS_3). Compound **181** exhibits an antitumour activity; therefore, studies of the ligand exchange in this complex and the biological activities of the products obtained arouse considerable interest.^{313,317} The replacement of chloride ions in complex **181** by successive treatment with diphenylthiocarbazone and 5-mercapto-1-methyltetrazolate anion to give mixed-ligand complex has been carried out.³¹⁷

The 5-mercapto-1-methyltetrazolate anion also reacts as a monodentate ligand to form technetium(III) and (V) complexes **183–185**.³¹⁸ During the synthesis of nitride complex **185**, Tc(VI) is reduced to Tc(V), which is also typical of reactions with other

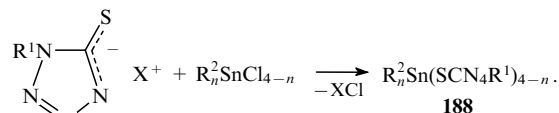


S-donor ligands. According to X-ray diffraction data, ionic complexes **184** and **185** have a square pyramidal structure, while neutral complex **183** has a trigonal bipyramidal geometry in which the triphenylphosphine and acetonitrile molecules are coordinated in the axial positions. An attempt has been made³¹⁹ to carry out quantum-chemical prediction of the spin state of transition metal complexes, including the technetium(III) complex **183**.

By exchange of thiosulfate ligands in complex **186** for the 1-methyltetrazole-5-thiolate anion, binuclear nitrosyl iron complex **187** has been synthesised.³²⁰ On the basis of IR and Mössbauer spectroscopy data, it was concluded that in this complex, tetrahedrally coordinated iron atoms are bound to each other by two $\text{N}=\text{C}-\text{S}$ bridges. Complex **187** is stable in air and can be used as a model to study the mechanism of transformations of the nitrosyl adducts of $[\text{2Fe},\text{2S}]$ -proteins *in vivo*.



The synthesis and structure of the complexes of organotin 1-R-5-thiotetrazoles **188** have been studied in detail. The complexes are obtained at room temperature according to the following scheme:

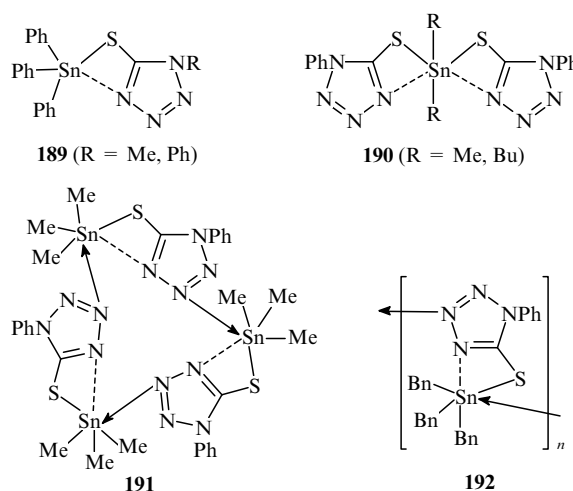


R^2	n	X	Yield (%)	Ref.
Ph ^a	3	Na	88	321
Me	3	Na	67	322
Me	3	NH ₄	59	323
Bu	3	Na	74	322
CH ₂ Ph	3	NH ₄	74	323
Ph	3	Na	70	322
Me	2	NH ₄	26	323
Bu	2	Na	58	322
CH ₂ Ph	2	NH ₄	79	323
Ph	2	Na	69	322
Me ^b	2	Na	52	322

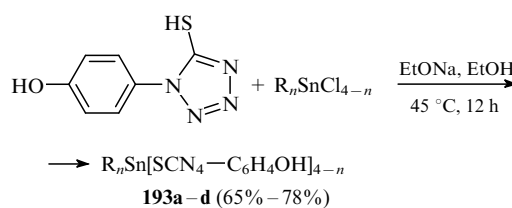
^a In this case, $\text{R}^1 = \text{Me}$, and in other cases, $\text{R}^1 = \text{Ph}$; ^b only one chloride ion is replaced under the synthesis conditions to give $\text{Me}_2\text{SnCl}(\text{SCN}_4\text{Ph})$.

These compounds can also be prepared by cycloaddition of organic isothiocyanates to R_3SnN_3 but this route is seldom used. Syntheses of the complexes $\text{Bu}_3\text{Sn}(\text{SCN}_4\text{Me})$ and $\text{Bu}_3\text{Sn}(\text{SCN}_4\text{Ph})$ have been reported.³²²

All the obtained complexes have been studied by ^1H , ^{13}C and ^{119}Sn NMR and Mössbauer spectroscopy and X-ray diffraction analysis. In solution, these compounds are monomers, the tin atom has a tetrahedral coordination and is bound to the tetrazole ligand through the donor sulfur atom. In the solid state, X-ray diffraction analysis shows the formation of an additional weaker intramolecular bond, $\text{Sn}-\text{N}(4)$, the length of which is 2.94–3.28 Å [for example, in compounds **189** ($\text{R} = \text{Me}$),³²¹ **190** ($\text{R} = \text{Me}$),³²⁵ **191** ($\text{R} = \text{Me}$),³²⁶ **192** ($\text{R} = \text{Bu}$)]. In the complexes $\text{R}_3\text{Sn}(\text{SCN}_4\text{Ph})$ [$\text{R} = \text{Me}$ (**191**),³²⁶ Bu (**192**)], the tetrazole ligand forms an intermolecular $\text{Sn}-\text{N}(3)$ bond thus increasing the coordination number of the central atom to 6. This bond (2.6–2.7 Å) is essentially shorter than the intramolecular bond (3.2–3.3 Å). As a result, the complex is a trimer for $\text{R} = \text{Me}$ and a linear polymer for $\text{R} = \text{Bu}$.



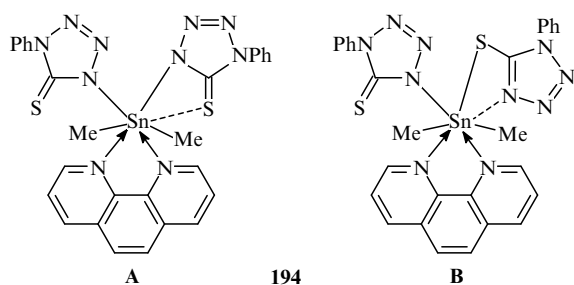
The presence of a hydroxy group in the benzene ring of 5-mercapto-1-phenyltetrazole was found³²⁷ to have a substantial influence on the structure of di- and trialkyltin compounds. A series of such compounds **193** have been prepared and studied by IR and ^1H NMR spectroscopy.



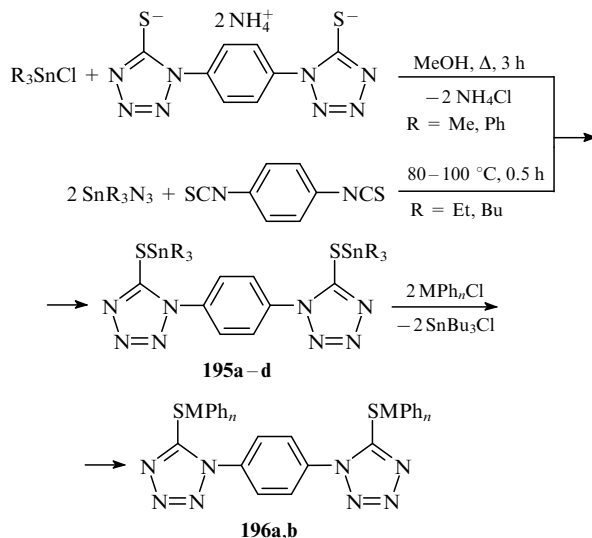
$n = 3$: $\text{R} = \text{Ph}$ (**a**), Bu (**b**); $n = 2$: $\text{R} = \text{Me}$ (**c**), Bu (**d**).

Complexes **193a–d** have also been studied by X-ray diffraction. The presence of an intermolecular $\text{Sn}-\text{N}$ bond in complex **193b** and intermolecular $\text{O}-\text{H}\cdots\text{X}$ hydrogen bonds ($\text{X} = \text{O}, \text{N}, \text{S}$) in the crystal structures of compounds **193a,c** gives rise to polymeric chains and two-dimensional networks. In addition, strong $\pi-\pi$ interaction of the hydroxyphenyl fragments was found in complexes **193b,c**. In compound **193c**, the intramolecular $\text{Sn}-\text{N}$ bond (2.704 Å) is shorter than that in related complex **190** ($\text{R} = \text{Me}$) (2.947 Å).

The 5-mercapto-1-phenyltetrazolate anion can be coordinated only through the tetrazole $\text{N}(4)$ atom. According to X-ray diffraction data,³²⁸ the unit cell of the crystalline mixed-ligand complex **194** contains two independent molecules **A** and **B**, which are formally bond isomers.



Organotin complexes **195** were prepared from 1,4-phenylenedi(tetrazolethiols) by two methods;³²⁹ the same ligands were used to synthesise lead- and mercurio-thiotetrazoles.



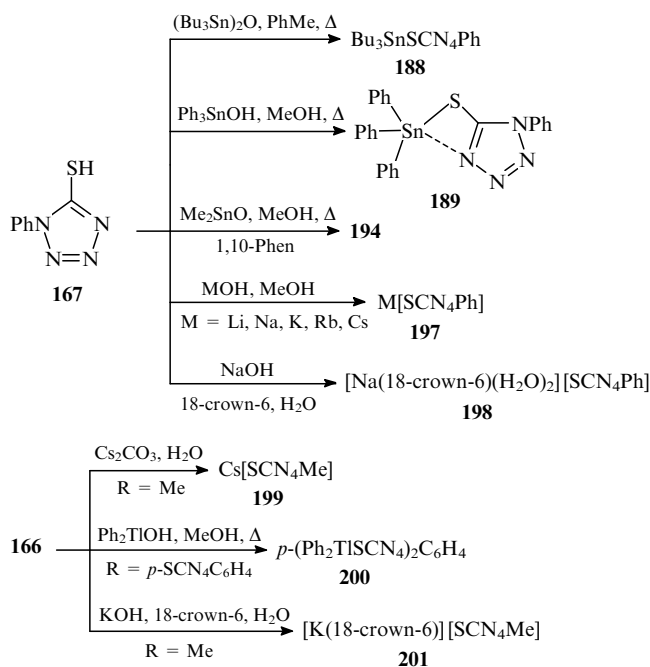
195: R = Me (**a**, 77%), Et (**b**, 53%), Bu (**c**, 55%), Ph (**d**, 40%);
196: M = Pb, $n = 3$ (**a**, 33%); M = Hg, $n = 1$ (**b**, 80%).

According to X-ray diffraction, the supramolecular structure of compound **195c** is a 2D polymer consisting of 32-membered rings $(\text{NC}_4\text{SSnN}_2\text{CSSnN}_3)_2$. The asymmetric cell contains two trigonal bipyramidal *trans*- NSSnN_3 fragments. The tin atom is bound to the ligand through sulfur and is coordinated by the N(4) atom of the tetrazole ring of the neighbouring molecule. Conversely, trimethyltin derivative **195a** crystallises with two methanol molecules and gives a linear polymeric structure due to hydrogen bonds, the tin atom having a trigonal bipyramidal environment, *trans*- SOSnN_3 . The polymer is formed by 14-membered rings $(\text{SnSCN}_2\text{HO})_2$ connected by phenylene bridges. A similar coordination polyhedron geometry and a polymeric structure were also found for complex **195b** by Mössbauer spectroscopy. Complex **195d** is monomeric and might contain a weak intramolecular Sn–S bond. According to ^{119}Sn NMR data obtained in DMSO, the metal atom in compounds **195c,d** has a tetrahedral coordination environment, while in the case of methyl and ethyl derivatives **195a,b**, the coordination number of tin increases to 5 due to coordination of the solvent. According to ^{207}Pb NMR data, a similar coordination mode is observed for the lead atom in compound **196a**.

Interesting data have been obtained³³⁰ for the compound $\text{Ph}_3\text{PbSCN}_4\text{Ph}$ synthesised by the exchange reaction of Ph_3PbCl with the ammonium salt of tetrazole **167**. The compound has a one-dimensional polymeric structure formed due to the intermolecular Pb–N(2) contact (the bond length is 3.339 Å). The unusual orientation of the tetrazole ring with respect to the lead atom [the intermolecular Pb–N(2)–N(1)–N(4) dihedral angle is 126.1°] prompted the hypothesis of π -coordination of the tetrazole ring to the metal atom.

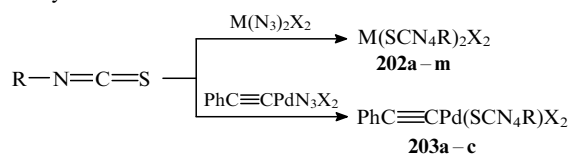
Due to the rather high acidity of 5-mercaptotetrazoles **166** ($\text{p}K_a = 2.8\text{--}3.6$),¹¹ their metal complexes, for example, com-

pounds **188**,³³¹ **189**,³²⁴ **194**,³²⁸ **197**,³³² **198**,³³³ **199**,³³⁴ **200**,³²⁸ **201**,³³⁵ can be prepared by the reaction of these tetrazoles with basic reagents.



X-Ray diffraction data confirm the different coordination modes of the anion of tetrazole **167** in compounds **197**.³³² The coordination number of the cations increases from 5 to 8 following an increase in the ionic radius on passing from Na^+ to Cs^+ . In K^+ , Rb^+ and Cs^+ complexes, four-membered MSCN rings are formed upon bidentate coordination of the ligand by the S and N(4) atoms, while in Rb^+ and Cs^+ compounds, $\text{Rb}\cdots\text{C}$ and $\text{Cs}\cdots\text{C}$ contacts with the carbon atom of the phenyl group were also found. As was to be expected, the alkali metal ion in complexes **198**³³³ and **201**³³⁵ is coordinated by the crown ether and, in the case of the sodium compound, no direct reaction between the metal and tetrazole takes place. Conversely, in the crystal structure of **201**, the potassium ion has a contact with the N(4)–C(5)–S fragment of the tetrazole ligand [bond lengths: K–N(4) 2.934(4) Å, K–C 3.469(4) Å, K–S 3.373(2) Å]; in this respect, this complex bears the similarity with the complexes of organotin compounds considered above where the Sn–S and Sn–N distances are in the range of 2.617–3.255 Å.

A series of Pd(II) and Pt(II) complexes with 1-R-5-mercaptotetrazoles **202**³³⁶ and **203**¹³³ have been obtained by 1,3-cycloaddition of the azido complexes of these metals to organic isothiocyanates.

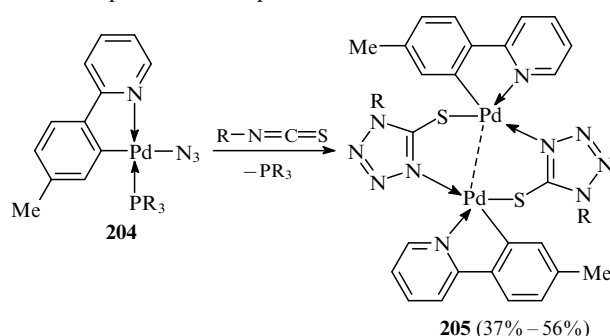


Compound	M	R	X or X ₂	Yield (%)
202a	Pd	Et	PMe ₃	88
202b	Pd	CH ₂ CH=CH ₂	PMe ₃	75
202c	Pd	PhCH ₂	PMe ₃	81
202d	Pd	Ph	PMe ₃	59
202e	Pd	Ph	PMe ₂ Ph	93
202f	Pd	2,6-Me ₂ C ₆ H ₃	PMe ₃	45
202g	Pd	2,6-Me ₂ C ₆ H ₃	PEt ₃	72
202h	Pt	Et	PMe ₃	91
202i	Pt	Ph	PMe ₃	92
202j	Pt	Ph	PEt ₃	64

Compound	M	R	X or X ₂	Yield (%)
202k	Pd	Ph	Et ₂ P(CH ₂) ₂ PEt ₂	76
202l	Pt	Ph	Et ₂ P(CH ₂) ₂ PEt ₂	66
202m	Pt	2,6-Me ₂ C ₆ H ₃	Et ₂ P(CH ₂) ₂ PEt ₂	92
203a	Pd	Et	PMe ₃	61
203b	Pd	2,6-Me ₂ C ₆ H ₃	PMe ₃	71
203c	Pd	2,6-Me ₂ C ₆ H ₃	PEt ₃	82

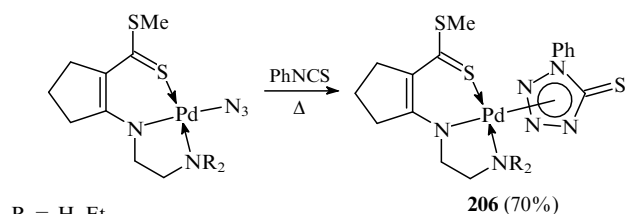
The binuclear complex 1,4-[PhC≡CPd(PEt₃)₂SCN₄]₂C₆H₄ was synthesised in a similar way from *p*-phenylene diisothiocyanate in 37% yield.¹³³ Treatment of azide complex **204** with alkyl isothiocyanates results in unusual binuclear palladium complexes **205**, which may contain an intramolecular metal–metal bond.

According to X-ray diffraction data, the Pd–Pd distance in complex **205** (R = Prⁱ) is equal to 2.9704(6) Å, which is smaller than twice the covalent radius of palladium (1.380 Å), but larger than the length of the single Pd–Pd bond (2.55–2.8 Å) in other binuclear palladium complexes.³³⁷



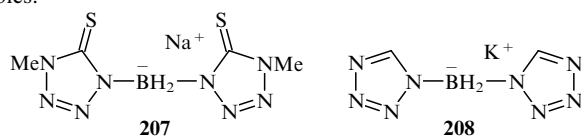
R = Et, Prⁱ, Buⁿ, CH₂=CHCH₂.

The data from IR and ¹H, ¹³C and ³¹P NMR spectroscopy and X-ray diffraction analysis of compounds **202b,d,h,m** and **203b** are indicative of S-coordination of thiotetrazoles in these complexes. The Pd–S bond lengths (2.325–2.365 Å) are typical of analogous neutral and anionic Pd and Au tetrazolethiolate complexes **170**, **171**, **175**–**177** prepared in a different way. Note that coordination of the tetrazole ring through the nitrogen atom has previously been suggested based on IR and ¹H NMR spectra for Pd(II) complexes **206** prepared by cycloaddition of azide complexes to phenyl thiocyanate.¹³² Apparently, spectroscopic data alone are inadequate to draw this conclusion, as the vibration frequency of the C=S fragment bound to nitrogen atoms has not been reliably assigned as yet.³¹⁶



R = H, Et.

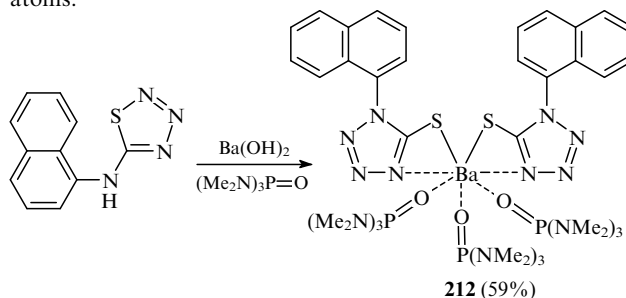
A number of MT based on tetrazolyldihydroborate anions have been synthesised; they were formed as salts **207**³³⁸ and **208**^{339,340} from sodium and potassium borohydrides and tetrazoles.



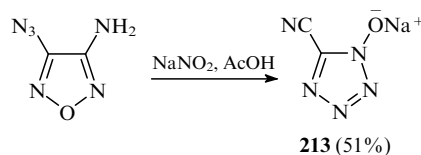
Compounds **207** and **208** react with bivalent metal salts in methanol and water, respectively, to give crystalline complexes [M{H₂B(SCN₄Me)₂}₂] [**209**; M = Co (**a**), Ni (**b**)]³³⁸ and

[M{H₂B(CHN₄)₂}₂(H₂O)₂](H₂O)₂ (**210**; M = Co, Zn, Cd, Mn, Fe).^{341–343} The reaction of compound **208** with nickel(II)³⁴² and copper(II)³⁴³ salts in water results in loose amorphous precipitates, which can be dissolved in ammonia and then crystallised as polymeric complexes [M{H₂B(CHN₄)₂}₂(NH₃)₂]_n (**211**; M = Cu, Ni).^{341,342} The structures of the resulting complexes were investigated by various spectroscopic methods and X-ray diffraction. It was shown³³⁸ that the dihydrobis(1-methyl-5-thiotetrazol-4-yl)borate anion is coordinated as a bidentate ligand (*k*²-S,S) in complex **209a** and as a tridentate ligand (*k*³-S,S,HB) in complex **209b**, i.e., rather strong Ni...H–B interaction is manifested. Conversely, in compounds **210**, dihydrobis(tetrazolyl)borate anion acts as a bridging ligand, being coordinated through the N(4) atoms of both rings and forming a 2D structure. Complexes **211** also have a 2D structure with polyhedron distortion due to the Jahn–Teller effect typical of copper. The coordination polyhedron is formed by four nitrogen atoms of two bis(tetrazolyl)borate ligands and two ammonia molecules in *trans*-positions.^{341–343}

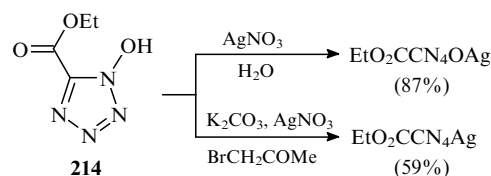
The properties and structures of two MT prepared by an unusual method, namely, by recyclisation, have been reported.^{344,345} 5-Aminothiatetrazoles are known to isomerise into 5-mercaptotetrazoles on treatment with an aqueous solution of sodium hydroxide. Using 5-(1-naphthylamino)-1,2,3,4-thiatetrazole as an example, it was shown³⁴⁴ that this isomerisation occurs more efficiently under the action of barium hydroxide in toluene in the presence of hexamethylphosphoramide. This gives solvated complex **212** in which the ligands form chelate rings due to coordination of the tetrazole ring through sulfur and nitrogen atoms.³⁴⁴



An unexpected transformation of aminoazidofurazan induced by sodium nitrite yields rather stable (m.p. = 255 °C) sodium salt of 5-cyano-1-hydroxytetrazole (**213**).³⁴⁵ In the crystal structure of the hydrate of salt **213**, the sodium atom in the NaN₃O₄ polyhedron is coordinated by the nitrogen atom of the nitrile group, by the N(3) and N(4) atoms of three anions and by oxygen atoms of four water molecules.



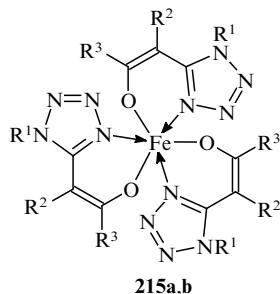
It is noteworthy that, being rather strong OH acids, 1-hydroxytetrazoles are capable of ready formation of stable salts with metals or nitrogen bases. A sequence of transformations of ethyl 1-hydroxytetrazole-5-carboxylate (**214**) has been reported;³⁴⁶ compound **214** readily forms a silver salt and, like other 1-hydroxytetrazoles, reacts with bromoacetone in the presence of potassium carbonate to be reduced to ethyl tetrazole-5-carboxylate, which was isolated as the silver salt. The structure of silver compounds of this type has not been determined as yet.



V. Applications of metal tetrazole derivatives

A key application of MT is organic synthesis, where they are used as the starting and intermediate compounds for the preparation of practically valuable substances. First, this is synthesis of *N*-substituted tetrazoles from various metal tetrazolates.^{1–3, 15, 16, 23, 347–349} By using metal derivatives **1b** and **2** containing covalently bound metal, it is possible in some cases to obtain selectively one of the possible *N*-substituted tetrazole isomers **110** and **111**.^{69, 89, 110, 121, 347–349} This approach is successfully used not only to prepare simplest *N*-alkyltetrazoles, but also for the synthesis of *N*-aryl- and *N*-hetaryltetrazoles^{23, 156, 186, 350} and for introduction of tetrazolyl groups into complex biologically active compounds.^{351, 352} The replacement of traditional alkylating agents in these processes by other halogen-containing compounds provides the route to 2-phosphinetetrazoles,³⁴⁸ 2,5-disubstituted triazolo[3,4-*b*][1,3,4]thiadiazoles,³⁵³ tetrazolylmethylaminoglyoximes and furazans³⁵⁴ difficult to prepare by other methods. Alkylation of metal 5-mercaptotetrazolates plays an important role in the synthesis of biologically active compounds incorporating a 1-*R*-tetrazole-5-thiolate fragment.^{355–365} Treatment of *N*-alkylstannyltetrazoles **16**, **103**^{88, 157–159, 161, 162} and metal tetrazolates^{75, 94} with acids is the final stage of a popular synthesis of 5-substituted tetrazoles **6** from nitriles. More readily available alkali and alkaline earth metal bis-tetrazolates, for example, salts **46** and **76**, are often used to prepare the corresponding ammonium and hydrazinium salts and salts of organic bases.^{366–368}

Metal derivatives of tetrazoles find use as catalysts. For example, iron(III) complexes **215a,b** demonstrated²⁹⁴ high efficiency as oxidation and dehydrogenation catalysts in the epoxidation of olefins and dehydrogenation of dihydropyridine with dioxygen and aldehydes. Owing to the use of mentioned compounds, these processes smoothly occur at room temperature and atmospheric pressure.



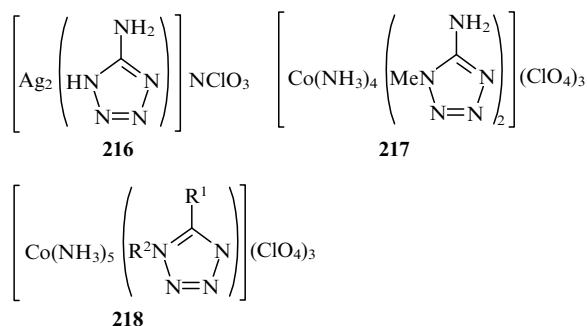
215a,b

$R^1 = \text{Bu}^t$, $R^2 = \text{CN}$, $R^3 = \text{OMe}$ (**a**); $R^1 = \text{Bu}^t$, $R^2 = \text{H}$, $R^3 = \text{Ph}$ (**b**).

Palladium(II) acetate complexes with *m*-phenylenedi(1*H*-tetrazole)³⁶⁹ and 1-(2-iodo-phenyl)tetrazole,³⁷⁰ prepared *in situ*, proved to be good catalysts in the Suzuki and Heck coupling reactions.

Many energetic MT able to pass from the combustion mode to detonation are promising as initiating explosives (IE) for safe initiating means including those operating from a low-voltage current sources or on exposure to laser radiation.^{31, 83} First of all, these are cobalt(III) amino tetrazolate complexes **69–71**,^{83, 87, 148, 371} which have a substantially lower impact sensitivity and are less toxic than traditional IE, namely, lead azide, fulminating mercury or lead trinitroresorcinolate.⁸⁷ Compound **69** ($R = \text{NO}_2$) is successfully used in light igniting charges applied in the pyrocontrol of guided missile systems.⁸³ Good operation parameters were found for non-hygroscopic and low-toxic complex **70**, which has a reduced sensitivity to the static electric discharge. The use of this compound as a key component in perforating equipment meant for operation in deep oil and gas wells markedly increases oil and gas condensate production rates and decreases the time of development of exploratory and producing wells.⁸³

An extremely high susceptibility to laser pulse was found recently for the complexes of 5-hydrazinotetrazole with mercury(II) perchlorate **37** and 5-aminotetrazole with silver(I) perchloramide **216**.^{52, 83, 371} For complex **37**, the initiation threshold by a neodymium laser ($\lambda = 1.06 \mu\text{m}$, pulse duration $\tau_q = 30 \text{ ns}$) is $\sim 5 \text{ mJ cm}^{-2}$. This complex has found use for the production of film light-sensitive charges employed for the formation of shaped shock waves and blast hardening of steels.⁸³ Other MT of type **1** proposed as IE include silver¹⁴⁸ and mercury salts of 5-nitrotetrazole,^{67, 148} caesium salts of 5-nitrotetrazole and 5,5'-azoditrazole,³⁷² cobalt(III), nickel(II), copper(II) and zinc(II) complexes with ammonia and 5-nitrotetrazole **71**, **72**⁸⁸ and cobalt(III) complexes with ammonia and *N*-substituted tetrazoles **217**, **218**.^{87, 277–279} These MT show a number of advantages over the conventional IE; many of them can be considered as promising low-toxic explosives valuable for the development of environmentally safe (green) energetic materials (see, for example, Ref. 279).



$R^1 = \text{NH}_2$; $R^2 = \text{Me}$, NH_2 ; $R^1 - R^2 = (\text{CH}_2)_5$.

It has been shown³⁷³ that 5,5'-bitetrazole or bis(tetrazol-5-yl)amine or their barium, strontium and copper salts can underlie the development of low-smoke pyrotechnic compositions to be used in colour fireworks.

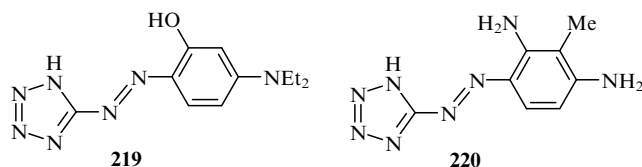
An important field of MT application is gas generation. Of most interest in this respect are salts of 5-substituted tetrazoles as they are safer than azides used previously.³⁷⁴ The compositions proposed for the use in car safety pads usually include an oxidant represented by metal oxides or salts (perchlorates, nitrates, etc.), and a fuel. As such fuels, 5-aminotetrazole,^{375–379} 5-nitraminotetrazole,^{380–382} 5,5'-bitetrazole^{35, 36, 379, 383} and salts with alkali, alkaline earth and transition metal cations [copper(II), zinc, cobalt(II), iron(III)] were patented. In addition, some of these compounds are catalysts of carbon monoxide and nitrogen oxide burning and conversion into carbon dioxide and nitrogen, respectively. Minor additives of these salts, in particular, those based on unsubstituted 5-aminotetrazole, decrease the toxicity of other gaseous products to a reasonable extent.^{377, 378} The formation of environmentally safe gaseous products from aminotetrazole-based compositions, for example, potassium salt of 5-aminotetrazole, has been proposed as a fire extinguishing means, instead of Freons or other halogenated compounds used currently in fire extinguishers.^{384, 385} The use of 5-substituted tetrazole salts **1a,b** ($M = \text{Na}$, K , Ca , Zn), which produce nitrogen at temperatures above 300°C or above 230°C , for the design of fire-resistant thermoset³⁸⁶ and thermoplastic³⁸⁷ polymers has been patented. Copper(II) 5-methyltetrazolate and other salts of 5-substituted tetrazoles and 5,5'-bitetrazole with melting points above 200°C have been proposed^{388, 389} for the manufacture of high-quality moulds for casting of foamed materials. The decomposition of tetrazoles accompanied by gas evolution and change in the state of the plastic surface underlies the laser beam marking of polymeric articles containing tetrazole derivatives, including their alkali and alkaline earth metal, zinc and copper salts.³⁹⁰

The ability of tetrazoles to form stable complexes with various metal ions is widely used in photoprocesses and for corrosion protection of metals.^{316, 391–395} 5-Substituted tetrazoles and their

salts as well as 5-mercapto-1-phenyltetrazole and its derivatives are used as light-sensitive materials and reagents that improve sharpness, enhance the mechanical and thermal stability of the image and prevent bleaching.^{396–399} 5-Mercapto-1-phenyltetrazole is the most effective metal corrosion inhibitor in the series of heterocyclic compounds. On a metal surface, this compound forms inert, insoluble and stable complexes with metal ions, which prevent the material from destruction.^{400–402} The film of these complexes inhibits corrosion of copper,^{403–407} nickel,⁴⁰⁸ iron,⁴⁰⁹ steel,^{410–413} bronze,^{406,414} and Cu–Zn⁴¹⁵ and Fe–B⁴¹⁶ alloys in acidic media. Treatment of silver,^{417,418} copper⁴¹⁹ and brass⁴²⁰ surfaces with compositions containing 5-mercapto-1-phenyltetrazole prevents them from dimming even in the presence of corrosive reagents such as sulfur-containing gases. It has been noted⁴²⁰ that this treatment is more efficient than that with agents used traditionally. 5-Phenyltetrazole and its potassium and sodium salts are fairly effective copper and steel corrosion inhibitors in aqueous solutions of sodium sulfate and chloride.^{421,422} In addition, tetrazoles inhibit not only electrochemical but also microbiological corrosion of metals.⁴²³

The interaction of tetrazoles with the surface of various parts and articles, resulting in a substantial change in their physico-chemical properties has been used for the manufacture of printed circuit cards,^{424–428} semiconductor devices,⁴²⁹ layered materials;⁴³⁰ for stabilisation of CdS colloid solutions⁴³¹ and Mo–S–Cu thermochromic films formed on the copper surface,⁴³² and for surface modification of silver nanoparticles.⁴³³ The use of tetrazolylacetic acid as a bidentate ligand allows the design of polynuclear heterometallic clusters, Cu₁₂Gd₆ and Cu₁₂Nd₆ (Ref. 434).

The formation of coloured metal complexes of azotetrazoles **219** and **220** stable in solution is used for spectrophotometric determination of traces of iron(III),⁴³⁵ bismuth(III)⁴³⁶ and palladium(II)⁴³⁷ in various mixtures and articles.

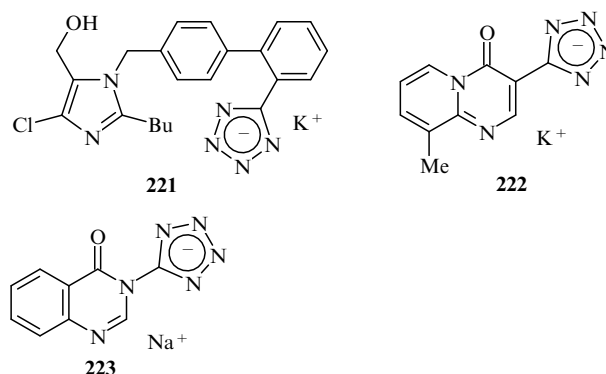


The high stability of the 5-diazotetrazole complex with copper(II) ions also underlies the voltammetric method for quantitative determination of copper present in low concentration (10^{–9} mol litre^{–1}).⁴³⁸ The ability of 1-substituted tetrazoles **110** to form easily separable crystalline complexes with copper(II) chloride, which liberate free tetrazole ligand upon hydrolysis, has been used⁴³⁹ for purification of this class of compound. This method is especially convenient for the production of low-volatile *N*-substituted tetrazoles sensitive to mechanical impact and capable of polymerisation. Since isomeric 1- and 2-substituted tetrazoles differ in the complexation properties, this process proved to be convenient for the separation of isomer mixtures.

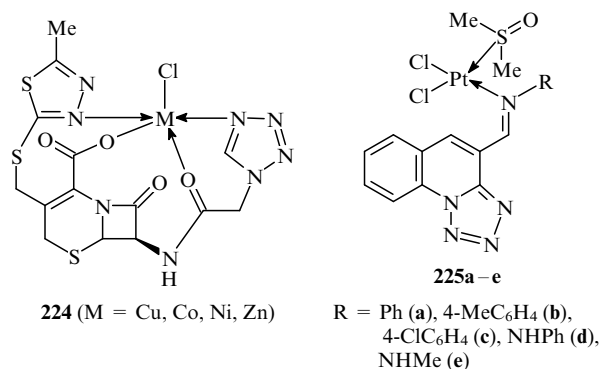
Immobilisation of tetrazoles on a polymeric matrix furnishes sorbents for selective binding of copper⁴⁴⁰ and europium,⁴⁴¹ filtering materials⁴⁴² and hydrogels^{443–445} suitable for purification of biological fluids and water from heavy metals and radionuclides. The ability of salt **7** to form hydrogel compositions under the action of Cr³⁺ ions is exploited in the application of this compound as a thickening agent in slurry explosives.⁴⁴⁶

Owing to high ionic conductivity and stability, lithium salts with heterocyclic anions, in particular, 5-cyanotetrazolate anion,⁴⁴⁷ and alkali metal salts with 1-methyltetrazole-5-thiolate anion^{334,448–451} are promising as components of polymeric electrolytes in galvanic and electrochemical (photovoltaic) current sources.

5-Substituted tetrazoles are known to be bioisosteres of the carboxy group, possessing a comparable acidity and lower toxicity. Tetrazoles are ionised in the physiological pH range, the tetrazolates thus formed being much more lipophilic than the corresponding carboxylates. This explains the interest in tetrazoles for the design of new effective drugs.¹⁰ The structures of such drugs can incorporate the tetrazole ring in the form of a salt having higher solubility in water and ability to crystallise. Examples are Losartan Potassium (**221**),¹⁰ which is a representative of new-generation antihypertensive drugs, and Pemirolast Potassium (**222**)⁴⁵² and MDL-427 (**223**),¹⁴ which are effective as antiallergenic and antiasthmatic drugs.

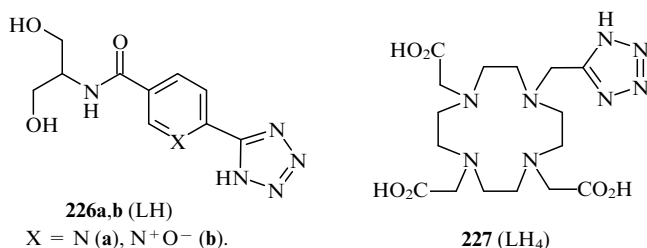


The complexes prepared by the reaction of the widely used antibacterial agent cephazolin or its sodium salt with metal(II) chlorides, ML₂Cl₂ and MClCl (**224**), Ag₂L₂Cl₂ (L is the deprotonated cephazolin), exhibit higher antibacterial activities *in vitro* compared to cephazolin with respect to *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis* and *Salmonella enteritidis*.^{453,454}



A similar activity should be expected of complexes of another tetrazole-containing antibiotic, cefamandole, with copper,⁴⁵⁵ cadmium⁴⁵⁶ and zinc⁴⁵⁷ salts. An antibacterial activity was also found for silver tetrazolate⁷³ and complexes **40**.^{55–57} Platinum(II) complexes **225** possess a cytotoxic action with respect to malignant cells; compounds **225d,e** are similar in activity to cisplatin, while complexes **225a–c** demonstrate a higher activity.⁴⁵⁸ Salt **7** shows a clear-cut polyelectrolyte activity toward an aseptic inflammatory process, which may be used to accelerate healing of wounds and to suppress scar formation.⁴⁵⁹ Trialkylstannyl derivatives of 5-aryl- and -hetaryltetrazoles **103** were patented as herbicides and animal parasite control means.⁴⁶⁰

Gadolinium(III) complexes **50** and **51**⁷¹ and the complexes GdL₃(H₂O)_n and Na[GdL(H₂O)] obtained from ligands **226**⁷¹ and **227**,⁴⁶¹ respectively, are promising for the use in medicine as contrasting agents for magnetic resonance diagnostics. They show a high proton relaxation ability, good solubility in water, high stability and low osmotic pressure. These complexes surpass conventional reagents in many performance characteristics.



For many MT, practically valuable properties were found, demonstrating good prospects for their use in various fields of science and engineering. These properties include photo- and thermochromism,^{6, 227, 228} ferromagnetism,^{185, 199, 202, 225, 276} mesomorphism,^{281, 282} nonlinear optical properties,^{100, 104} luminescence,^{44, 48, 49, 462, 463} and electrolytic production of nitrogen.⁴⁶⁴

VI. Conclusion

The ready availability of tetrazole and its derivatives containing four electron-donating atoms in the five-membered ring and existing as different isomeric forms and the high reactivity of the functional groups attached to the heterocycle ensured successful development of the investigations dealing with synthetic routes to, and physicochemical properties of, diverse MT. Numerous MT containing almost all known metals have now been obtained. The substituents in the tetrazole ring and the method used to prepare MT have a pronounced influence on the MT composition, structure and properties. Of course, the classification of MT proposed in this review is not all-round. There exist a number of compounds that cannot be assigned unambiguously to any type of metal tetrazole derivatives. Nevertheless, analysis based on this classification allows one to carry out deliberate selection of the rational routes to new MT with specified structure and properties. The successful development of synthetic methods forms the grounds for the practical use of many MT in various fields of science and engineering. For other compounds of this series, new practically valuable properties, not always predictable, have been found. Owing to the ability of tetrazole derivatives to be coordinated through different nitrogen atoms of the ring and donor atoms of substituents and to the structural, chemical and functional diversity of the MT formed, these compounds present considerable interest for the study of self-assembly of supramolecular structures and self-organisation of molecules through coordination to transition metal ions and the design of polymeric structures of different dimensionality. The subsequent systematic studies would provide information of what structural features of MT determine the appearance of particular useful properties and would enable targeted synthesis of such derivatives.

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^a — *Russ. J. Coord. Chem. (Engl. Transl.)*

^b — *Russ. J. Org. Chem. (Engl. Transl.)*

^c — *Chem. Heterocycl. Compd. (Engl. Transl.)*

^d — *J. Appl. Spectrosc. (Engl. Transl.)*

^e — *Polym. Sci. (Engl. Transl.)*

^f — *J. Struct. Chem. (Engl. Transl.)*

^g — *Russ. J. Appl. Chem. (Engl. Transl.)*

^h — *Russ. Chem. Bull., Int. Ed. (Engl. Transl.)*

ⁱ — *Chem. Sust. Devel. (Engl. Transl.)*

^j — *Russ. J. Electrochem. (Engl. Transl.)*

^k — *Russ. J. Gen. Chem. (Engl. Transl.)*

^l — *Mendeleev Chem. J. (Engl. Transl.)*

^m — *Chem. Phys. Rep. (Engl. Transl.)*

ⁿ — *Russ. J. Inorg. Chem. (Engl. Transl.)*

Chemical modification of oxide surfaces with organophosphorus(V) acids and their esters

P G Mingalyov, G V Lisichkin

Contents

I. Introduction	541
II. Modification of silica and mica surfaces	542
III. Modification of alumina surface	543
IV. Modification of titania surface	548
V. Modification of zirconia surface	550
VI. Modification of iron oxide surfaces	550
VII. Other oxides and metals	551
VIII. Applications of materials with surfaces modified with organophosphorus compounds	552
IX. Conclusion	555

Abstract. Published data on modification of oxide materials with phosphonic and phosphinic acids and their derivatives are systematised and generalised. The regularities of formation of grafted modifier layers on the oxide surfaces are considered. It is shown that phosphonic acids and their derivatives can form dense well-ordered layers. The factors affecting the properties of such layers are analysed. The key applications of these modifiers are considered. The bibliography includes 146 references.

I. Introduction

Chemical modification of the surface of mineral supports is a common method for fabrication of a broad spectrum of surface-modified materials, such as chemical and biological sensors, modified electrodes, separation membranes, selective adsorbents, sorbents for HPLC, heterogeneous metal complex catalysts, implants, antiadhesants, anticorrosion coatings, *etc.*¹ The most widely used materials are based on silica, which can be best chemically modified with organosilicon compounds.^{2–5} However, at present the family of surface-modified materials has been considerably extended due to the use of other mineral supports (various oxides and metals) and some other modifiers. As a result, organosilicon compounds no longer play the role of universal modifiers.

Generally, the molecule of a modifier must contain three fragments (Fig. 1). These are a functional group that determines the chemical properties of the surface-modified material, an anchoring group responsible for immobilisation of the modifier molecule on the support surface through covalent bonding and a spacer (or linker) that connects the functional group to the anchoring group, thus completing the structure of the modifier molecule.

P G Mingalyov, G V Lisichkin Department of Chemistry, M V Lomonosov Moscow State University, Leninskie Gory, 119992 Moscow, Russian Federation. Fax (7-495) 236 05 33, tel. (7-495) 939 52 57, e-mail: glo@petrol.chem.msu.ru (P G Mingalyov), tel. (7-495) 939 46 38, e-mail: lisich@petrol.chem.msu.ru (G V Lisichkin)

Received 8 June 2005

Uspekhi Khimii 75 (6) 604–624 (2006); translated by A M Raevskiy

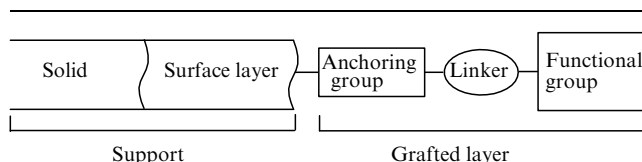


Figure 1. Structure of the surface of a chemically modified support.

Modification of the surface of oxide materials usually involves electrophilic substitution (a surface hydroxyl proton is replaced by the anchoring group of the modifier). From this it follows that the modifier molecule must contain a leaving group that forms a stable compound with proton.

The requirements for the anchoring group are as follows: the anchoring fragment should have a valence of at least two, because otherwise it cannot be bound to the surface; the reaction between the groups present on the support surface and the anchoring group should follow an unambiguous pathway and proceed as fast as possible; and the system of chemical bonds between the support and the grafted layer should be stable under the operational and storage conditions of the surface-modified material. It is also desired that the modifier be non-toxic[†] and the synthesis of this compound be not too complicated. Most often, silicon and phosphorus are used as the anchoring elements. Other anchoring elements include B, C, N, S, Ge, As, Sn, Sb, Hg and Pb.

The surface of silica is usually modified with silicon anchoring groups SiX_n because they meet the requirements mentioned above. The interaction of these groups with the surface hydroxyl groups of silica results in the formation of a hydrolytically stable system of chemical bonds $\text{Si}-\text{O}-\text{Si}-\text{C}$. The next in use are organophosphorus compounds to which this review is devoted. In order to provide strong bonds with the surface OH groups of oxide materials, the anchoring phosphorus atom in organophosphorus compounds should be bound to such reactive groups, as OH, OR or Hal; *i.e.*, the modifier molecule should be an organic phosphorus acid or its derivative. Trivalent phosphorus acids (phosphonous and phosphinous acids) are oxidised in air, which

[†] The use of alkyl compounds of tin or mercury as surface modifiers is permissible, but special care should be taken.

makes them undesired as modifiers because the properties of the grafted layer of a sample exposed to atmosphere will change with time in an uncontrollable and unpredictable manner. From this it follows that the most appropriate organophosphorus modifiers of oxide surfaces are phosphorus(V) acids (phosphonic and phosphinic acids) and their derivatives.

II. Modification of silica and mica surfaces

At present, 60% to 80% of all surface-modified materials are based on silica. This is due to considerable advantages of this material and first of all, to the possibility of varying its structural characteristics (specific surface area, pore diameter and volume, and particle shape and size) over a wide range. A great advantage of silica is also its low catalytic activity, which appreciably decreases the probability of undesired side reactions. Silicas are also well studied, readily available and cheap. Modification of silica with organosilicon compounds has long been known and well studied (see, *e.g.*, Refs 1, 2) and we will not dwell on it. Our attention will be focussed on the modification of silica with phosphonic acids.

The interaction of phosphonic acids with silica has been documented.^{6–10} When silica is refluxed with phosphonic acids for 2 h in chlorobenzene, a signal appears in the ³¹P NMR spectra, which differs from the signal of the acid adsorbed on silica and remains after washing the support with *n*-propanol and propan-2-ol. The signal was attributed⁶ to phosphonate groups formed on the silica surface. This is quite surprising because phosphonic acids do not undergo esterification (with, *e.g.*, ethanol) on reflux. The authors assumed that the interaction of phosphonic acids with the silica surface involves the formation of an intermediate containing a pentacoordinate silicon atom (here, the role of Lewis acid site is played by the silicon atom).

Boiling silica with *tert*-butylphosphonic acid in toluene results in grafting of the acid to the surface.⁸ The grafting density is 1.5 nm^{−2} (from this point on the term 'grafting density' means the number of molecules per nm² of the surface area). The granulometric composition of the support remained unchanged after modification. The grafted layer is hydrolytically stable in a neutral medium (the grafting density decreases by 15% after storage of the modified samples in distilled water for 2 days at room temperature); however, its stability in acidic and alkaline media is much lower.⁹

The interaction of silica with methylphosphonic and phenylphosphonic acids was studied (Ref. 10). ³¹P NMR experiments revealed the formation of a system of P—O—Si bonds on the silica surface.

Phosphonic acids interact with the silica surface much less readily than with the surfaces of most metal oxides. It was reported that long-chain phosphonic acids do not interact with the silica surface at all⁷ and that dialkyl esters of phosphonic acids behave analogously.^{9,10} Nevertheless, slow decomposition of dimethyl methylphosphonate into methanol and methyl methylphosphonate on hydroxylated silica under severe conditions is possible.¹¹ Methyl methylphosphonate can be partially grafted on the surface, however the grafting density is very low even under such conditions. Deydroxylated silica does not interact with dimethyl methylphosphonate.¹¹

The surface of silica was modified by dichloroanhydride of butylphosphonic acid and by dibutylphosphonic acid.⁹ The grafting density was ~1 nm^{−2} in both cases. The hydrolytic stability of the layers prepared was low, being similar to that of the layers formed in the modification of silica with phosphonic acids.⁹

Considerable attention is paid to chemical modification of the surface of mica crystals. Mica is a convenient object for wetting studies and for atomic force microscopy (AFM) studies of the surface, because its crystals can be broken with ease into smaller pieces with extended smooth facets. The facet surfaces contain oxygen–silicon tetrahedra and are very similar to the silica surface. It should be noted that the surface of a perfect facet of a

mica crystal contains only siloxane groups, and a real facet can contain defects (silanol groups).^{12, 13}

Octadecylphosphonic acid does not form a dense monolayer on the mica surface.¹⁴ Modification of the surface of a fresh facet on a mica crystal with octadecylphosphonic acid by melting followed by heating at 130 °C for 2 h leads to incomplete coverage of the mica surface. Besides, the modified regions can be multiply covered (additional octadecylphosphonic acid molecules are attached to the surface through van der Waals interactions with neighbouring molecules). Similarly to clean mica surface, non-modified areas are highly hydrophilic,[‡] whereas modified regions are hydrophobic and non-hygroscopic.

Treatment of mica facets with a solution of octadecylphosphonic acid in tetrahydrofuran results in the formation of self-assembled monolayers comprised of the acid molecules on the mica surface.¹⁵ An AFM study of the samples characterised by different modification time revealed the formation of 'islands' of strongly grafted molecules on the surface (surface coverage of about 25%) after 1 min of treatment, which begin to grow and merge, thus producing a dense monolayer. Only small surface defects (surface coverage of about 85%) remain unmodified after 30 min while after 120 min the surface becomes almost uniformly covered (surface coverage of about 95%).

Octadecylphosphonic acid forms round 'islands' on the mica surface in contrast to octadecyltrichlorosilane 'islands' that have a fractal morphology¹⁶ due to qualitatively different mechanisms of grafting of these compounds. Octadecyltrichlorosilane rapidly and almost irreversibly reacts with the mica surface and forms strong covalent bonds with surface hydroxyl groups and neighbouring modifier molecules. The modifier molecules are grafted at the positions where the anchoring groups contact the support surface. This leads to diffusion-controlled aggregation and fractal morphology of 'islands' thus formed. The octadecylphosphonic acid molecules are not linked to one another and interact with the silica surface slowly and (to a great extent) reversibly. This allows them to be involved in some kind of lateral diffusion and, as a consequence, makes possible molecular rearrangements within the grafted layer. The fact that most 'islands' are round suggests linear tension (analogue of surface tension for two-dimensional case) at the 'island' – bare surface interface. It should be noted that although the grafted layer formed after treatment of the surface with octadecylphosphonic acid is highly ordered, the alkyl chains are characterised by rather loose packing. Namely, each molecule occupies a surface area of nearly 0.25 nm² while the angle between the alkyl chains and the normal to the surface (tilt angle) is 40°. It is interesting that even at the shortest modification times (less than 1 min) the surface coverage is rather high (about 25%).

Contact angle measurements for the mica crystal surfaces modified with octadecylphosphonic acid¹⁵ revealed the following regularities. The cosine of the contact angle of the hexadecane on modified surface is a linear function of the surface coverage with the modifier molecules. The contact angle changes from 20° for bare mica crystal to 45° for the fully modified crystal. The contact angle on fully modified surface compares well with that obtained for well-formed thiolate monolayers, which indicates a high degree of ordering of the monolayer.

The cosine of the contact angle of water on the modified mica surface linearly decreases only to nearly 50% coverage and then reaches a maximum value.[§] The contact angle of water on bare mica surface is 3°.

The inflow and outflow contact angles were also determined, the former being about 5° larger than the static contact angle while the latter being very small (<10°). It should be noted that the contact angles of water on the mica surface decrease with time. This can be due to hydrolytic instability of layers formed.

‡ In air, a water film up to a nanometre thick is formed on these areas.

§ The maximum attainable contact angle for the monolayers under study is 90°.

An AFM study¹⁷ of *in situ* growth of octadecylphosphonate 'islands' on mica in tetrahydrofuran confirmed the conclusions made earlier.¹⁵ Namely, modification of the mica surface begins with nucleation followed by growth of 'islands' which then merge into a monolayer. No motions of 'islands' relative to one another were observed in the course of modification. It is likely that a proportion of octadecylphosphonic acid molecules is aggregated in solution; these aggregates grafted in the surface serve as nuclei. The growth of 'islands' is consistent with an accretion model, according to which disordered acid molecules present on bare mica surface (they cannot be detected by AFM) gradually diffuse towards an 'island', thus making its growth possible. Bubbling air through the solution led to a jumpwise increase in the surface coverage. This is due to the presence of octadecylphosphonic acid monolayer at the solution–air interface.¹⁷ To check this assumption, experiments involving multiple short-term (less than 1 s) dips of samples into the modifier solution. It was found that the surface coverage increases with the number of dips and the fraction of a monolayer per dip increases in proportion to the octadecylphosphonic acid concentration in the solution. This substantiates the assumption made above.

A comparative analysis of the growth of octadecylphosphonic acid monolayers on sapphire and mica surfaces was reported.¹⁸ It was found that mica is less reactive than sapphire. At room temperature, a monolayer providing a water contact angle of 90° is formed after 1 min on sapphire (from 5×10^{-5} M solution) and after several hours on mica. Octadecylphosphonic acid layers on sapphire are more ordered than on mica, namely, at room temperature the acid forms a highly ordered quasi-crystalline layer on sapphire while disordered liquid-expanded layers are formed under identical conditions on mica.

The thermal stability of grafted phosphonic acid layers is almost independent of the nature of support.¹⁹

III. Modification of alumina surface

Following silica, alumina is the next in significance among oxide supports used in the synthesis of surface-modified materials. As silica, alumina is relatively cheap and available. Significant drawbacks of Al₂O₃ compared to SiO₂ are a nonuniform surface and the dependence of the surface properties on the sample prehistory. Additionally, the presence of strong Brønsted or Lewis acid sites on the Al₂O₃ surface can cause undesired transformation of the modifier molecules. At the same time alumina offers certain advantages over silica, *e.g.*, higher mechanical stability and greater stability in alkaline media.

The importance of studies on the regularities of modification of Al₂O₃ surface is first of all determined by the fact that such valuable material as metallic aluminium is always covered with oxide film.

Phosphonic acids offer considerable advantages over organosilicon compounds in the modification of Al₂O₃ surface. This is first of all due to the presence of strong acid sites on the Al₂O₃ surface, which significantly facilitates the donor–acceptor interaction of phosphoryl group of the modifier with the Lewis acid sites (unoccupied sites or those formed from a proportion of Brønsted sites due to competitive displacement of other nucleophilic groups). This interaction makes the phosphorus atom more electrophilic and facilitates a subsequent reaction between the modifier and the surface hydroxyl groups. Besides, this donor–acceptor interaction helps the anchoring groups of the modifier molecules to block efficiently the surface acid sites, so the surface becomes more uniform and non-specific.

Conventional organosilicon modifiers (*e.g.*, ethoxysilanes) do not readily react with the alumina surface (see, *e.g.*, Ref. 20). High grafting density can be reached only with silanes that contain two or three leaving groups at silicon atom and can therefore form horizontal cross-links with neighbouring modifier molecules. The use of chlorosilanes for modification of alumina is complicated by the fact that hydrogen chloride evolved in the reaction causes

destruction of Al₂O₃ surface and uncontrollable changes in the structural and geometric parameters of the support and the surface acidity. The addition to the reaction mixture of a compound that can react with hydrogen chloride (*e.g.*, organic amine) leaves the situation unchanged, because this component is sorbed on specific (acid) surface sites and also causes uncontrollable changes in the properties of the modified support thus formed. It seems likely that good results would be obtained with silicon hydrides as modifiers; however, the interaction of these compounds with Al₂O₃ surface has been poorly studied. Additionally, such compounds (especially those having small substituents at silicon atom) are less available and less stable than chloro- and alkoxy-silanes. Therefore, it is not surprising that most studies on the modification of Al₂O₃ surface were carried out using phosphonic acids or their derivatives as modifiers.

1. Phosphonic acids

Phosphonic acids are one of three classes of compounds (in addition to thiols and trifunctional silanes) capable of forming dense self-assembled monolayers on support surfaces. Therefore, a large number of studies on the modification of Al₂O₃ surface are concerned with phosphonic acids. It should be noted that a self-assembled monolayer is the best grafted layer, because it provides the highest extent of screening of the support surface.

Self-assembled monolayers comprised of *n*-octadecylphosphonic acid molecules on the (1000) and (1 $\bar{1}$ 02) faces (C- and R-faces, respectively) of a sapphire single crystal were studied by AFM, contact angle measurements and FTIR spectroscopy.¹⁸ It was established that the formation of monolayer strongly depends on temperature. This was explained by a three-phase model for film deposition. At low temperature, close-packed molecular 'islands' nucleate and grow on almost bare substrate surface (two-dimensional transition vapour–solid),[‡] while at high temperature two-dimensional transition liquid–solid occurs and a film is formed on the surface.

A change in the contact angle in the surface modification implies the formation of a surface film, however AFM measurements failed to detect it. As the modification time increases, structures with poorly defined boundaries appear on the surface, which can be detected by AFM. These structures become larger as the treatment duration increases. The height of the structures (0.8 nm for the C-face and ~0.55 nm for the R-face) does not reach a value consistent with a fully extended octadecylphosphonic acid molecule (~2.5 nm). The water contact angle on the sapphire surface treated with octadecylphosphonic acid (1 min) is 90° and remains unchanged upon increase in the modification time. However, treatment of sapphire surface with *n*-hexadecylphosphonic acid for 1 min results in the formation of a layer for which the water contact angle is 31°; the contact angle increases to 36° as the treatment time increases to 0.5 h for the C-face and to 1 h for the R-face.

At low temperatures, the growth of a surface modifier layer is significantly different from that described above. At 2 °C, small 'islands' with well-defined boundaries are formed. The height of the 'islands' is about 1.1 nm. The surface coverage increases with time, but slowly, and the surface remains incompletely covered even after treatment for 15.5 h.

A FTIR study of the modified sapphire surface showed that treatment of the surface for 1 min at room temperature is followed by the formation of disordered ('liquid-expanded') layers, which become much more ordered after 1 h. Modification at 2 °C leads to the formation of highly ordered layers. The results obtained suggest a two-dimensional phase diagram for the grafted layer (in

‡ Two-dimensional transition means that molecules are transferred over a surface. In this case highly ordered close-packed regions of the grafted layer are treated as solid, disordered close-packed regions are treated as liquid and regions with a grafting density much lower than that characteristic of the monolayer are treated as vapour.

the 'temperature-grafting density' coordinates). The 'liquid-expanded' disordered state of the grafted layer in this system is only possible at temperatures above 11 °C. This temperature corresponds to a triple point.

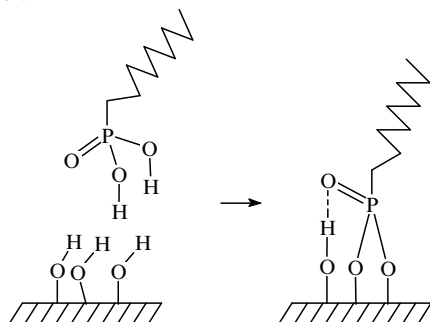
The kinetics of growth of the modifier layer on the C- and R-sapphire faces are different. Namely, the growth rate on the C-face is higher and the growing layer is thicker; this is due to different surface energies of these faces. The R-face is formed by a layer of oxygen atoms while the C-face is formed by a layer of aluminium atoms (the surface area of the C-face is smaller than that of the R-face); the C-face contains a larger number of coordinatively unsaturated sites and is characterised by higher surface energy. Assuming epitaxial growth of a modifier layer, it is clear that the layer growing on the C-face will be thicker. The modification temperature can be shifted towards high-temperature region owing to proximity to the face edge or other surface defects. Generally, by varying the temperature it is possible to control the amount of defects within the grafted layer.

Self-assembled monolayers comprising the molecules of three phosphonic acids, namely, $\text{CF}_3(\text{CF}_2)_7(\text{CH}_2)_{11}\text{PO}_3\text{H}_2$,[†] $\text{n-C}_{16}\text{H}_{33}\text{PO}_3\text{H}_2$ and $\text{n-C}_{22}\text{H}_{45}\text{PO}_3\text{H}_2$ on the surface of aluminium covered with native oxide film were studied by IR spectroscopy, ellipsometry and contact angle measurements.²¹ It was shown that the layers formed by these three acids are characterised by significantly different structures and growth kinetics. For instance, the lack of ordering was observed for fluorinated phosphonic acid in all cases (layer becomes insignificantly more ordered with an increase in the modification time) while the layer thickness increases with time (from 1.8 nm after modification for 5 s to 2.3 nm after 24 h).

It should be noted that the behaviour of partially fluorinated phosphonic acids on the surface of oxidised aluminium is basically different from that of perfluorothiols on silver and gold surfaces.^{22–24} This was explained by two factors, namely, larger size of the anchoring group PO_3H_2 compared to the thiol group and low lateral mobility of phosphonate groups on Al_2O_3 surface compared to that of thiol group on the noble metal surfaces.²¹

At long treatment times, the acids $\text{n-C}_{16}\text{H}_{33}\text{PO}_3\text{H}_2$ and $\text{n-C}_{22}\text{H}_{45}\text{PO}_3\text{H}_2$ form ordered layers in which alkyl chains are in fully transoid conformation. Different behaviour of these acids and the partially fluorinated acid is due to the presence of a bulky, conformationally rigid perfluorinated segment in the last-mentioned molecule; this precludes the close packing of alkyl groups. Additionally, some contributions from low solubility of the partially fluorinated acid in ethanol (solvent for modification) and micellisation in solution (although the authors reported no unambiguous proofs of micellisation) are also possible.

The IR spectra of the samples modified with these three acids exhibit no AlOH bands, which is associated with the interaction of these groups with OH groups of phosphonic acid molecules accompanied by the formation of a surface alumophosphonate layer.



[†] Acid $\text{CF}_3(\text{CF}_2)_7(\text{CH}_2)_{11}\text{PO}_3\text{H}_2$ forms on Al_2O_3 surface a grafted layer characterised by minimum surface energy.

The modification of Al_2O_3 surface with fluorinated phosphonic acid approaches its equilibrium rapidly. This acid forms disordered 'islands' on the surface, which then merge. The formation of a monolayer takes $\sim 5\text{--}10$ min. A considerable increase in the water contact angle for the modified surface is observed after modification over a period of 5 s. Docosylphosphonic acid $\text{n-C}_{22}\text{H}_{45}\text{PO}_3\text{H}_2$ also modifies the surface following the 'island' mechanism; however, alkyl chains in the 'islands' formed are ordered. In this case the kinetics of modification is similar to that of fluorinated acid. At the same time hexadecylphosphonic acid $\text{n-C}_{16}\text{H}_{33}\text{PO}_3\text{H}_2$ initially forms a disordered 'liquid-like' layer on the aluminium surface, which becomes more ordered as the modification time increases. In this case the equilibrium is attained after about 4 h. (An increase in the rate of formation of self-assembled monolayers in the presence of fluorinated modifiers was also detected in the case of fluoro derivatives of trichlorosilanes^{25,26} and thiols.²⁷)

Contact angle measurements showed that water spills over the starting oxidised aluminium plates (contact angle equals zero). Surface modification imparts highly hydrophobic properties to the surface, that is, the contact angle for the surface modified with hexadecylphosphonic and docosylphosphonic acids is 110° (cf. 122° for partially fluorinated acid).

At low degree of modification, all modifier molecules are tridentate, *i.e.*, they form three covalent bonds with the oxidised aluminium surface. One of them is a donor-acceptor bond between the phosphoryl oxygen and the Lewis acid surface site.²¹ As the modification time increases, bidentate and even monodentate modifier molecules appear on the surface. This is confirmed by the fact that for the tridentate molecules in the transoid conformation of alkyl chains within the grafted layer the tilt angle should be 35° . The films studied at high degrees of modification are characterised by much larger angles that increase with increasing the modification time.

A theory developed by the authors of Ref. 28 treats the surface layers as gas-like, liquid-like and crystal-like ones (layers can also be represented using a two-dimensional state diagram). The triple point of the layer comprising docosylphosphonic acid molecules is much higher than room temperature while that of a layer comprised of hexadecylphosphonic acid molecules is near room temperature. The triple point of the fluorinated acid and the crystalline-like state of the grafted layer are apparently inaccessible. Efforts were made in order to reach the crystal-like state for a fluorinated acid film by heating the modified sample followed by cooling, however heating to moderate temperatures (at most 250°C) left the structure of the grafted layer unchanged, whereas heating above 250°C led to irreversible destruction of the grafted layer.

Adsorption and self-assembly of phosphonic acids on oxidised surfaces of metallic aluminium were studied by X-ray photoelectron spectroscopy, Auger spectroscopy and FTIR spectroscopy.²⁹ The surfaces of high-purity aluminium (99.999%) and an industrial alloy containing 98.87% of aluminium, 0.76% of magnesium, 0.29% iron and 0.08% silicon were modified. Prior to modification, the samples were thoroughly polished. As a result, the surface of bare aluminium was optically smooth while iron inclusions were seen on the alloy surface. It was shown that self-assembly of layers is possible on both types of surfaces. Full coverage of the bare aluminium and alloy surfaces was reached after 100 s. Studies of the alloy samples characterised by shorter modification time showed that adsorption of phosphonic acids first of all occurs on iron inclusions and then on the aluminium surface. Magnesium and silicon impurities do not affect the formation of the grafted layer.

A packing study of alkyl chains in the grafted layer revealed initial formation of disordered layers followed by gradual ordering with an increase in the modification time. The formation of fully ordered grafted layers takes about 70 h.²⁹ The tilt angle of alkyl chains was determined from IR spectroscopy data.^{30,31} Its value (31°) is similar to the corresponding angle for alkyl chains in

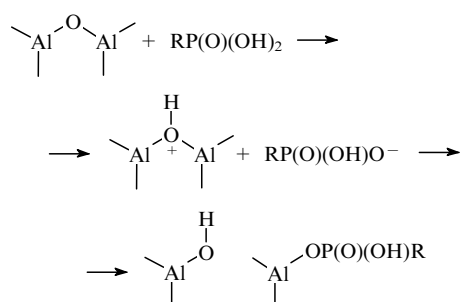
phosphonic acid bound to the surface in a tridentate fashion (35°). The somewhat lower magnitude of tilt angle may indicate the presence of coordinated groups of lower denticity on the surface. Unfortunately, the authors²⁹ did not report which alkylphosphonic acids were used for modification. This complicates the understanding of the results obtained.

Decylphosphonic acid can form films on the surfaces of bare aluminium and aluminium alloy 2024T3 containing inclusion phases of $\text{Al}_7\text{Cu}_2\text{Fe}$ of size up to a few micrometres. The structure of such films was studied by X-ray photoelectron spectroscopy.³² Prior to modification the samples were thoroughly polished and the oxide film was removed by bombarding them with argon ions. Immediately prior to modification the samples were exposed to air for a short time, which led to formation of a thin surface oxide layer.

X-Ray photoelectron spectra showed that the oxide layer on the alloy surfaces contain small amounts of copper. P(2s) X-ray photoelectron spectroscopy data revealed a uniform coverage of the aluminium and aluminium alloy surfaces with decylphosphonic acid molecules and the absence of preferred or reduced sorption of the modifier on inclusions. At the same time the contact angle for the modified bare aluminium sample was 110° , being only 97° for the alloy, which indicates a lesser ordering of the grafted layer on the alloy surface. The reason for this is to be clarified.

The influence of preliminary long-term exposure of samples to air, nature of solvent and random sorption of hydrocarbon contaminations on sample surface on the quality of coatings were also studied.^{32,33}

The interaction of alumina with phosphonic acids is often accompanied by the formation of a surface aluminium phosphonate phase.³⁴



For instance, a phosphonate phase is formed in the course of adsorption of phenylphosphonic acid from water at pH 4 and during treatment of alumina with bis(trimethylsilyl) phenyl phosphonate. However, the phosphonate phase was not detected when the modification was performed at pH 6.

An attempt to prepare a monolayer coating by treating Al_2O_3 surface with octadecylphosphonic acid was reported.⁷ However, breakdown of particles of the starting oxide and formation of only bulk phase of aluminium phosphonate were observed under the experimental conditions.

Adsorption of a range of organic molecules on the surface of magnetron-sputtered aluminium was studied.³⁵ Prior to modification the aluminium surface was exposed to air for a short time, which resulted in the formation of a thin oxide layer. Alkylphosphonic and alkanecarboxylic acids and aliphatic triethoxysilanes, trichlorosilanes, amines and epoxides were used as surface modifiers. The modification was carried out in toluene. It was found that phosphonic and carboxylic acids form well-ordered layers with the grafting density of about 5 nm^{-2} on aluminium surface, whereas trichlorosilanes form polymeric layers and other compounds form disordered layers with low grafting density. Under the experimental conditions, trichlorosilanes can destroy the aluminium surface and, in the limiting case, dissolve the sample. One can assume that this is due to hydrolysis of silanes with trace amounts of water present on the metal surface and in solvent (toluene).

Polarisation modulated IR reflection spectra revealed a low proportion of *gauche*-defects within the layers formed by phosphonic and carboxylic acids and a small tilt angle. Water contact angle measurements for acid treated aluminium surface showed that the contact angle remains unchanged after modification for 4–6 h in the case of carboxylic acids and after only 0.5 h in the case of phosphonic acids. The maximum contact angle values attained in these experiments were 120° for phosphonic acids and 117° for carboxylic acids. The water contact angles for surfaces of copper, silver and gold, modified with alkanethiols are 115° , 116° and 120° , respectively.³⁶ Taking into account that alkanethiols form highly ordered layers on the surfaces of these metals, one can consider that the layers formed by carboxylic and, especially, phosphonic acids are well-ordered. This is in good agreement with the published data³⁷ obtained for monolayer coatings formed by alkylphosphonic and alkylsulfonic acids.

The longer the alkyl group in the modifier molecule the larger the contact angle.^{37–39} At the same time, sessile drop measurements of the contact angle provide information on the state of the modifier layer at a depth of at most four methylene units.⁴⁰ From this it follows that the effect mentioned above can be explained only by an increase in the degree of ordering of the grafted layer with elongation of the alkyl chain.

Higher density and ordering of the grafted layers of phosphonic acids compared to those of carboxylic acids are due to the ability of phosphonic acids to displace contaminants from the support surface. According to X-ray photoelectron spectroscopy data, the aluminium surface is always covered with carbonaceous contaminants. One can assume that they block the adsorption sites suitable for grafting. It was established that undecanoic acid is incapable of displacing all contaminants from aluminium surface, whereas decylphosphonic acid does it. This is apparently a reason for the higher degree of ordering of the grafted layer. Higher ability of phosphonic acids to displace contaminants from the support surfaces compared to carboxylic acids is likely due to greater stability of the tridentate anchoring group compared to bidentate carboxyl group.[‡]

A methodology for the formation and derivatisation of self-assembled monolayers of α,ω -alkanediyl-diphosphonic acids on conventional engineering metals, such as soft and stainless steels, aluminium, copper and brass was reported.⁴¹ Diacids with different number of methylene units $[(\text{CH}_2)_{2n}, n = 1–6]$ between phosphonic groups were studied. The surface modification was carried out in ethanol at room temperature and the treatment time was 15–30 min. Prior to modification, 1 equiv. of sodium hydroxide was added to the diphosphonic acid solution in order to bind only one phosphonate group to the surface and to leave the second acid group in the solution. The degree of ordering of monolayers formed increased with an increase in the length of the polymethylene chain. For instance, short-chain acids formed disordered surface layers while dodecylidiphosphonic acid formed highly ordered layers. Modification of steel surface in ethanol led to the formation of monolayers while the process in water mainly lead to formation of polylayers. The nature of this phenomenon is still unclear.

Further modification of diphosphonic acid monolayers involved complexation of free phosphonate groups with Zn^{2+} , Cu^{2+} , Mg^{2+} , Mn^{2+} , Ni^{2+} , Pb^{2+} , ZrO^{2+} , VO^{2+} , Al^{3+} , Cr^{3+} , Fe^{3+} and Ce^{3+} cations. Layers thus modified could participate in complexation with organic acids and polymers containing acid groups. The cations served as linkers connecting the phosphonate groups of the grafted layer to carboxylate or phosphonate groups of the 'incoming' acids. The thermal stability of such layers is rather high. For instance, thermal decomposition of a layer

‡ The ability to displace contamination from sorption sites is governed by the energy of the bond between the displacing group and the surface (other conditions being equal, the higher the denticity the higher the bond energy).

formed by a diphosphonic acid in the presence of Zn^{2+} cation linker in air begins at 250 °C. When the process is completed, a phosphate phase was left on the surface.

The action of a copolymer of ethylene and methacrylic acid on diphosphonic acid monolayer films results in a very strong composite. Composites based on long-chain diphosphonic acids efficiently inhibit metal corrosion in 5% hydrochloric acid, whereas composites based on short-chain diphosphonic acids exhibit no protective effect; moreover, in some cases corrosion of metal surfaces is enhanced.⁸

It should be noted that metal-modified monolayers possess a surprisingly high stability against organic acids. In particular, complexation of such layers with such a strong acid as perfluorooctanoic acid did not lead to destruction of the grafted layer.

Thermal stability and stability in various solvents (in particular, water) are important parameters of grafted layers. They determine the possibility of using grafted layers in liquid and gas chromatography, in catalysis, for corrosion protection, etc.

The dependence of the grafting density of alkylphosphonic acids on $\gamma\text{-Al}_2\text{O}_3$ surface on the structure of alkyl group and on the amount of the modifier employed was studied.⁸ It was shown that alkylphosphonic acids readily interact with the oxide surface. In all cases the granulometric composition of oxide particles changed significantly, namely, relatively large oxide particles (100–200 μm) were transformed into small particles at most 2 μm in diameter. This is due to the fact that the interaction of alkylphosphonic acids with Al_2O_3 is not stopped at the stage of monolayer formation (grafting). The grafted phosphonic groups interact with the surface AlOH fragments to give aluminium phosphonate and the starting particles are destroyed, which is confirmed by high content of carbon in the samples obtained.

The dependence of the grafting density on the amount of modifier is strongly different for normal and branched alkyl groups. For instance, for *tert*-butylphosphonic acid the maximum grafting density is $\sim 2.5 \text{ nm}^{-2}$ and remains almost unchanged as the content of the modifier in the reaction mixture increases. In the case of isopropylphosphonic acid the grafting density slightly increases with an increase in the modifier concentration, whereas for *n*-butylphosphonic acid the grafting density increases to almost complete consumption of modifier in the reaction mixture.

A study⁸ of the hydrolytic stability of the grafted layers obtained showed that it is maximum, but not too high, in the range of neutral pH values (grafting density of the samples stored for 2 days in an aqueous medium at room temperature decreased by about 15%), being even lower in acid and alkaline media. The pore volume in the modified support was studied in relation to the type of the modifier and to the modification conditions. In most cases, modification strongly affects the pore volume in the support.

A thermogravimetric study of thermal stability of phosphonic acid monolayers on alumina surface was reported.¹⁹ The modified samples exposed to nitrogen atmosphere showed a dramatic mass loss in the temperature interval 200–600 °C due to degradation of the grafted layer. Interestingly, the degradation onset temperature (200–250 °C) and the maximum mass loss temperature (400–450 °C) depend only slightly on the support nature. The activation energy of the degradation process ($265 \pm 15 \text{ kJ mol}^{-1}$ for the samples under study) behaves analogously. According to IR spectroscopy and elemental analysis data, after degradation of the grafted layer the support surface is covered with small amounts of carbon (mainly in the form of carbides) and the total phosphorus (as phosphates). It is significant that the grafted layers in air remain almost as stable as in inert atmosphere; the only exception is a decrease in the maximum mass loss temperature by 50–100 °C.

The thermal stabilities of layers of phosphonic acids, alkylsilanes (RSiH_3) and alkyltrimethylchlorosilanes supported on

Al_2O_3 surfaces were compared.¹⁹ The thermal stability of the RSiH_3 layers is similar to that of the phosphonic acid layers while alkyltrimethylchlorosilane layers are much less stable.

A computer simulation study of the reaction of vinylphosphonic acid with the (0001) face of alumina and its energy characteristics was reported.⁴² In this system the acid molecules are attached to the support surface in a tripodal fashion.^{43,44} Because of this, three types of sorption sites capable of interacting in such a manner were studied.⁴² They differed in distances between adjacent hydroxyl groups and between the aluminium ion lying below the surface and the phosphorus atom. Additionally, bi- and monodentate interactions of vinylphosphonic acid with the surface were also simulated.

According to calculations, the binding enthalpy of vinylphosphonic acid depends on the geometry of the sorption site and on the distance from the phosphorus atom to the aluminium ion located under the surface plane. It was found that tripodal binding is characterised by the largest negative enthalpy, while monodentate binding by the smallest negative enthalpy. The arrangement of the vinyl fragment relative to the tridentate anchoring group has no effect on the enthalpy of reaction. The Al-O-P bonds that anchor the modifier molecule on the support surface are mainly ionic, with a small contribution of covalent bonding.

2. Phosphonates

Compared to phosphonic acids, phosphonates are much more rarely used for the modification of alumina. There are only a few studies on surface modification using this class of compounds. In particular, a study³⁴ on the modification of alumina with diethyl phenylphosphonate revealed the formation of monolayer diethyl phenylphosphonate film on the surface and the lack of bulk phase of aluminium phosphonate.[†] The modification of $\gamma\text{-Al}_2\text{O}_3$ surface with diethyl *n*-butylphosphonate also ceases at the stage of monolayer formation; no bulk phase of aluminium phosphonate was also observed. However, the grafting density attained under these conditions was low ($\sim 0.9 \text{ nm}^{-2}$).

The authors of a gas chromatographic study⁴⁵ of $\gamma\text{-Al}_2\text{O}_3$ surface modified with diethyl *n*-butylphosphonate reported a procedure for fabrication of coatings with high coverage (3.4 nm^{-2} , or about 70% of monolayer). The modified sorbents are significantly different from the starting Al_2O_3 and from alumina coated with squalane (20 mass %), being similar in properties to silica. This was attributed to the effect of the phosphoryl groups of grafted ester molecules that interact with the acid sites on the oxide surface, thus efficiently making the surface less accessible to the adsorbate.

The density of grafting of diethyl phosphonates on $\gamma\text{-Al}_2\text{O}_3$ surface was studied in relation to the grafting conditions.⁹ The highest grafting density ($4.5\text{--}5.0 \text{ nm}^{-2}$) was achieved upon heating of an alumina-ester slurry at 120 °C for 20 h. It should be noted that, despite all advantages, the procedure requires a consumption of large amount of the modifier. Similar grafting density values were also achieved using a method involving the coating of oxide surface with small amounts (sufficient for the formation of 2–3 monolayers) of modifier in a volatile solvent followed by evaporation of the solvent and heating of the support at 120 °C for 20 h. Changes in the pore volume in the support upon modification of Al_2O_3 with phosphonic acid esters were estimated.⁹ It was shown that this parameter decreases only slightly (by a few per cent) in the course of modification, which is comparable with the accuracy of its determination.

A number of studies are devoted to adsorption of esters of various phosphorus-containing acids (in particular, dimethyl

[§] Diphosphonic acid monolayers themselves almost do not inhibit metal corrosion by 5% hydrochloric acid.

[†] Seemingly, in this case it is possible to avoid destruction of the support, which is observed in the modification of Al_2O_3 with free phosphonic acids or their bis(trimethylsilyl) esters.

methyl phosphate) from the vapour phase on the surfaces of various oxides including Al_2O_3 . These studies are of considerable interest because the authors reported a comprehensive study of the interaction between these compounds and the oxide surface.

In particular, chemisorption of phosphoric acid, trimethyl phosphate, methyl and dimethyl methylphosphonates on bare and oxidised (111) faces of alumina was studied.⁴⁶ Preliminary chemisorption studies of dimethyl methylphosphonate on the (111) face of platinum,⁴⁷ (100) face of rhodium⁴⁸ and on alumina surface⁴⁹ showed that the process begins with the donor–acceptor interaction of the phosphoryl oxygen atom with the surface. The energy of the donor–acceptor bond formed can be rather high ($\sim 58 \text{ kJ mol}^{-1}$ according to Ref. 48). Desorption of such samples occurs only upon heating to high temperatures. Noteworthy is that not dimethyl methylphosphonate but products of its decomposition (H_2 , H_2O , CO , CO_2 , CH_4 and MeOH) are desorbed. Decomposition of ester molecule begins with cleavage of the $\text{P}=\text{O}(\text{C})$ bonds followed by cleavage of the $\text{P}-\text{C}$ bonds at higher temperatures. Taking sorption of trimethyl ester of phosphorous acid on the (110) face of iron as an example, it was shown⁵⁰ that sorption is accompanied by the formation of grafted methoxyl groups, which decompose to carbon monoxide and hydrogen at high temperatures.

Adsorption of dimethyl methylphosphonate on the (111) face of aluminium cleaned from the oxide film is accompanied by essential degradation of the ester molecule, as indicated by desorption of alkanes and alkenes from the surface and by the formation of a graphite-containing surface phase. A dimethyl methylphosphonate layer formed on the surface of oxidised aluminium is much more stable. According to X-ray photoelectron spectroscopy data, the ester bonds $\text{P}-\text{O}-\text{C}$ are rapidly cleaved to form $\text{Al}-\text{O}-\text{P}$ bonds while the $\text{P}-\text{C}$ bond remains stable up to 550 K. [It should be noted that exposures of the gaseous ester to the surface were rather low, namely, from 0.5×10^{-4} to 1.0×10^{-4} Torr s (see Ref. 49).]

Sorption of dimethyl (diisopropyl, diphenyl) methylphosphonates on Al_2O_3 surface was studied by tunnelling electron microscopy.⁵¹ The surface of Al_2O_3 was formed by plasma oxidation of Al films. Experiments were carried out in the temperature interval from 200 to 673 K; the diisopropyl and dimethyl esters were deposited from the gas phase (exposure of 1 Torr s) and the diphenyl ester was applied from 0.025 M solution in hexane.

At sorption temperatures below 295 K, adsorption of the esters on the surface involves formation of donor–acceptor bonds between the phosphoryl oxygen atoms and surface Al atoms. Above 295 K, decomposition of the dimethyl and diphenyl esters begins with cleavage of one ester bond $\text{P}-\text{O}-\text{C}$ and formation of one $\text{Al}-\text{O}-\text{P}$ bond. In other words, layers of grafted methyl methylphosphonate and phenyl methylphosphonate groups are formed on the surface. In the case of diisopropyl ester the process begins only at temperatures above 373 K, which seems to be due to considerable steric hindrance produced by the isopropyl groups. At temperatures above 473 K, the second methoxyl group of the grafted methyl methylphosphonate decomposes and a layer of methylphosphonate groups is formed on the surface (methylphosphonate groups are stable in inert atmosphere up to 750 K). Elimination of the second phenoxyl group from the grafted phenyl methylphosphonate occurs only at 673 K. The mechanism of the interaction of these three esters with Al_2O_3 surface was documented.⁵¹

A similar study⁴⁹ of adsorption of gaseous dimethyl methylphosphonate on the surface of Al_2O_3 film was carried out in the temperature range from 200 to 673 K at exposures from 3×10^{-4} to 10 Torr s. The results obtained were in excellent agreement with the published data⁴⁶ on sorption of dimethyl methylphosphonate. It was also pointed that sorption of methyl methylphosphonate proceeds by the same mechanism as sorption of carboxylic acids. In both cases, interaction of the surface hydroxyl group with the proton of carboxylic acid (or methyl methylphosphonate) and interaction of the carbonyl (or phosphoryl) oxygen atom with the

surface Lewis acid site is accompanied by the formation of a water molecule and a modifier molecule attached to the surface in bidentate fashion.

Sorption of dimethyl methylphosphonate without dissociation can proceed by two mechanisms.⁴⁹ One of them involves formation of hydrogen bonds between the phosphoryl oxygen atoms and surface hydroxyl groups while the other involves formation of a donor–acceptor bond of the same oxygen atom with a surface Lewis acid site. In the latter case the energy of the bond between the ester molecule and alumina surface (~ 100 – 120 kJ mol^{-1}) is about four times higher than in the former. A product of sorption proceeding by the first mechanism can be detected based on the shift of the IR absorption band of the surface hydroxyl groups from 430 to 415 cm^{-1} . Actually, such a product was detected in a study of low-temperature (200 K) sorption of dimethyl methylphosphonate. However, IR spectroscopy data showed that the surface of the starting oxide rapidly takes its initial appearance, from which it follows that almost all amount of ester is desorbed from the surface at this temperature.

One can assume that the preferred mechanism of molecular sorption involves formation of hydrogen bonds. This is in agreement with the fact that at 295 K some amount of chemisorbed ester (product of either donor–acceptor interaction or dissociative sorption) is present on the surface of non-dehydroxylated Al_2O_3 in addition to a rather low concentration of surface Lewis acid sites.

The IR spectra support the dissociative mechanism of sorption. In particular, this is confirmed by the detection of methanol formation. However, it is still unclear whether or not does dissociative sorption follow the donor–acceptor interaction. In order to answer this question, adsorption of trimethylphosphine oxide on the surface of Al_2O_3 was studied.⁴⁹ The Lewis basicity of this compound is similar to that of dimethyl methylphosphonate, however trimethylphosphine oxide cannot be dissociatively sorbed under these conditions. It was shown that trimethylphosphine oxide is bound to the surface to a temperature of 473 K, which indicates a strong interaction between the molecule and the surface. At the same time phosphonic acid esters are known to possess relatively low reactivities, so the interaction of inactivated ester molecule with such nucleophiles as the hydroxyl groups of Al_2O_3 surface is unlikely. From this it follows that dissociative adsorption is preceded by the formation of donor–acceptor bonds between the phosphoryl oxygen atom and surface Lewis acid site. Probably, in this case the ester groups displace the water molecules and hydroxyl groups bound to the Lewis acid sites. It was also shown that hydroxylation of the surface has little effect on the results of grafting, thus substantiating the last-mentioned assumption.

Dissociation of the second methoxyl group in methyl methylphosphonate grafted on the surface is difficult to proceed. Even at 673 K, only 60% of methoxyl groups are eliminated from methyl methylphosphonate attached to the surface.

3. Other phosphonic acid derivatives

Chemisorption of isopropyl methylphosphonofluoridate on Al_2O_3 was studied.⁵² It was shown that at room temperature the grafting of ester molecules on the surface is accompanied by selective elimination of HF. The grafted molecules gradually decompose, which results in liberation of propene and formation of a monolayer of methylphosphonate molecules on Al_2O_3 surface. At 295 K, the process is rather slow (only $\sim 2\%$ of grafted monoester groups are decomposed) but accelerates on heating.

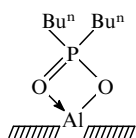
Modification of $\gamma\text{-Al}_2\text{O}_3$ surface with phosphonodichloridates was reported.⁹ The dichloridates interact with the surface rapidly under mild conditions. It was found that this type of modification radically changes the granulometric composition of $\gamma\text{-Al}_2\text{O}_3$ particles. Namely, relatively large particles (100–200 μm in diameter) are transformed to fine dust (particles at most 2 μm in diameter). The pore volume in the support abruptly (by an order of magnitude) and uncontrollably (it can either increase or

decrease) changes in the course of modification. These data and an abnormally high grafting density of the phosphonodichloridate molecules ($\sim 6 \text{ nm}^{-2}$) indicate that the interaction is accompanied by degradation of the particulate surface layer and formation of aluminium phosphonate and, probably, aluminium chloride phases.

The interaction of $\gamma\text{-Al}_2\text{O}_3$ particles with 0.1 M aqueous potassium *n*-octylphosphonate $\text{n-C}_8\text{H}_{17}\text{P}(\text{O})(\text{OK})_2$ was investigated in the same study. It was shown that the salt slowly reacts with $\gamma\text{-Al}_2\text{O}_3$ surface (the grafting density of phosphonate groups is only 1.2 nm^{-2} after 100 h of modification). The modification is accompanied by dispersion of the oxide particles, which indicates degradation of the surface layer.

4. Phosphinic acids

Di-*n*-butylphosphinic acid interacts with $\gamma\text{-Al}_2\text{O}_3$ to give an aluminium dibutylphosphinate surface layer.⁹ The grafting density is very high (4.8 nm^{-2}). The interaction is accompanied by dispersion of the support, being indicative of degradation of the surface oxide layer.



The hydrolytic stability of the coating obtained is relatively high (phosphoryl oxygen atom forms a rather strong donor–acceptor bond with the Lewis acid site), namely, the grafting density remains almost unchanged after two days of treatment with aqueous dioxane in the range of pH values from 2 to 7. However, the grafting density appreciably decreases beyond the limits of this interval of pH values.

IV. Modification of titania surface

Interest of researchers in the chemical modification of titania surface is due to the wide use of metallic titanium owing to unique properties of the material (high strength, corrosion resistance, relatively low density). A significant advantage of titanium consists in its good biocompatibility, which makes it possible to use this material for fabrication of bone prostheses. Being a wide-band semiconductor, titania has found applications in solar energy converters and in photocatalysis.

Modification of TiO_2 surface (metallic titanium is always covered with a dioxide layer) makes it possible to vary the properties of titanium surface over a wide range. Here, conventional organosilicon modifiers are inappropriate because they do not form dense and stable coatings. At the same time organic phosphorus acids and their derivatives readily react with TiO_2 and form dense ordered layers on its surface. Moreover, as in the case of Al_2O_3 , these modifiers significantly improve the uniformity and non-specific character of titania surface, *i.e.*, its inability to be involved in any interactions except for the van der Waals ones.

1. Phosphonic acids

A pioneering study on the modification of TiO_2 surface with phosphonic acids dates back to the early 1980s.⁵³ In the last decade the emphasis was placed on the investigation of fine details of the grafted layer morphology.

Modification of TiO_2 surface with phenylphosphonic acid under different conditions makes it possible to obtain different coatings.³⁴ At room temperature, treatment of TiO_2 surface causes coordination of the phosphoryl oxygen atom to acid sites of the oxide surface followed by condensation of P-OH and Ti-OH groups (analogously to the interaction with alumina). Modification of TiO_2 with phenylphosphonic acid under severe conditions (boiling in water or toluene in a tube at 120°C for 24 h)

results in the formation of a bulk phase of titanium phosphonate. This phase can be detected in ^{31}P NMR spectra. The amount of titanium phosphonate formed in water exceeds that formed in toluene. The content of carbon in such samples corresponds to a grafting density of 10 nm^{-2} . Reduction of the surface treatment time to 5 h causes a decrease in the grafting density, which in this case corresponds to a monolayer coverage.

Modification of TiO_2 surface with bis(trimethylsilyl) phenylphosphonate under severe conditions can also lead to formation of bulk phosphonate phase, however the content of this phase is lower compared to the modification with phenylphosphonic acid.⁵⁴ The authors assumed that the formation of this phase involves migration of the trimethylsilyl group from the adsorbed modifier molecule to the oxygen atom of titanoxane fragment followed by cleavage of one Ti-O bond. Diethyl phenylphosphonate forms only a monolayer coating on TiO_2 surface under these conditions.

An IR spectroscopic study⁵⁴ of the structure of the grafted layers showed that the IR spectra of the samples modified with phenyl phosphonates exhibit neither P=O , Si-C , nor C-O absorption bands. Based on this fact, it was concluded that the molecules of phosphonic acid esters are mainly attached to the surface of TiO_2 in a tridentate fashion. At the same time the IR spectra of the samples modified with phenylphosphonic acid exhibit a P-OH band, which points to bidentate bonding of a fraction of the modifier molecules to the surface (heating of the modified samples at 120°C leads to disappearance of P-OH groups).

Photolysis of P-C bonds on the surface of the modified samples under the action of soft UV radiation (350 nm) was also investigated in the study cited.⁵⁴ It was found that irradiation of the samples placed in water causes cleavage of the P-C bonds and subsequent formation of a surface layer of titanium phosphate, whereas these bonds are retained upon irradiation of the samples placed in toluene.

Modification of TiO_2 surface with octadecylphosphonic acid⁷ does not lead to complete coverage; the surface coverage is $\sim 61\%$ of the monolayer (the use of short-chain alkylphosphonic acids causes the formation of dense monolayers).⁵⁵ Most likely, the octadecylphosphonic acid molecules are attached to the surface in a bidentate fashion (grafted layer contains free P-OH groups). According to ^{13}C NMR spectroscopy data, these layers are poorly ordered especially in the region of terminal chain segments.

A structure of monolayers formed by molecules of long-chain phosphonic acids deposited on the surface of nanocrystalline titania using Langmuir–Blodgett techniques was reported.⁵⁶ Unfortunately, the authors gave no indications of the character of the bonding between the acid molecules and the surface; because of this, it remains unclear whether or not this process can be considered as chemical modification of the surface.

A study of self-assembly of ordered monolayers of phosphonic acids on hydroxylated native oxide layer of metallic titanium⁵⁷ showed that monolayers resulted from surface modification performed at room temperature can be removed with ease by washing the samples with organic solvents, *e.g.*, hot tetrahydrofuran. (In this case low surface coverage was explained by inertness of the oxide film on the surface of metallic titanium to phosphonic acids.⁵⁸) Heating of the modified samples at 120°C significantly improves the stability of the grafted layers, however attempts to fabricate a dense coating in one step failed because of a high content of physisorbed acid molecules on the surface. By repeating the modification–heating–washing cycle it is possible to attain a higher surface coverage. A monolayer coating is formed only after six treatment cycles. Analysis of AFM micrographs showed that the acid molecules chemisorbed on TiO_2 surface form roundish ‘islands’. According to IR spectra, the ‘islands’ are characterised by ordered molecular arrangement similar to crystalline one.

Grafting of ω -carboxyalkylphosphonic acids[†] on TiO₂ surface occurs selectively and involves formation of a system of Ti—O—P bonds (carboxyl group remains unattached to the surface). Here, a high surface coverage is attained after a single modification cycle, which was explained by the interactions between carboxyl groups of the modifier molecules.⁵⁷ Monolayers thus formed are rather stable and cannot be removed by washing.

The selectivity of grafting of ω -carboxyalkylphosphonic acids RP(O)(OH)_2 with $\text{R} = (\text{CH}_2)_n\text{CO}_2\text{H}$ on the surface of titania through the phosphonic group was confirmed in a more recent study.⁵⁹ The conformations of $(\text{CH}_2)_n\text{CO}_2\text{H}$ chains in the grafted layer formed depends on the chain length. Ordered quasi-crystalline all-*trans* layers[‡] are formed only at $n \geq 16$ (proportion of *gauche*-defects in such chains is low). The acid with $n = 12$ also forms a sufficiently ordered layer with preferred *trans*-conformation of chains, but in this case the proportion of *gauche*-defects is high (at room temperature, alkylphosphonic acids with this chain length do not form ordered layers). Acids with shorter chain length form disordered layers. The possibility of polylayer formation on the surface was also reported; however, polylayers are removed by washing the samples with polar solvents (*e.g.*, acetone).

Ordered layers undergo a thermally induced transition from the quasi-crystalline to a 'liquid-like' state. The conformational mobility of alkyl chains in the layers formed by ω -carboxyalkylphosphonic acids is lower compared to that of the layers formed by alkylphosphonic acids with the same number of carbon atoms. This can be explained by the presence of hydrogen bonds between carboxyl groups (according to IR spectroscopy data, all carboxyl groups of the grafted layer are involved in the formation of hydrogen bonds). The hydrogen bonds are completely disordered, which dramatically differs layers formed by such acid molecules from the layers of ω -mercaptoalkylcarboxylic acids on gold nanoparticles.^{60, 61}

Similar results were obtained in a study⁶² on the modification of titania surface with carboxyalkylphosphonic acids $\text{HO}_2\text{C}(\text{CH}_2)_n\text{PO}(\text{OH})_2$, where $n = 2, 3, 11$ and 15 . The authors pointed to bidentate bonding of these compounds to the surface through the phosphonate groups because of a large proportion of surface P—OH groups (analogous results were obtained in another study⁵⁴).

A comparative analysis⁶³ of stability of the grafted layers formed on TiO₂ (anatase) surface treated with octadecylphosphonic acid and various octadecylsilanes [with SiH₃, SiCl₃, Si(OMe)₃ and SiMe₂Cl anchoring groups] revealed the formation of highly ordered monolayers with grafting densities of $4.3\text{--}4.8\text{ nm}^{-2}$ in all cases except for the modification with dimethyloctadecylchlorosilane. Treatment with the latter compound results in the formation of a disordered layer characterised by a low grafting density (about 1.5 nm^{-2}).

The kinetic curves of sorption are similar for all modifiers and show a fast anchoring of the modifier molecules to the surface followed by a slow increase in the grafting density and gradual ordering (in those cases where ordering does occur). The sorption curves obtained are correctly described by a first-order equation with two rate constants differing by 1–2 orders of magnitude. Based on the rate constant values, the anchoring groups can be ordered as follows with respect to their activities: $\text{SiCl}_3 \gg \text{PO}(\text{OH})_2 > \text{SiMe}_2\text{Cl} > \text{Si}(\text{OMe})_3 > \text{SiH}_3$. Two types of interaction between the modifier molecules and the support surface were proposed based on the analysis of the IR spectra of the samples obtained. The modifiers capable of forming horizontal cross-links (unsubstituted trichloro- and trimethoxysilanes) gave highly

ordered layers at low surface coverages (40%–50% of the limiting coverage). This was interpreted⁶⁵ as an indication of the 'island' mechanism of modification. Contrary to this, an ordered layer of octadecylphosphonic acid molecules was formed only at high grafting densities, which indicates a uniform surface coverage similar to the case of dimethyloctadecylchlorosilane that does not form ordered layers under the conditions studied. The thermal stability of the grafted layers is rather high, namely, their degradation begins at $\sim 200^\circ\text{C}$ in air and at 300°C in inert atmosphere.

The hydrolytic stabilities of the grafted layers formed on the surface of anatase treated with octadecylphosphonic acid, dimethyloctadecylchlorosilane and octadecylsilane were compared.⁶⁴ It was established that the layers formed upon modification of anatase surface with dimethyloctadecylchlorosilane are characterised by low stability, namely, the grafted layer is completely removed from the surface after 24 h of storage in a neutral medium at room temperature. The other two layers show higher hydrolytic stabilities, the phosphonate layer being much more stable. Nevertheless, the grafting density of the phosphonate layer decreased by about 15% after seven days of hydrolysis in a neutral medium at room temperature.

A study⁶⁵ on the enthalpies of the reactions of phosphonic acids with TiO₂ surface revealed an increase in the enthalpy with an increase in the length of alkyl group. The enthalpy can even take positive values; in this case, the modification reactions are driven by the entropy factor.

2. Phosphonic acid esters

Diethyl phenylphosphonate and bis(trimethylsilyl) phenylphosphonate are also used for the modification of TiO₂ surface.³⁴ In all cases the diethyl ester formed only monolayer coatings, whereas the bis(trimethylsilyl) ester under severe conditions (boiling with support in toluene) destroyed the oxide surface with the formation of bulk titanium phosphonate phase.

The possibility of using TiO₂ as photocatalyst gave an impetus to studies on the photodegradation of phosphonic acid esters on the surface of TiO₂. A study⁶⁶ on the kinetics of photodegradation of the dimethyl and diethyl methylphosphonates in aqueous solutions showed that only physisorption of these compounds occurs on the TiO₂ surface.

Gas-phase photodegradation of dimethyl methylphosphonate supported on glass coated with a TiO₂ layer (ester concentration in air varied from 1 to 90 ppm⁻¹) results in methylphosphonic acid which interacts with the oxide surface.⁶⁷ Activity of the photocatalyst drops owing to progressive poisoning of its surface with degradation products, but can be completely recovered after several cycles of washing with distilled water.

In a study⁶⁸ of the interaction of dimethyl methylphosphonate, dimethyl phosphite and trimethyl phosphate with the surface of highly disperse TiO₂ it was established that at low temperatures adsorption of these compounds on the surface is accompanied by the formation of hydrogen bonds with surface hydroxyl groups. At higher temperatures, dissociative adsorption with elimination of methoxyl groups is observed, which ceases at $T > 473\text{ K}$. At $T > 573\text{ K}$, the P—C bonds are cleaved, which results in the formation of a phosphate phase on the TiO₂ surface.

3. Phosphinic acids and their esters

The interaction of diphenylphosphinic acid and its ethyl and trimethylsilyl esters with TiO₂ surface was studied by IR and NMR spectroscopy.⁵⁴ From the spectra of the TiO₂ samples modified with ethyl diphenylphosphinate it follows that this modifier forms a monolayer coating on the surface of TiO₂ under the conditions studied. The spectra of the TiO₂ samples treated with diphenylphosphinic acid or trimethylsilyl diphenylphosphinate exhibit complex patterns and are difficult to interpret. The authors suggested the formation of some amount of titanium diphenylphosphinate on the surface in these cases.

[†] According to IUPAC nomenclature, these compounds are called ω -phosphonoalkancarboxylic acids.

[‡] Probably, the quasi-crystalline state of the grafted layer is stabilised through the formation of hydrogen bonds between carboxyl groups.

V. Modification of zirconia surface

The surface of ZrO_2 is similar in chemical properties to the surface of TiO_2 . At the same time there is a number of significant differences between them. In particular, the concentration of hydroxyl groups on the surface of ZrO_2 is nearly 1.5 times higher than on the surface of TiO_2 and the basicity of zirconia surface is also higher than that of amphoteric titania. These features manifest themselves in the modification of ZrO_2 surface with organic acids of phosphorus and their esters.

The structure of a grafted monolayer formed by octadecylphosphonic acid molecules on the surface of ZrO_2 powder has been a subject of detailed NMR studies (Refs 69, 70). ^{31}P NMR spectra indicate a significantly non-uniform structure of the monolayer formed (the peak is rather broad, which points to different fashion of denticity of the bonding between the phosphonate group and the surface). Phosphonate groups on ZrO_2 surface are not strictly immobilised, because the corresponding reorientation time varies in the range 0.1–1 s. This is likely due to high ionicity of the $\text{Zr}-\text{O}$ bond in the surface monolayer of zirconium phosphonate.

^{13}C NMR spectra provide indications of high ordering of alkyl chains in the grafted layer and of transoid conformation for a vast majority of $\text{C}-\text{C}$ bonds in these chains. At the same time the proportion of *gauche*-defects in the grafted layer is relatively high even at room temperature and increases on heating.

The structure of layers formed on the surface of non-porous ZrO_2 nanopowder ($S_{\text{sp}} = 40 \text{ m}^2 \text{ g}^{-1}$) treated with partially deuterated octadecylphosphonic acid (deuterium atoms were introduced at the carbon atom in α -position with respect to phosphonate group) was studied by ^2H NMR spectroscopy at 200–340 K.⁷¹ It was shown that at 340 K the mobility of the anchoring phosphonate group is sufficiently high to be detected by solid state ^2H NMR echo technique. It is believed that so high reorientation rates can be explained, in particular, by bulkiness of the phosphonate group and by monodentate fashion of its bonding to the surface. Simulation of NMR spectra also shows that phosphonate groups can be anchored to the surface of ZrO_2 in different mode.

A ^1H NMR study of phosphonate monolayers on zirconia surface showed the possibility of attainment of all-*trans*-arrangement of alkyl chains.⁷ Nevertheless, here we do not deal with crystalline layers because of rather loose chain packing and large vibrational amplitudes.

The effect of the temperature and alkyl chain length on the ordering of the films formed on the zirconia surface treated with alkylphosphonic acids $n\text{-C}_n\text{H}_{2n+1}\text{P}(\text{O})(\text{OH})_2$ ($n = 8-18$) was studied.⁷² It was found that the acids with $n < 16$ do not form ordered layers on the surface of ZrO_2 at room temperature. The acids with $n = 16$ and 18 form layers with almost all-*trans* alkyl chains at room temperature, but the transition temperature of the hexadecylphosphonic acid layer to the disordered state is only slightly higher than room temperature. The transition temperature of a monolayer formed by octadecylphosphonic acid molecules is about 50 °C; however, in this case the alkyl chains are disordered at lower temperatures compared to crystalline zirconium phosphonates with the closest packing of alkyl chains. Close packing of alkyl chains in the layer is hampered by the phosphonate group whose cross-section is $\sim 0.25 \text{ nm}^2$ (cf. 0.18 nm^2 for methylene unit).

In the monolayers studied the tilt angle is 31°. ⁷² This is somewhat smaller than the equilibrium value for alkylphosphonate bound to the surface in a tridentate fashion; however, this deviation can be compensated by strengthening of the van der Waals interactions between alkyl chains in the case in point.

Structures formed on the surface of ZrO_2 nanopowders (two samples with an average particle size of 5 and 30 nm were used) treated with ω -carboxyalkylphosphonic acids with the spacer length of 2, 3, 11 and 15 methylene units were studied.^{59, 60} The results obtained were to a great extent similar to those obtained

for TiO_2 (see Section IV), however there is a number of distinctions. First, no $\text{P}-\text{OH}$ groups were detected within the layer grafted on ZrO_2 ; this probably indicates a stronger anchoring of phosphonate groups to the ZrO_2 surface. Second, a trend to formation of polylayer coatings on ZrO_2 surface is observed (the second and other layers are bound to the surface and first layer through hydrogen and van der Waals bonds). These layers are stable to multiple washing with acetone, while washing with methanol or aqueous acetone results in removal of the second and subsequent layers.

The selectivity of bonding between the modifier molecules and ZrO_2 surface is also lower than in the case of TiO_2 surface. Namely, the surface of the ZrO_2 powder with a particle diameter of 5 nm contains a small amount of ω -carboxyalkylphosphonic acid molecules bound to the surface through the carboxyl group (this was not observed for the powder with a particle diameter of 30 nm).

The formation of octadecylphosphonic acid monolayers on the surfaces of ZrO_2 and zirconated silica was studied.⁷ In both cases ordered monolayers were formed, although the end groups of the grafted chains were disordered. The monolayer on zirconated silica is much more ordered than on ZrO_2 . The limiting surface coverage on ZrO_2 was not attained (maximum grafting density was $\sim 73\%$ of the limiting value). The grafting density on zirconated silica is only 26% of the theoretical value; this is probably due to nonuniform coating of the silica surface with the ZrO_2 layer (long-chain phosphonic acids do not interact with silica).

A number of structurally similar types of phosphonate groups were found on the surfaces of the modified ZrO_2 samples. This was associated with the presence of different types of sorption sites on the surface of ZrO_2 .⁷ The formation of a small amount of zirconium phosphonate on the surface of zirconated silica was detected by ^{13}C NMR spectroscopy.

The surface of ZrO_2 was also modified⁷³ with regioregular amphiphilic polythiophenes containing phosphonic group in side chains.⁸ It was found that such polythiophenes form self-assembled monolayers on the surface.

A comparison of the structures and hydrolytic stabilities of monolayers formed on the surface of monoclinic ZrO_2 crystal modified with octadecylphosphonic acid and dimethyloctadecylchlorosilane showed⁶⁴ that the acid forms highly ordered surface monolayers with a grafting density of $4-5 \text{ nm}^{-2}$ while the silane forms disordered layers with a grafting density of at most 2.2 nm^{-2} . Hydrolysis was performed using tetrahydrofuran–water mixtures (tetrahydrofuran was added in order to attain better wettability of the modified support). The hydrolytic stability of the layers formed by the modifier with the dimethylchlorosilyl anchoring group is low. Namely, the grafted layer is completely destroyed after 24 h in neutral medium at room temperature. Layers formed by octadecylphosphonic acid molecules are much stronger bound to the surface. Here, an insignificant mass loss (about 2%) was observed after a week of hydrolysis at pH values from 1 to 10 at room temperature. At 65 °C, the stability of layers somewhat decreases but remains rather high.

The thermal stability¹⁹ and the enthalpy of formation⁶⁵ of phosphonate layers on ZrO_2 surface are similar to the corresponding parameters of phosphonate layers supported on TiO_2 .

VI. Modification of iron oxide surfaces

Studies on the interaction of organophosphorus acids and their esters with iron oxide surfaces are mainly aimed at fabricating stable and thin anticorrosion coatings supported on iron and iron alloys.

§ Multilayered ordered structures that can be formed by such compounds have been documented.^{74, 75}

1. Phosphonic acids

Phosphonic acids are widely used for modification of the surfaces of iron (usually, coated with a native oxide layer) and iron oxides. Most studies on the modification of iron surface with phosphonic acids are carried out to solve certain applied problems; however, attention has also been paid to the problem of the structure of the grafted layer. The structure of the octadecylphosphonic acid layer grafted on amorphous Fe_2O_3 particles synthesised⁷⁶ by sonication of a solution of iron carbonyl in decane has been reported.⁷⁷ Thermogravimetric analysis of the modified Fe_2O_3 particles 5–10 nm in diameter showed that thermal decomposition of the grafted octadecylphosphonate layer occurs at 340 °C. It was established that the phosphonate group is anchored to the surface in at least bidentate fashion and that thermal desorption involves cracking of hydrocarbon chains of the modifier.

The magnetisation of the iron oxide particles coated with octadecylphosphonic acid is three times lower than that of identical samples modified with sulfonic acids and at least an order of magnitude lower than the magnetisation of the starting iron oxide or iron oxide modified with alkanolic acids.^{78,79} This was explained by the action of the phosphonic acid molecules that change the spin state of the near-surface Fe^{3+} ions by promoting their transition from the high-spin to the low-spin state (as a result of formation of donor–acceptor bonds between these ions and the phosphoryl groups of the modifier) and by the fact that unoccupied phosphorus d-AOs enhance the magnetic interaction between neighbouring Fe^{3+} ions.

The assumption that the decrease in magnetisation is due to breakdown of Fe_2O_3 particles under the action of phosphonic acid is apparently incorrect. Indeed, sulfonic acids are much stronger than phosphonic acids and surface modification with the former should result in greater reduction of the magnetisation, which is not observed actually. Additionally, the specific surface area of the Fe_2O_3 particles modified with octadecylphosphonic acid is almost the same as that of the particles modified with carboxylic acids (71.5 and 72 m² g^{−1}, respectively). An IR study of the structure of the grafted layer showed that it is highly ordered and that the packing of alkyl groups in this layer is similar to crystal packing.

A dramatic decrease in the magnetisation of the iron oxide particles modified with phosphonic acids was also detected in an EPR study.⁸⁰ No broadening of the microwave absorption line of the modified particles was observed on cooling (this behaviour is characteristic of superparamagnetic particles).

An electron microscopic study carried out by the same authors⁸⁰ showed that the modified particles do not dissolve in phosphonic acids. These results as well as EPR spectroscopy data suggested that the reason for different magnetisation of the starting and modified particles consists in different types of the interaction of surface iron atoms (as was mentioned in Ref. 77). Most probably, antiferromagnetic interactions realise on the surface of the particles modified with phosphonic acids,⁸¹ which eventually leads to superantiferromagnetic particles.⁸²

The procedure for self-assembly and derivatisation of monolayers of α,ω -alkanediphosphonic acid molecules on the surfaces of soft and stainless steels⁴¹ is similar to that described in Section III.

2. Phosphonic acid esters

Dimethyl methylphosphonate adsorbed on $\alpha\text{-Fe}_2\text{O}_3$ surface from the gas phase at 170 K readily interacts with the oxide surface by the dissociative mechanism involving elimination of methoxyl groups.¹¹ At 250 K, both methoxyl groups dissociate and a methylphosphonate layer is formed on the surface. Further heating leads to decomposition of the ester with evolution of volatile products (carbon oxides, water, methanol, hydrogen, formic acid) and formation of iron phosphate on the surface. Dissociative chemisorption with elimination of two MeO groups at temperatures above 250 K was also observed in the modification of the (110) face of iron crystal with trimethyl phosphate.⁵⁰

Modification of iron powder with diethyl esters of octyl- and tetradecylphosphonic acids is highly efficient.²⁰ The coatings obtained exhibited good corrosion resistance (no corrosion was observed even after a few weeks of storage in aerated 0.1 M NaCl solution). The conductivities of the modified powders remained rather high, being almost equal to the conductivity of untreated iron powder freshly cleaned from native oxide film. This indicates that the monolayer coating thus formed presents no difficulties to electron transport (electron tunnelling effect manifests itself at distances of the order of the thickness of monolayer coating). This differs the phosphonate coatings from the triethoxysilane-based ones. The latter also efficiently protect iron from corrosion, but reduce the conductivity by three to six orders of magnitude (probably, due to formation of a thick insulating polymer layer on the surface). The phosphonate coatings also have a high thermal stability, namely, they protect iron from oxidation in air up to 350–400 °C.

VII. Other oxides and metals

The action of diethyl methylphosphonate vapours on tin dioxide at 300 °C causes dissociative sorption of the ester with elimination of ethylene (from one EtO group) and formation of ethyl methylphosphonate layer grafted on SnO_2 surface.⁸³ Raising the temperature leads to elimination of the second EtO group. Diethyl methylphosphonate is used as a model compound in detecting organophosphorus compounds (in particular, warfare agents) using semiconductor (SnO_2) sensors.⁸³

A study⁵⁶ of monolayer films formed by eicosylphosphonic acid molecules deposited on SnO_2 surface using Langmuir–Blodgett technique showed that at a surface area per acid molecule of 0.23 nm² the tilt angle is 17°; reduction of the surface area to 0.2 nm² causes the tilt angle to decrease to 16°. Unfortunately, the nature of bonding between the acid molecules and the SnO_2 surface was not studied; therefore, it is unknown whether the chemical grafting of the acid molecules on the surface or physisorption occurs.

The formation of eicosylphosphonic acid layers on silver and gold supports was also investigated in the study cited,⁵⁶ and again the nature of sorption was not studied. However, one can assume that no chemical grafting occurs, because bare gold surfaces do not adsorb phosphonic acids⁸⁴ while a layer of phosphonic acid molecules physisorbed on a gold substrate can be removed with ease by washing with organic solvents (even isooctane). Taking into account the fact that monolayer films formed by alkanethiol molecules that readily interact with the surface of gold substrates exhibit not too high oxidation stability (oxidation causes desorption and degradation of the grafted layer), elaboration of methods for modification of gold surfaces remains topical.

A procedure involving deposition of submonolayers formed by copper atoms on the surface of gold supports followed by modification of the surface with phosphonic acids was proposed.⁸⁴ A grafted layer thus obtained is stable and cannot be removed from the surface using such solvents as isooctane, ethanol and water. Octadecylphosphonic acid monolayers on copper-plated gold surface show the water and hexadecane contact angles of 111° and 28°, respectively, which indicates a high density and ordering of the layers. This was also substantiated by IR spectroscopy data.

At the same time IR spectroscopy data revealed a larger tilt angle of alkyl groups of octadecylphosphonic acid molecules compared to alkanethiol molecules grafted on gold surface. This is likely due to the fact that the amount of copper on the gold surface is less than that required to provide a monolayer coating. According to X-ray photoelectron spectroscopy data, the copper : oxygen : phosphorus ratio at the surface is 2 : 3 : 1, i.e., there is one phosphonate group per two copper atoms.

The layer formed by octylphosphonic acid molecules on copper-plated gold surface is disordered and has a liquid-like structure.⁸⁴ The octadecyl- and octylphosphonic layers are 2 and

0.8 nm thick, respectively (ellipsometry data). Electroactive 11-ferrocenylundecylphosphonic acid can also be grafted on copper-plated gold surface. However it does not form ordered monolayers (probably, due to the bulkiness of the ferrocenyl group, which precludes the close packing of alkyl groups). The density of grafting of ferrocenylundecylphosphonic acid molecules on the surface is $4 \mu\text{mol m}^{-2}$ (see Ref. 84), which is somewhat lower than the value obtained for thiols ($4.3 - 5.6 \mu\text{mol m}^{-2}$).⁸⁵⁻⁸⁸

The formation of monolayers of α,ω -alkyldiphosphonic acid molecules on the surface of copper, brass, tantalum and chromium was reported.⁴¹ The properties of these monolayers are generally similar to those of corresponding monolayers formed on aluminium and titanium (see Section III). Monolayer films of ω -carboxyalkylphosphonic acids formed on tantalum surface⁸⁹ are similar to the layers prepared on aluminium surface (see Section III). Self-assembled monolayers formed by octadecylphosphonic acid molecules on tantalum surface was also studied.⁹⁰ A rather high degree of ordering of alkyl groups in these layers is similar to that observed for alkylthiol layers formed on gold surface.

Monolayer films formed by *n*-amyl- and *n*-tetradecylphosphonic acid molecules on zinc surface were prepared⁹¹ by treating a polished zinc plate with solutions of corresponding acids in ethanol or aqueous ethanol. Both acids form dense layers, rather highly ordered for C_{14} and much lower ordered (almost disordered) for C_5 . The water and hexadecane contact angles for the tetradecylphosphonic acid layer almost coincide with the values characteristic of fully methylated surface, thus confirming high density and ordering character of the layer. Nevertheless, such layers do not protect zinc from electrochemical corrosion.

Dimethyl methylphosphonate vapours interact with tungsten trioxide surface⁶⁸ similarly to the case for titania (see Section IV). The only significant difference between sorption of ester on these two substrates is the formation of much stronger hydrogen bonds between the ester phosphoryl group and the surface hydroxyl groups on WO_3 . This was attributed to a much higher Brønsted acidity of WO_3 surface compared to TiO_2 surface.

Information on the interaction of phosphonic acids with hafnia-coated silica surface is also available.^{92,93}

VIII. Applications of materials with surfaces modified with organophosphorus compounds

1. Separation membranes

One of the key avenues of practical use of phosphonic acids as modifiers of Al_2O_3 and TiO_2 surfaces is fabrication of organoceramic membranes. Such membranes were prepared⁹⁴ by chemical grafting of *n*-butylphosphonic acid on the surface of an alumina membrane. The modification was carried out in order to change the gas transport properties of the membrane, because efficient separation of gases with similar molecular masses using the initial mesoporous membrane with a pore diameter of 5 nm was impossible. Changes in the surface properties of the modified membrane provided a way to controllable variation of the contributions of different transport mechanisms and to improvement of the membrane's permeability and selectivity. *n*-Butylphosphonic acid modified membranes were used for separation of CH_4 , C_2H_6 , C_3H_8 , N_2 , H_2 and CO_2 at room temperature. The best results (high permeability and high selectivity coefficient) were obtained for the separation of a propane–nitrogen mixture. The authors pointed that the *n*-butylphosphonate layer can be removed from the surface by washing with alkali (in this case the properties of the initial membrane are recovered; if necessary, the membrane can be re-modified).

Membranes for separation of bovine serum albumin from native bovine serum by ultrafiltration were synthesised.⁵⁵ When using TiO_2 membranes, albumin is adsorbed irreversibly and cannot be removed from the membrane surface until complete denaturation. However, sorption of albumin becomes reversible

upon treatment of the membrane with *n*-butylphosphonic acid, which forms a monolayer with a grafting density of about $5 \mu\text{mol m}^{-2}$ on TiO_2 surface (this corresponds to a cross-section area of $\sim 0.3 \text{ nm}^2$). The acid modified membrane is highly hydrophobic, which precludes water transport across the membrane under the experimental conditions. Wetting the membrane with ethanol–water mixture makes the surface hydrophilic and transport of water or aqueous solutions across the membrane becomes possible. This is not accompanied by desorption of butylphosphonate groups from the surface. Albumin is not adsorbed on this membrane, being filtered with a nearly 100% efficiency.

Membranes made of alumina or silica cannot be used because of breakdown of the former and instability of grafted layers on the latter material.⁵⁵

The IR spectra of modified TiO_2 exhibit no $\text{P}=\text{O}$ and $\text{P}-\text{OH}$ absorption bands. This was interpreted as an indication of tridentate grafting of butylphosphonic acid molecules. The grafted layer can be removed from the surface by washing with a NaOH solution following a known procedure;⁹⁵ this is followed by recovery of the initial properties of the membrane.

Similar results were obtained for a ZrO_2 -based membrane.⁵⁵

2. Heterogeneous metal complex catalysts

Phosphonate anchoring groups are used for immobilisation of metal complex catalysts on solid supports. The activity of metal porphyrinate complexes immobilised on TiO_2 surface in the alkene oxidation reactions was studied.⁹⁶ Catalysts were prepared by grafting metal porphyrinates with phosphonate groups on TiO_2 surface. The authors also reported the possibility of grafting such complexes on the surface of TiO_2 electrodes, which can be used in electrochemical catalysis and in fabrication of electrochemical sensors.

The synthesis of heterogeneous metal complex catalysts based on bipyridyl complexes of rhodium and iridium grafted on TiO_2 surface was reported.⁹⁷ The complexes were grafted through phosphonate groups in the ligand side chains. These compounds exhibit a rather high catalytic activity similar to that of homogeneous analogues. The highest activity was obtained for the complexes immobilised on freshly prepared (by hydrolysis of tetraisopropoxytitanium) titania, whereas grafting on a commercially available oxide (specific surface area of $429 \text{ m}^2 \text{ g}^{-1}$) gave somewhat less reactive samples.

Phenylphosphine ligands are very often used for the synthesis of catalytically active metal complexes. The possibility of immobilisation of phosphines $\text{Ph}_2\text{P}(\text{CH}_2)_3\text{Si}(\text{OEt})_3$ on the surfaces of various inorganic oxides (MgO , TiO_2 , Al_2O_3 and SiO_2) was studied.⁹⁸ It was found that these phosphines can be easily grafted on the surfaces of Al_2O_3 and SiO_2 , but cannot be grafted on the surfaces of TiO_2 or MgO .⁹⁸ At the same time similar ligands with phosphonate anchoring groups⁹⁹ can be grafted on the surfaces of the last-mentioned two oxides.

The catalyst performance was studied⁹⁷ in relation to the pH of the medium. The highest performance was achieved at pH 5.6 and remained unchanged up to pH 12.5 for two days (the authors reported a slight increase in performance), thus indicating stability of the grafted layer at $5.6 \leq \text{pH} < 12.5$. However, at pH 12.9 the catalyst performance dramatically decreases with time due to degradation of the grafted layer.

3. Modified electrodes

Phosphonic acids are often used for modification of oxide electrode surfaces. In particular, the surface of TiO_2 (anatase) nanocrystals supported on conducting glass was modified with viologen (1,1'-dieicosyl-4,4'-bipyridinium dichloride) and eicosylphosphonic acid.¹⁰⁰ A mixture of eicosylphosphonic acid and viologen was deposited using Langmuir–Blodgett technique. At high dilution of viologen with the acid, only one viologen molecule with known orientation is adsorbed on each TiO_2 nanocrystal and no electron transfer between viologen molecules adsorbed on different nanocrystals occurs. This system can be used as photo-

sensitive electrode for a photoelectrochemical cell (such a cell is highly sensitive in the visible spectral region).

A rather large number of studies are devoted to modification of electrodes fabricated from indium–tin oxide (ITO) ceramics (91% In_2O_3 , 9% SnO_2). In particular, ITO electrodes can be modified with phosphonic acids to form a salt monolayer on the surface.¹⁰¹

The electrochemical properties of an ITO electrode modified with 2,5-bis(phosphonomethyl)hydroquinone and a ZrO_2 -coated ITO electrode were studied¹⁰² by cyclic voltammetry.[¶]

The molecules of 2,5-bis(phosphonomethyl)hydroquinone spontaneously and irreversibly react with the surface of the ITO electrode irrespective of the presence of a zirconium layer. The grafting density is $\sim 2.6 \mu\text{mol m}^{-2}$ (about 40% of theoretically possible value). The modified electrodes showed good characteristics in electrochemical molecular recognition of alkali metal and ammonium cations. Namely, they permitted the observation of unique redox peak potential shifts depending on the molar concentration of each type of cations in the range 0.01 – $1.0 \text{ mol litre}^{-1}$. The electrodes are selective to potassium cation in the presence of sodium cations. Initially, the electrochemical characteristics of the non-zirconated modified electrode almost coincides with those of the zirconated electrode, but gradually changes with time (probably, due to a lower hydrolytic stability of the grafted layer on the non-zirconated electrode). The grafted layer on the zirconated electrode was stable at $0 \leq \text{pH} < 12$.

The interaction of 6-(ferrocenyl)hexylphosphonic acid with the surface of an ITO electrode was studied.¹⁰³ This acid can be grafted on the electrode surface (the grafting density is $3.1 \mu\text{mol m}^{-2}$ or about 70% of the limiting value¹⁰⁴). The grafted layer is characterised by strong intermolecular interactions between ferrocenyl fragments. Monolayers thus obtained are stable in acetonitrile in both (ferrocene and ferricinium) forms, however protic solvents gradually destroy the grafted layer. As a result, the grafted molecules are desorbed from the surface (the process in ethanol at room temperature is slow while proceeds faster in water). Boiling of the modified samples in water leads to complete desorption of the grafted molecules from the surface.

Owing to strong intermolecular interactions between ferrocenyl fragments the modifier molecules are grafted on the support surface in 'island' fashion even at low surface concentrations. Attempts to obtain a more uniform grafting by 'diluting' 6-(ferrocenyl)hexylphosphonic acid with short-chain phosphonic acids failed. Apparently, ferrocenyl fragments interact with one another much stronger than with short alkyl chains. When dodecylphosphonic acid was used as diluent, a 'dilution' effect was observed, but attempts to efficiently isolate ferrocenyl fragments also failed. Apparently, acids with longer chains should be used in this case.

ITO electrodes are most often used as anodes in organic bilayer based electroluminescent devices, because ITO glass is transparent (optical transmission of 90%) and possesses good conducting properties; various metals can serve as cathodes. Unfortunately, the metals characterised by low work function of electron are highly reactive and readily oxidisable (e.g., calcium or a magnesium/silver alloy), which limits the lifetime of the devices.

Phosphonic acids are known to form self-assembled monolayers on the surface of ITO glass.¹⁰⁵ Using an ITO electrode coated with electron-acceptor 2-chloroethylphosphonic acid and an aluminium cathode, the threshold voltage was considerably reduced¹⁰⁶ to a value characteristic of a much less stable magnesium–silver electrode. The use of the modified ITO electrode eliminates the need of electrodes made of highly reactive metals and makes it possible to exclude a factor that limits the operational life of electroluminescent devices (because the grafted layer of such devices is stable under the operation conditions).

Modification of the ITO electrode with 2-chloroethylphosphonic acid led¹⁰⁷ to considerable improvement of the stability of

a light-emitting diode based on poly(5-methoxy-2-octyloxy-1,4-phenylenevinylene) owing to reduction of the onset voltage. Electronic effects at the polymer/ITO electrode interface in the electroluminescent devices based on an ITO electrode modified with 2-chloroethylphosphonic acid were also considered.¹⁰⁸

4. Biosorbents

Porous beads made of ZrO_2 modified with ethylenediamino- N,N,N',N' -tetrakis(methylenephosphonic) acid were used as pseudoaffinity sorbents for chromatographic separation of human immunoglobulin G from untreated blood serum.¹⁰⁹ The particle diameter varied from 25 to 38 μm . The effects of the temperature, of sodium chloride content in eluent and of the eluent pH on the maximum binding capacity of the protein and the equilibrium binding constant were studied. Measurements were carried out in the temperature range from 4 to 35 $^{\circ}\text{C}$ at sodium chloride concentrations in the eluent of 0.05, 0.1 and $0.2 \text{ mol litre}^{-1}$ and at pH values of 5.5, 6.0, 6.5, 7.0 and 8.0. Temperature changes in the range given above had almost no effect on the binding constant, whereas an increase in the salt concentration or in pH value led to a marked decrease in the maximum binding capacity and to an increase in the binding constant. The maximum binding capacity of immunoglobulin G at the lowest pH value (5.5) is 55 mg ml^{-1} (see[†]). The sorbent obtained allows immunoglobulins A, G and M in untreated serum to be separated. At a linear elution velocity of 4.32 cm min^{-1} , the yields of these immunoglobulins were respectively 29.5 ± 6.3 , 3.22 ± 0.70 and $6.84 \pm 0.70\%$, respectively. The purity of the immunoglobulins obtained from a single chromatographic run was $89.0 \pm 2.6\%$.

The decrease in the maximum binding capacity with the increase in the electrolyte (sodium chloride) concentration suggests that the binding of immunoglobulin to the sorbent the most important role is played by electrostatic interactions and, probably, hydrogen bonds. The mechanism of the interaction between immunoglobulin and the sorbent is still to be clarified.

At all temperatures studied, the shape of adsorption curves is correctly described by the Langmuir equation. The values of the binding constant indicate a moderate degree of affinity of the sorbent, which is characteristic of pseudoaffinity ligands.^{110, 111}

A more recent study on optimisation and modelling of chromatography on this sorbent was reported.¹¹² The maximum static binding of human immunoglobulin G on this sorbent was 55 – 65 mg ml^{-1} and the maximum dynamic binding was 12 – 20 mg ml^{-1} . It was emphasised¹¹² that ZrO_2 offers significant advantages over conventional silicas and polymeric supports, namely, high strength and excellent thermal and chemical stabilities, which also allows this material to be used as support.^{110, 113–115}

The phosphonic acid used for modification is¹¹² a highly efficient blocker of Lewis acid sites present on the surface of unmodified zirconia in a concentration of 4 – 5 mmol m^{-2} (see Ref. 116). The sorbent studied also possesses a high hydrolytic stability. Namely, the composition of the grafted layer remained unchanged in the range of pH values from 1 to 10. Possible mechanisms of the pseudoaffinity interaction of the sorbent with immunoglobulin G were also considered.¹¹²

5. Implants

Titanium is widely used for production of bone implants. One of the key problems concerned with titanium implants is passive integration. No chemical bonds are formed between the growing bone tissue and the implant, which deteriorates the strength of the system at the junction. To increase the adhesive force between the implant and the bone tissue, ethane-1,1,2-triphosphonic and methylenediphosphonic acids were grafted on titanium disks.¹¹⁷ These disks were used to study proliferation, differentiation and

[¶]This electrode was fabricated by pre-soaking of the starting ITO electrode with Zr(IV) -containing solutions.

[†]Amount of immunoglobulin per ml of sorbent.

protein production for rat osteoblasts (*in vitro* experiments). No statistically significant deviations of proliferation compared to blank run were observed. Thus, the phosphonic acids studied have no cytotoxic effect on osteoblasts. At the same time production of type I collagen on the modified samples increased significantly (up to 16%) compared to non-modified samples, which indicates a stronger binding of the modified implants to the surrounding bone tissue.

Similar results were obtained in a study¹¹⁸ of the possibility of using modified titanium samples in dental implantology (here, the situation is similar to osteoplastics). Ethane-1,1,2-triphosphonic and propane-1,1,3,3-tetrakisphosphonic acids were used as modifiers. The results obtained confirmed better biocompatibility of the modified implants, the samples modified with ethane-1,1,2-triphosphonic acid showed a greater sorption of calcium compared to the samples modified with propane-1,1,3,3-tetrakisphosphonic acid.

6. Magnetic materials for medicine

Magnetite nanoparticles (average diameter 6–8 nm) with grafted biocompatible layers formed by dodecyl- or hexadecylphosphonic acid molecules can find applications in magnetic resonance imaging.¹¹⁹

Using IR spectroscopy, it was shown that phosphonic acids form 'islands' with ordered arrangement of alkyl groups and high grafting density on the surface of magnetite nanoparticles. Thermogravimetric analysis (TGA) of the particles fabricated indicates that the phosphonate coatings are more stable than carboxylate ones. From the TGA data it follows that thermal desorption of molecules involves two steps. This was also observed for Fe₂O₃ (Ref. 77) and Ta₂O₅ particles (Ref. 120) and explained by (i) occurrence of two types of the interaction between the modifier molecules and the surface^{77, 120} and (ii) formation on the surface of particles of a modifier bilayer similar to the phospholipid layer of biomembranes.¹¹⁹

The latter assumption is substantiated by the following facts. First, complete interaction between acids and the surface is difficult to attain; therefore, it is clear that the excess amounts of the acids bound to the surface through weak hydrogen and van der Waals bonds will be desorbed with ease. Second, two-step desorption was observed for not only phosphonic but also carboxylic acids that are attached to the oxide surfaces in a similar fashion.⁷⁷ Third, transitions in the differential scanning calorimetry spectra occur at temperatures that correspond to TGA peaks, having a more convex shape in the temperature range corresponding to the second TGA peak. This was interpreted as a substantiation of the formation of a modifier bilayer on the surface of the oxide particles.

7. Anticorrosion coatings

Phosphonic acids are widely used for fabrication of anticorrosion coatings on aluminium, iron and iron alloys. Traditionally, aluminium is protected from corrosion by chromation, which is used in industry on a large scale. However, weak adhesion of chromated aluminium to paintwork materials and toxicity of hexavalent chromium compounds[‡] used for chromation give an impetus to search for and elaboration of alternative methods for protecting aluminium from corrosion. For instance, cellulose derivatives with phosphonate groups were proposed¹²¹ as protective coatings. The surface layers were formed by immersion of metal samples into dilute solutions of phosphorylated cellulose. According to scanning electron microscopy data, the surface defects of the starting metal are no longer detected after this treatment. Fourier transform IR data indicate that cellulose units in the surface layers are mainly aligned to the support surface. The

properties of the layers formed depend on the concentration of the modifier solution. The thickness of the newly formed layer is ~1 nm in a 0.1% solution and about 6 nm for a concentration of 2%. At concentration of 3% the layer thickness was not determined (according to electron microscopy data, the surface layer has a highly nonuniform structure).

Contact angle measurements showed¹²¹ that after the first immersion the contact angle somewhat decreases, but remains unchanged in the subsequent measurements. The plates modified with the 0.1% solution are characterised by the same contact angle values for the whole surface area of the sample. Modification with more concentrated solutions results in different contact angle values at different points, thus indicating an inhomogeneous structure of the layers formed using concentrated solutions. These conclusions are also confirmed by corrosion tests. For instance, a thin layer formed from a dilute solution of phosphorylated cellulose is a good protector of aluminium from corrosion, whereas thicker layers prepared from concentrated solutions provide no protection at all (apparently, because of inhomogeneous structure). In spite of positive results obtained¹²¹ it should be noted that chromation of aluminium is a more efficient technique.

It was also proposed to protect aluminium from corrosion using self-assembled layers of organic molecules.¹²² Numerous classes of modifiers were studied, namely, alkylphosphates, alkylphosphonic acids, tetraalkylphosphonium salts and alkyliminobis(methylphosphonic) acids, alkyltrimethoxysilanes, alkyltrimethoxysilanes, alkanolic acids, aliphatic alcohols, bromides, amines, thiols, sodium alkyl sulfates and sodium alkyl sulfonates. Among them, only monoalkylphosphate, phosphonic acid and trimethoxysilane layers showed good results in studies of their hydrolytic stability at pH values of 7 and 12. Because all other layers possess low hydrolytic stability, only these three types of modifiers were included in further studies.

Contact angle measurements (with water as the process liquid) showed that the silane layers have lower hydrophobicity and corrosion stability than the alkylphosphate and phosphonate layers that are characterised by similar values of the contact angle.

Phosphorus-containing grafted layers thus obtained were studied by IR spectroscopy¹²² and it was shown that the anchoring phosphorus-containing group is linked to the alumina surface by three oxygen atoms. For simple alkyl derivatives the degree of ordering of alkyl groups within the grafted layer increases with the treatment time and reaches a limiting value after about 70 h (this is in good agreement with the published data²⁹). High grafting density almost equal to the limiting value is reached after a few hours. At the same time bifunctional derivatives containing polar groups in their molecules provide no limiting coverage even after 24 h of modification. The authors failed to estimate the degree of ordering of such layers.

A large number of studies on the modification of metal surfaces with phosphonic acids are devoted to protection of metallic iron from corrosion. In particular, phosphonic acids are used for protection of heat exchangers as both inhibitors of corrosion and heat exchange stabilisers.^{123, 124} Due to low toxicity, high chemical stability and ability to inhibit corrosion of iron in neutral media phosphonic acids are widely used as additives to heat-transfer fluid (water).^{125, 126} Short-chain phosphonic acids are good inhibitors of corrosion of iron and steels.^{124, 127}

The anticorrosion effect of 1-hydroxyethylidenediphosphonic acid (HEDPA) in the presence of calcium cations[§] on the properties of metallic iron was studied.¹²⁸ Treatment of iron with a combination of HEDPA with calcium cations makes it possible to reduce the anodic current and to inhibit the reaction of oxygen reduction at cathode. Using electrochemical methods, X-ray

‡ Special care should be taken when using toxic Cr(VI) derivatives. As time passes, these compounds adsorbed on aluminum diffuse to the environment, thus polluting it.

§ The acid itself is a very poor inhibitor of corrosion of soft steel,¹²⁹ while the anticorrosion ability significantly increases in the presence of calcium ions.¹³⁰

photoelectron spectroscopy data and Auger spectroscopy, it was shown that the optimum ratio of the molar concentrations of calcium ions and HEDPA is 1 : 2. As the concentration of calcium cations increases, the corrosion potential is shifted to the cathode.¹²⁸

Synergistic inhibition of corrosion of a soft steel modified with zinc cations and 3-phosphopropionic acid in 0.006% chloride solution was studied¹³¹ by electrochemical and weight change methods. It was found that the grafted layer contains iron phosphonate complexes and zinc hydroxide (it slows the diffusion of iron phosphonate complexes and hydrogen cations through the grafted layer, which in turn inhibits corrosion).

The possibility of protecting iron from corrosion by treatment with phosphonic acids was studied by researchers from another group.¹³² The surface of iron was modified at pH 7 with alkylphosphonic and α,ω -alkanediylphosphonic acids from aqueous solutions using sodium hydroxide as alkalisng agent. It was found that the formation of a surface phosphonate layer changed the polarisation resistance potential and the surface capacitance of the iron sample. The formation of dense grafted layer led to significant inhibition of corrosion (anodic type of protective mechanism).

A study on the kinetics of modification of iron surface with phosphonic acids showed that the process begins with fast adsorption of phosphonic acids and formation of poorly ordered layers. The second stage involves ordering of the grafted layer, as indicated by slow increase in the polarisation resistance. The grafted layer becomes completely ordered after a few days of modification. The major difference between the layers formed by mono- and diphosphonic acids consists in that alkylphosphonic acids form a hydrophobic monolayer coating on the surface, whereas diphosphonic acids can form thin polylayers owing to relatively strong intermolecular interactions.

Piperidin-1-ylmethylphosphonic and piperazin-1,4-diylbis(methylphosphonic) acids were also used as inhibitors of iron corrosion.¹³³ The addition of these phosphonic acids causes a shift of the pitting potential in chloride solutions to the region of positive values, which inhibits the pitting attack. The corrosion potential is shifted to the region of negative values and the corrosion current and, hence, the corrosion rate decrease. This was explained by the formation of a dense protective film from phosphonic acid molecules on the electrode surface. It was found that the efficiency of both acids increases as their concentrations in solution increase and reaches a maximum at a concentration of $\sim 5 \text{ mmol litre}^{-1}$. Piperazin-1,4-diylbis(methylphosphonic) acid was also shown to be a more efficient inhibitor of corrosion compared to piperidin-1-ylmethylenephosphonic acid.

Inhibition of iron corrosion in hot potassium hydrocarbonate solution (it is often used for absorption of CO_2) was studied.¹³⁴ Since HEDPA is also a good inhibitor of soft steel corrosion,¹³⁵ it was interesting to consider the inhibiting effect of this acid on stainless steel corrosion. It was found¹³⁴ that HEDPA does inhibit corrosion of stainless steel. The addition of small amounts of 2-aminothiophenol to HEDPA significantly enhances the inhibiting effect. Diethanolamine also enhances the protective effect. The best results were obtained with a ternary mixture 2-aminothiophenol/HEDPA/diethanolamine (1 : 10 : 30 000); this mixture is also a good inhibitor of soft steel corrosion.

8. Maintenance of adhesion

In a study⁸⁹ on adhesion of organic compounds to metal surfaces it was pointed that ω -functionalised phosphonic acids possess good adhesive properties to aluminium. Phosphorylation provides a good alternative to chromation. In particular, the formation of a phosphonate monolayer on aluminium surface takes only 20 min.⁸⁹

Phosphonic acids can be used as components of base coatings for iron. Such coatings improve the adhesion of varnishes and paints to the metal surface. In a study¹³⁶ on novel base coating

systems for iron and soft steels the major components were dodecylphosphonic acid and a number of phosphonic acids containing thienyl groups. They form self-assembled monolayers on the passivated iron surface. The samples were coated by immersion into aqueous solutions of modifiers. Prior to modification, iron was treated with 10% HNO_3 solution for passivation.

The formation of self-assembled monolayers of thienylphosphonic acid molecules on the surface was confirmed by voltammetry and contact angle measurements. Measurements showed an efficient hydrophobisation of iron surface. The water contact angle is $18.5 \pm 4.0^\circ$ for passivated iron, $51.4 \pm 4.0^\circ$ for non-passivated iron and 121.2 ± 2.0 and $148.5 \pm 3.0^\circ$ for iron treated with 6-(3-bithienyl)hexylphosphonic acid and dodecylphosphonic acid, respectively. Large contact angles indicate the formation of dense and ordered layers on the iron surface. Despite the larger contact angle obtained for iron treated with dodecylphosphonic acid compared to iron treated with thienylphosphonic acids, the use of the last-mentioned compounds makes it possible to carry out polymerisation of thienyl groups and thus to improve the stability of the grafted layer.

Adhesion of organic compounds to the surface of titanium can also be improved by phosphorylation.⁸⁹

IX. Conclusion

The published data considered in this review show that phosphonic acids and their esters, as well as phosphinic acids are important and promising modifiers of oxide surfaces. Often, organophosphorus compounds provide the possibility of fabrication of highly ordered surface monolayers with grafting densities approaching the limiting values. By and large, phosphonic acids are more preferable than phosphinic acids because they form more ordered grafted layers and are more synthetically accessible. Despite the fact that phosphonic acid esters are less reactive than the parent acids, the former are quite often used for modification of oxides (in particular, alumina), because they do not destroy the surface of this support.

It should be noted that organophosphorus compounds are the best modifiers of titania and zirconia. They form grafted layers of better quality compared to organosilicon compounds. Phosphonic acids are similar to silanes in efficiency of the modification of alumina and iron oxide surfaces. Phosphorus-containing layers grafted on these oxides are more dense, but have a lower hydrolytic stability. If alumina is used under anhydrous conditions, it can be protected with organophosphorus compounds. Silica can be better protected with silanes rather than organophosphorus modifiers because the latter provide a lower grafting density and have a much lower hydrolytic stability, although can form highly ordered layers on the silica surface.

In spite of intensive research in the field in question, many problems are still to be solved, *e.g.*, the mechanisms of the interaction of phosphonic acid esters with the surface of TiO_2 . The effects of the crystal structure of Al_2O_3 and TiO_2 on the results of surface modification are also poorly studied. At present, only a narrow range of oxide surfaces can be modified with phosphonic acids and their esters. These are the mineral supports considered in this review.

Organophosphorus modifiers of oxide surfaces are thought to be quite promising for practical use in chemistry, biology and medicine. It is believed that they will be useful for fabrication of selective chemical sensors, in particular, those based on semiconductor SnO_2 ,^{137,138} efficient titania-based photocatalysts,¹³⁹ biocompatible titanium, tantalum and calcium-phosphate implants with grafted phosphonate layers,^{140,141} asymmetric heterogeneous metal complex catalysts;^{142,143} very thin and stable anticorrosion coatings;¹⁴⁴ specific sorbents for separation and concentration of biomolecules;¹⁴⁵ materials for molecular recognition,¹⁴⁶ *etc.*

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^a — *Russ. Chem. Bull., Int. Ed. (Engl. Transl.)*^b — *Russ. J. Anal. Chem. (Engl. Transl.)*^c — *Mendeleev Chem. J.*^d — *Protect. Met. (Engl. Transl.)*^e — *Colloid. J. (Engl. Transl.)*

Chemical design of high spin polynuclear manganese(II) and iron(II) carboxylates

M A Kiskin, I L Eremenko

Contents

I. Introduction	559
II. Binuclear carboxylate complexes	559
III. Mn(II) and Fe(II) carboxylate complexes with three and more metal sites	563
IV. Polymeric carboxylate complexes	565
V. Mixed-valence complexes containing manganese(II) and iron(II)	568
VI. Conclusion	572

Abstract. Methods for synthesis and the structures of high spin polynuclear carboxylate complexes of divalent manganese and iron are considered. The bibliography includes 153 references.

I. Introduction

Currently, polynuclear coordination compounds containing high spin atoms of transition elements have become the focus of keen attention of specialists of various profiles. Due to the presence of open-shell metal sites, these compounds are, as a rule, extremely reactive with respect to different donating organic and inorganic molecules, inducing their unusual chemical transformations in the coordination sphere of the metal core.¹ In addition, the presence of unpaired electrons on the metal atoms of polynuclear coordination compounds determines their unique magnetic and electro-physical properties. It is these particular properties that suggest that in the future this kind of compounds can be used as building blocks of electronic molecular devices.^{2–5}

Carboxylate complexes of high spin 3d-metals are special among a wide variety of polynuclear molecular systems. Their distinguishing feature is high solubility in organic solvents (particularly, the derivatives with alkanoate anions). This is quite important, because performing the reactions in organic solvents excludes hydrolysis, which, as a rule, results in decomposition of polynuclear molecules. Moreover, this provides an opportunity of chemical assembly of the molecules in relatively inert media (including non-polar ones), which significantly simplifies the methods of targeted synthesis of magneto-active polynuclear molecules.

Carboxylate complexes are not only the subject of fundamental investigations, but are also compounds of potential industrial importance. For instance, it has recently been shown that pivalate complexes with three and six Fe(III) atoms are promising components of a homogeneous catalytic Gif-system for hydrocarbon oxidation.⁶ High solubility of polynuclear complexes in hydro-

carbon solvents facilitates the transfer of the metal ions into non-aqueous media. This is of great importance for manufacturing diverse metal-containing films on surfaces of different supports. It is known that thermolysis of pivalate complexes results in elimination of the carboxylate ligands thus building up the metal core and yielding ultimately oxide materials.⁷ Currently, the methods of synthesis of molecular ferromagnets based on polynuclear carboxylate systems are being intensively developed. These compounds can potentially be used as materials for molecular electronics.^{8–15}

The present review describes the methods of synthesis of high spin polynuclear manganese(II) and iron(II) carboxylates. In spite of the obvious interest in these compounds, their synthetic chemistry is not well developed due to problems in the preparation and, especially, isolation of the complexes related to their extreme sensitivity to atmospheric oxygen. Manganese(II) and iron(II) carboxylate derivatives undergo much easier oxidation than similar cobalt(II), nickel(II) and copper(II) compounds, yielding various stable polynuclear Mn(III) and Fe(III) oxocarboxylate systems.^{16, 17} This feature largely determines specific demands as regards synthetic methods and physicochemical studies, which seriously impedes the development of this promising branch of inorganic chemistry.

II. Binuclear carboxylate complexes

Binuclear carboxylate complexes represent the most numerous class of Mn(II) and Fe(II) polynuclear structures. Their potential use as models with bridging carboxylate groups for mimicking active sites of enzymes is a reason for the increased attention to this class of compounds.^{18–27} Usually, these complexes contain high spin metal sites and therefore, magnetic methods can successfully be employed to reveal the structure–property relationships. This is extremely important for the development of advanced methods for calculations of the magnetic properties and for more efficient search for new ‘magnetic’ molecules.^{28–30} Such studies are undoubtedly valuable as a significant contribution to the development of approaches to control the magnetic properties of complexes by chemical methods.

Preparation of binuclear complexes requires special conditions such as to enable a carboxylate group to bind only two metal sites. Therefore, geometrical and electronic parameters of the carboxylate ligand [or rather the substituent R in the RC(O)O group] as well as other donating ligands in the complex should be adjustable. The number of donating ‘non-carboxylate’ ligands should not be too large to prevent the formation of mononuclear

M A Kiskin, I L Eremenko N S Kurnakov Institute of General and Inorganic Chemistry, Russian Academy of Sciences, Leninsky prosp. 31, 119991 Moscow, Russian Federation. Fax (7-495) 954 12 79, tel. (7-495) 955 48 35, e-mail: mkiskin@igic.ras.ru (M A Kiskin), ilerem@igic.ras.ru (I L Eremenko)

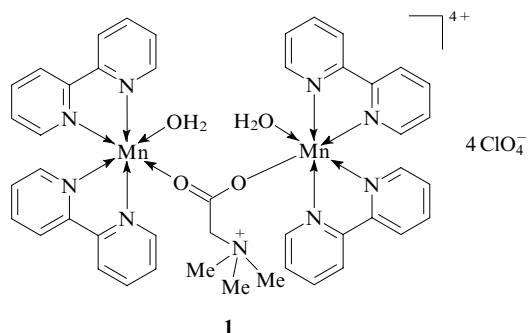
Received 17 March 2006

Uspekhi Khimii 75 (7) 627–644 (2006); translated by D S Yufit

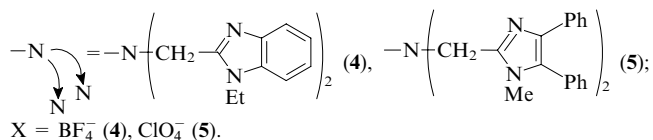
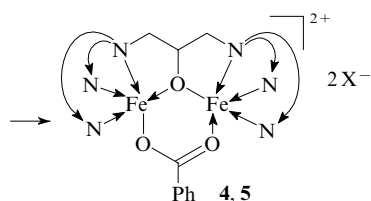
complexes. Therefore, it is necessary to measure out the number of donating ligands per metal atom when carrying out the synthesis.

The Mn(II) and Fe(II) binuclear complexes may be subdivided into complexes with one, two, three and four carboxylate bridges. The molecules of the first two groups usually contain a bridging ligand of another type (*e.g.*, a water molecule, a hydroxyl group, *etc.*).

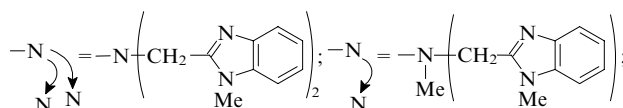
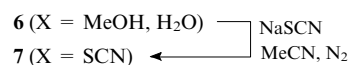
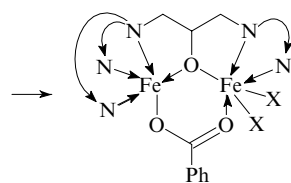
'Singly bridged' manganese binuclear carboxylate complexes are formed in the reaction of manganese(II) inorganic salts with salts of the corresponding carboxylic acids in the presence of strong chelating ligands such as 2,2'-bipyridyl (2,2'-bipy), 1,10-phenanthroline (1,10-phen), *N,N,N',N'*-tetrakis(2-pyridylmethyl)-1,2-ethylenediamine (tpen) and others. The complexes $[\text{Mn}_2(\mu\text{-OOCCH}_2\text{NMe}_3)(2,2'\text{-bipy})_4(\text{H}_2\text{O})_2](\text{ClO}_4)_4$ (**1**), $[\text{Mn}_2\cdot\{(\text{OOC})_2\text{CH}_2\}(1,10\text{-phen})_3(\text{H}_2\text{O})_2(\text{Cl})]\text{Cl}$ (**2**) and $[\text{Mn}_2(\mu\text{-OAc})\cdot(\text{tpen})_2](\text{ClO}_4)_3$ (**3**) belong to this class.^{31–33}



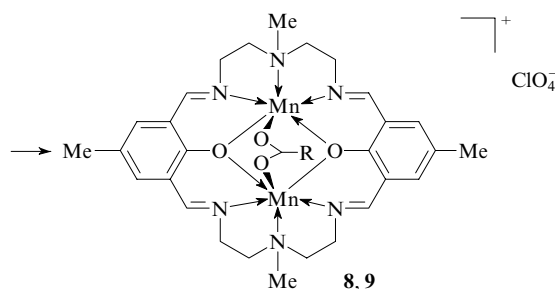
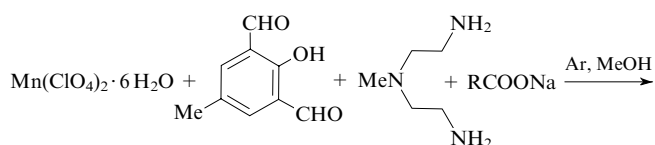
The binuclear iron complexes $[\text{Fe}_2(\mu\text{-OOCPh})(\mu\text{-L})]\text{X}_2$ [HL is *N,N,N',N'*-tetrakis(1-ethylbenzimidazol-2-ylmethyl)-2-hydroxy-1,3-diaminopropane, X = BF_4 (**4**); HL is *N,N,N',N'*-tetrakis(1-methyl-4,5-diphenylimidazol-2-ylmethyl)-2-hydroxy-1,3-diaminopropane, X = ClO_4 (**5**)], in which iron ions are linked together by a bridging carboxylate group and by a bridging oxygen atom of polydentate ligand HL, are known. These complexes were obtained by the reaction of iron(II) salts with benzoic acid and the corresponding ligand in the presence of triethylamine.^{22, 23}



Similar reactions with less sterically hindered polydentate ligands, for example, *N,N,N',N'*-tris(1-methylbenzimidazol-2-ylmethyl)-*N'*-methyl-2-hydroxy-1,3-diaminopropane (HL), in which the number of donating nitrogen atoms is insufficient to fill the metal coordination sphere, result in the formation of complexes with coordinated solvent molecules or anions of salts. Thus the binuclear ionic complex $[\text{Fe}_2(\mu\text{-OOCPh})\cdot(\mu\text{-L})(\text{MeOH})_{1.5}(\text{H}_2\text{O})_{0.5}](\text{BF}_4)_2$ (**6**) was obtained by the reaction of $\text{Fe}(\text{BF}_4)_2 \cdot 6 \text{H}_2\text{O}$ with benzoic acid and HL. Treatment of this complex with a solution of NaSCN results in substitution of thiocyanate anions for the coordinated water and alcohol molecules and in the formation of a neutral complex $[\text{Fe}_2(\mu\text{-OOCPh})(\mu\text{-L})(\text{SCN})_2]$ (**7**).³⁴



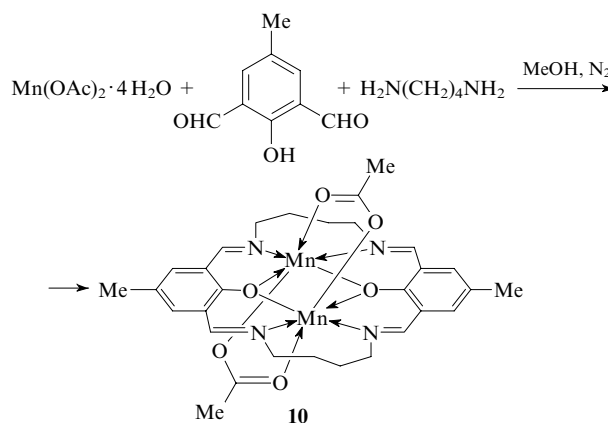
Macrocyclic ligands normally produce mononuclear complexes due to their geometrical features. However, complexes containing two carboxylate-bridged metal atoms in the cavity of macrocycle are known. For instance, high spin manganese binuclear complexes **8** and **9** with one bridging carboxylate group and [2 + 2]-macrocyclic ligands were obtained by the condensation of 2,6-diformyl-4-methylphenol with *N,N*-bis(2-aminoethyl)methylamine in the presence of manganese(II) ions.^{18, 19}



R = Me (**8**), 2-O₂NC₆H₄ (**9**).

Two manganese atoms in molecules of complexes **8** and **9** linked by one bridging carboxylate group occur inside a distorted macrocycle and coordinate the donating atoms of the macrocyclic ligand.

Complexes with two carboxylate bridges can be obtained using simpler N-donating ligands (with fewer number of functional groups or less sterically hindered). Thus the complex $[\text{Mn}_2(\mu\text{-OAc})_2\text{L}]$ (**10**) was obtained by the condensation of 2,6-diformyl-4-methylphenol with 1,4-diaminobutane in the presence

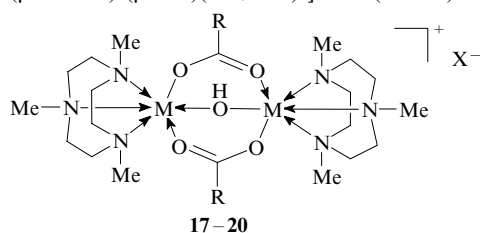


of magnesium acetate. In this complex, two metal atoms are located inside the macrocycle formed and are additionally linked by two bridging acetate groups.²¹

The binuclear complexes $[\text{Mn}_2(\mu\text{-OAc})_2(\text{L})](\text{ClO}_4)$ (**11**, **12**), $[\text{Mn}_2(\mu\text{-OAc})_2(\text{L})(\text{SCN})](\text{MeOH})$ (**13**), $[\text{Mn}_2(\mu\text{-OOCPh})_2(\text{L})(\text{SCN})](\text{MeOH})$ (**14**), $[\text{Mn}_2(\mu\text{-OAc})_2(\text{L})(\text{MeOH})](\text{ClO}_4)$ (**15**), $[\text{Mn}_2(\mu\text{-OPh})_2(\text{L})](\text{BPh}_4)$ (**16**), HL is 2,6-bis[bis(2-pyridylmethyl)aminomethyl]phenol (**11**), 4-methyl-2,6-bis[bis(2-pyridylmethyl)aminomethyl]phenol (**12**), 2,6-bis[2-(dialkylamino)ethyliminomethyl]-4-methylphenol (Alk = Me, Et) (**13**), 2,6-bis[*N*-(2-dimethylaminoethyl)-*N*-methylaminomethyl]-4-methylphenol (**14**), 4-methyl-2-[bis(2-pyridylmethyl)aminomethyl]-6-[(2-pyridylmethyl)benzylaminomethyl]phenol (**15**) and 4-methyl-2,6-bis[bis(2-methoxyethyl)aminomethyl]phenol (**16**), with two carboxylate bridges^{35–40} were obtained by direct reaction of manganese carboxylates (or of a solution of an inorganic manganese salt and a carboxylic acid salt) with the ligand HL in the presence of a base (for example, triethylamine). NaSCN can be used to precipitate the reaction products, as has been done for complexes **13** and **14**.

Aza-crown ethers containing three tertiary amino groups [for example, *N,N',N''*-trimethyl-1,4,7-triazacyclononane (Me_3tacn)] form binuclear complexes in reactions with manganese, iron, cobalt and nickel salts. The metal atoms in these complexes are linked by bridging oxygen atom of the hydroxyl anion and by two bridging carboxylate anions.^{41–47} The complexes containing the labile bridging OH-fragment constitute active sites of a number of enzymes and therefore can be of interest for bioinorganic chemistry as potential catalysts.

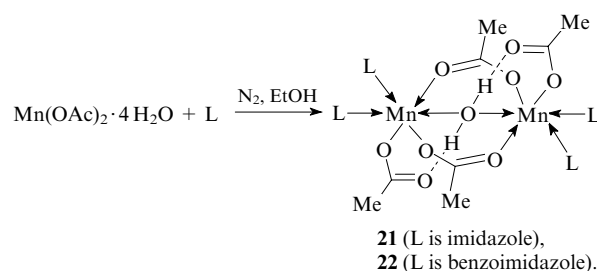
Binuclear manganese(II) and iron(II) complex cations $[\text{M}_2(\mu\text{-OOCR})_2(\mu\text{-OH})(\text{Me}_3\text{tacn})_2]^+ \text{X}^-$ (**17–20**)



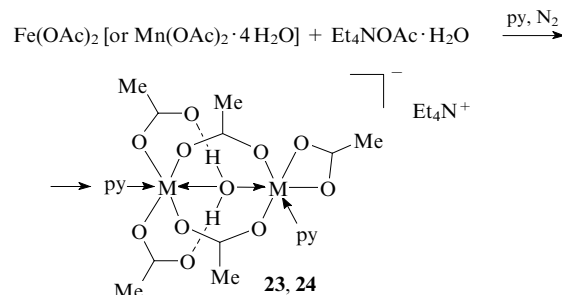
M = Fe (**17**, **20**), Mn (**18**, **19**); R = Me (**17**, **18**), Bu^t (**19**), CPh₃ (**20**);
X = ClO₄ (**17**, **19**), PF₆ (**18**), BPh₄ (**20**)

can be obtained both by direct reaction of inorganic metal salts with RCOONa (or RCOOH) and Me_3tacn (syntheses of compounds **17–19**) and by reaction of mononuclear complex $[\text{Fe}(\text{Me}_3\text{tacn})(\text{MeCN})_3](\text{CF}_3\text{SO}_3)_2$ with triphenylacetic acid and triethylamine in acetonitrile (synthesis of complex **20**). Since three out of six coordination sites of each metal atom are blocked by tridentate aza-crown, all dimers of this type are cations. The metal atom and three donating nitrogen atoms of *N,N',N''*-trimethyl-1,4,7-triazacyclononane in dimers **17–20** form a triangular pyramid with nitrogen atoms at the base. The mean values of the N–M–N bond angles are equal to 76.8° (M = Mn) and 79.5° (M = Fe) (in an ideal octahedral environment, these angles are equal to 90°). Thus, the tridentate aza-crown ligand proves to be relatively compact and leaves enough space for dimerisation of metal fragments through various bridges.

Binuclear complexes with a bridging water molecule can be formed even if trace amounts of water are present in solvents or in the starting materials. Thus the complexes $[\text{Mn}_2(\mu\text{-OH}_2)(\mu\text{-OAc})_2(\text{L})_4(\text{OAc})_2]$ [L is imidazole (**21**) and benzoimidazole (**22**)] are obtained by reactions of manganese acetate with imidazole or benzoimidazole in dry ethanol,²⁴ the bridging water molecule in complexes **21** and **22** originates from the starting acetate.

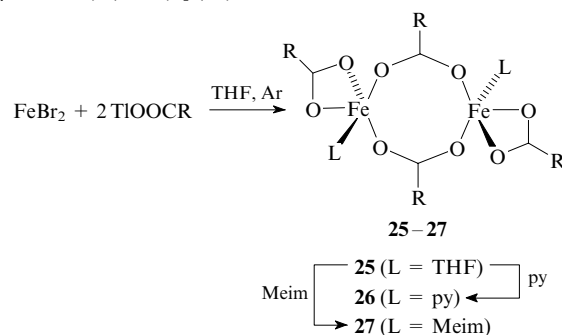


Complex anions $[\text{M}_2(\mu\text{-OH}_2)(\mu\text{-OAc})_2(\text{py})_4(\text{OAc})_3]^-$ (**23**, **24**) are formed in the reaction of the corresponding acetates with Et₄NOAc·H₂O in pyridine.²⁵



M = Mn (**23**), Fe (**24**).

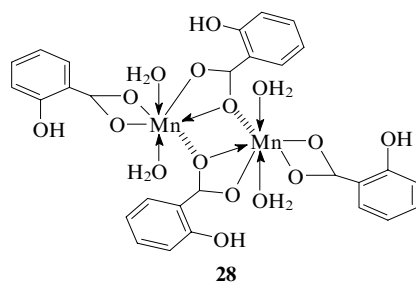
The complexes containing two metal atoms linked by two carboxylate groups are the functional precursors of triply bridged hydroxo-carboxylate (oxo- or aqua-carboxylate) binuclear complexes of the type **17–24**. In contrast to the previously discussed compounds, the carboxylate groups in these complexes can be both bridging and chelating. Such complexes are usually formed when the reaction is carried out in anhydrous solvents. For example, the reaction of iron(II) bromide with thallium 2,6-di(*p*-tolyl)benzoate in THF yields the complex $[\text{Fe}_2(\mu\text{-OOCR})_2(\eta^2\text{-OOCR})_2(\text{THF})_2]$ (**25**).



R = 2,6-(4-MeC₆H₄)₂C₆H₃.

It was shown that the reaction of complex **25** with N-donating ligands, such as pyridine and 1-methylimidazole (Meim), results in the substitution of these ligands for THF molecules to give the corresponding complexes **26** and **27** of similar structures.^{26, 27} Doubly bridged manganese complex $[\text{Mn}_2(\mu\text{-OOCCH}_2\text{Cl})_2(\text{bipy})_4](\text{ClO}_4)_2$ was obtained in the reaction of $\text{Mn}(\text{OOCCH}_2\text{Cl})_2 \cdot \text{H}_2\text{O}$ with 2,2'-bipyridyl in dry ethanol in the presence of NaClO₄.⁴⁸

Polynuclear carboxylate systems can also be prepared in aqueous solutions. Thus the reaction of an aqueous solution of sodium salicylate (NaHsal) with manganese chloride yields binuclear complex $[\text{Mn}_2(\text{Hsal})_4(\text{H}_2\text{O})_4]$ (**28**) in which the carboxylate groups are chelating-bridging.⁴⁹



Complexes containing two carboxylate bridges together with other labile donating ligands are convenient starting compounds for the synthesis of triply bridged dimers. For instance, the reaction of complex **25** with 2-diphenylphosphinopyridine or 2-phenylthiopyridine results in the substitution of two THF molecules and transformation of one chelating carboxylate group into a bridging one (Scheme 1).

However, in the reaction of complex **25** with 3-diphenylphosphinopyridine only the replacement of THF molecules occurs with retention of the original metallo-carboxylate core. The reaction of **25** with 4-phenylphosphinopyridine results in rearrangement of two chelating carboxylate groups into the bridging ones and in formation of a quadruply bridged binuclear complex in which the metal atoms have a pseudo-octahedral coordination formed by four oxygen atoms of four symmetrical bridging carboxylate groups and one donating atom of the axial ligand $\text{NC}_5\text{H}_4\text{PPh}_2$ -4. The second metal atom formally occupies the sixth position in the coordination sphere of each Fe atom. This rearrangement is accompanied by shortening of the $\text{Fe}\cdots\text{Fe}$ distance upon the transition from doubly bridged complexes **25** and **31** [4.283 Å (in **25**) and 4.035 Å (in **31**)] to triply bridged complexes **29** and **30** [3.310 Å (in **29**) and 3.272 Å (in **30**)] and to quadruply bridged complex **32** (2.813 Å).⁵⁰ It was suggested that the type of the resulting binuclear system is mostly determined by the geometrical parameters of the pyridine ligand, particularly by the position of a bulky PPh_2 -substituent in the ring.

Binuclear manganese(II) and iron(II) tetracarboxylates $[\text{LM}(\mu\text{-OOCR})_4\text{ML}]$ are known to a lesser extent than similar cobalt, nickel and copper derivatives. In spite of relatively short distances $\text{M}\cdots\text{M}$ [~ 3.1 Å ($\text{M} = \text{Mn}$) and ~ 2.8 Å ($\text{M} = \text{Fe}$)],

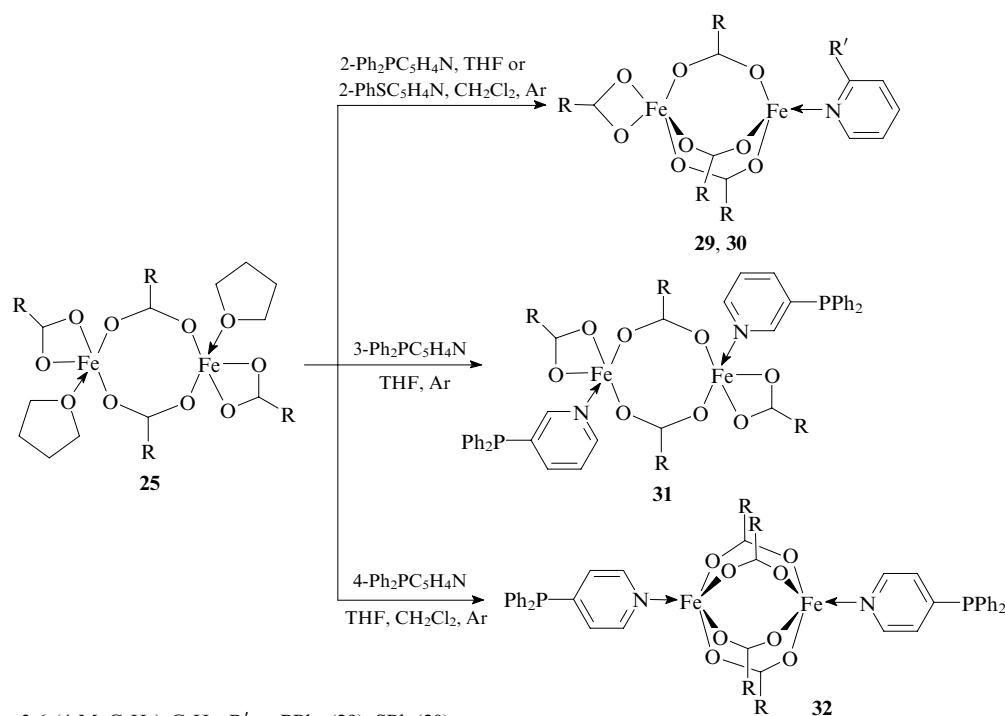
such dimers are paramagnetic, which suggests the presence of high spin metal atoms in these complexes.

Binuclear antiferromagnetic dimanganese tetracarboxylates $[\text{M}_2(\mu\text{-OOCR})_4\text{L}_2]$ containing quinoline as a labile N-donating ligand are formed in the reaction of quinoline with the reaction product of diphenylacetic acid with manganese acetate.⁵¹ The pivalate binuclear complex $[\text{Mn}_2(\mu\text{-OOCBu}^t)_4(\text{Bu}^t\text{COO}\cdot\text{HNEt}_3)_2]$ (**33**) has been obtained by reaction of manganese acetate with pivalic acid and triethylamine in hexane at room temperature. The structure of compound **33** is similar to that of complex **32**, but the axial positions of both metal atoms are occupied by oxygen atoms of the salt $\text{Bu}^t\text{COO}\cdot\text{HNEt}_3$.⁵²

Binuclear quadruply bridged iron(II) carboxylates **34–36** were obtained by reactions of complex **25** with 4-(*tert*-butyl)pyridine, benzylamine or 4-methoxybenzylamine, respectively, under the conditions similar to those shown in Scheme 1 for complex **32**.^{53, 54} The change in the nature of the axial ligand results in distortion of the dimer structure. The fragment $\text{N}-\text{Fe}\cdots\text{Fe}-\text{N}$ in complex **34** is almost linear (the $\text{Fe}-\text{Fe}-\text{N}$ bond angles are equal to 177.5 and 179.5°), these angles in complexes **35** and **36** are significantly smaller [157.1 and 160.7° (in **35**) and 161.1 and 176.2° (in **36**)]. The $\text{Fe}\cdots\text{Fe}$ distances in complexes **35** and **36** are ~ 0.03 – 0.06 Å shorter than that in compound **34**. It should be noted that in contrast to other paramagnetic quadruply bridged dimers of 3d-elements where antiferromagnetic exchange interactions occur, structural distortions in complexes **35** and **36** bring about ferromagnetic intramolecular exchange interactions. Presumably, this effect is due to the difference in electronic and geometrical characteristics of the apical ligands.

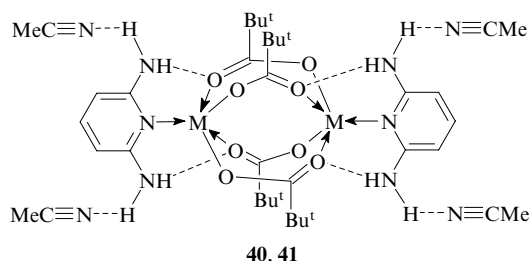
Earlier studies aimed at the synthesis of manganese, iron, cobalt and nickel quadruply bridged pivalate complexes have revealed that α -substituted pyridines as apical ligands favour the formation of such complexes,^{55–57} while with unsubstituted pyridine or γ -picoline monomeric or polymeric complexes $[\text{L}_2\text{M}(\text{OOCBu}^t)_2]$ are formed. Undoubtedly, the chemical properties of α -substituents in the pyridine rings are extremely important in subsequent transformations of the complex. However, it has recently been shown that the reaction of polymers $[\text{Fe}(\mu\text{-OOCBu}^t)_2]_n$ and $[(\text{EtOH})\text{M}(\mu\text{-OOCBu}^t)_2]_n$ ($\text{M} = \text{Fe}, \text{Mn}$) or the tetranuclear complex $[\text{Fe}_4(\mu_3\text{-OH})_2(\mu\text{-OOCBu}^t)_4(\eta^2\text{-OOC}\cdot\text{Bu}^t)_2(\text{EtOH})_6]$ with 2,3-lutidine or 2,6-diaminopyridine results

Scheme 1



$\text{R} = 2,6\text{-(4-MeC}_6\text{H}_4)_2\text{C}_6\text{H}_3$, $\text{R}' = \text{PPh}_2$ (**29**), SPh (**30**).

in the formation of dimers $[(\text{Me}_2\text{C}_5\text{H}_3\text{N})_2\text{Fe}_2(\mu\text{-OOCBu}^t)_4]$ (**37**) and $[(\eta^1\text{-(NH}_2)_2\text{C}_5\text{H}_3\text{N})_2\text{M}_2(\mu\text{-OOCBu}^t)_4]$ [$\text{M} = \text{Mn}$ (**38**), Fe (**39**)], respectively,^{58–60} with virtually the same structures regardless of the chemical properties of the α -substituent in the pyridine ring. The only difference is that α -amino groups of pyridine ligands in complexes **38** and **39** form strong hydrogen bonds with the solvent molecules (MeCN) yielding the solvates $[\{2\text{ MeCN} \cdot (\text{NH}_2)_2\text{C}_5\text{H}_3\text{N}\}_2\text{M}_2(\mu\text{-OOCBu}^t)_4]$ (compounds **40**, **41**).

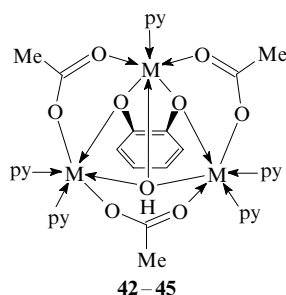


$\text{M} = \text{Mn}$ (**40**), Fe (**41**).

Strong antiferromagnetic[†] exchange interactions have been observed in binuclear compounds **40** and **41**. The structural phase transitions that occur in complexes **40** and **41** at 173 and 184 K, respectively,^{59,64} do not affect the character of these spin–spin interactions. Presumably, such indifference of the magnetic behaviour of the dimers with respect to the change in molecular packing due to phase transition suggests a predominantly intra-molecular nature of spin exchange in these compounds.

III. Mn(II) and Fe(II) carboxylate complexes with three and more metal sites

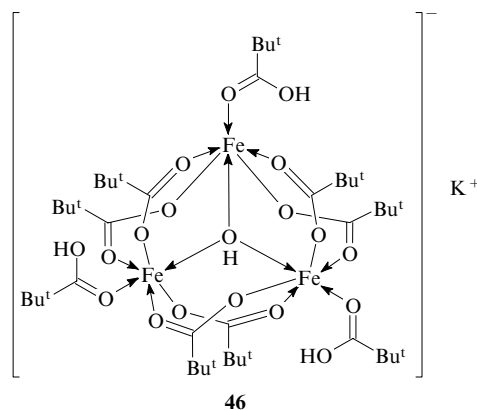
Trinuclear manganese(II) and iron(II) high spin complexes are represented by a small group of compounds with triangular or linear arrangement of metal sites. Isostructural complexes $[\text{M}_3(\mu_3\text{-OH})(\mu\text{-OAc})_3\text{L}(\text{py})_5]$ [$\text{M} = \text{Mn}$ (**42**), Fe (**43**), Co (**44**), Ni (**45**), $\text{L} = \text{C}_6\text{H}_4\text{O}_2^-$] are trinuclear complexes of divalent metals with a triangular metal core of the $\text{M}_3^{\text{II}}(\mu_3\text{-OH})$ type.⁶⁵



$\text{M} = \text{Mn}$ (**42**), Fe (**43**), Co (**44**), Ni (**45**).

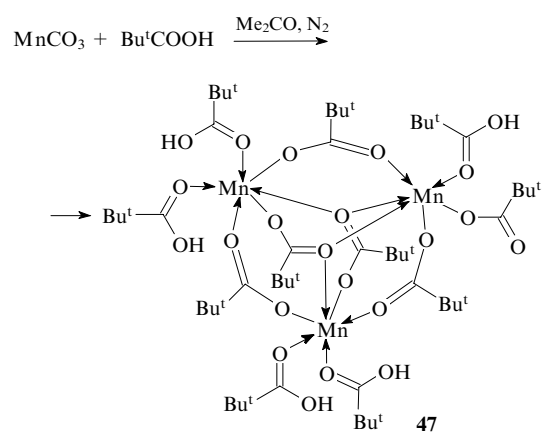
This is a rare example of a series of structurally studied, similar polynuclear carboxylate complexes of divalent metals. All these complexes were obtained by reactions of stoichiometric amounts of $\text{M}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ with catechol in pyridine in the presence of 0.2 M ethanolic triethylammonium hydroxide.

A triangular iron(II) complex containing only the molecules of a carboxylic acid and carboxylate anions as the organic ligands, viz., a hydroxo-pivalate ionic antiferromagnetic complex $\text{K}[\text{Fe}_3(\mu_3\text{-OH})(\mu\text{-OOCBu}^t)_6(\text{HOOCBu}^t)_3]$ (**46**), is known.⁶⁶



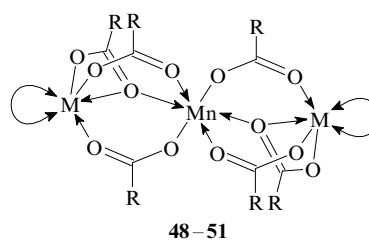
Complex **46** is formed in the reaction of $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ with KOOCBu^t and HOOCBu^t in acetonitrile under argon.

Yet another triangular antiferromagnetic manganese(II) complex $[\text{Mn}_3(\text{OOCBu}^t)_6(\text{HOOCBu}^t)_3] \cdot 2\text{HOOCBu}^t$ (**47**) was obtained in the reaction of manganese carbonate with pivalic acid.¹⁶



This compound is unique, because the triangular fragment is composed only of bridging carboxylate ligands, while in the majority of known trinuclear systems the metal atoms are linked by μ_3 -bridging oxygen atoms of oxo or hydroxo groups.

Linear trinuclear manganese(II) and iron(II) complexes of $[\text{M}_3(\text{OOCRR})_6\text{L}_2]$ are formed in the reactions of the corresponding metal carboxylates with N,O- and N,N-donating chelating ligands. Thus the complexes $[\text{Mn}_3(\mu, \eta^2\text{-OOCR})_2(\mu\text{-OOCR})_4(2,2'\text{-bipy})_2]$ [$\text{R} = \text{Me}$ (**48**), CH_2Cl (**49**)] were isolated from the reaction of manganese acetate or chloroacetate with the stoichiometric amount of 2,2'-bipyridyl. The Mn(II) atoms in these complexes form a linear structure and are linked by bridging and chelating-bridging carboxylate groups, the peripheral metal sites are additionally chelated by 2,2'-bipyridyl molecules.^{67–69}



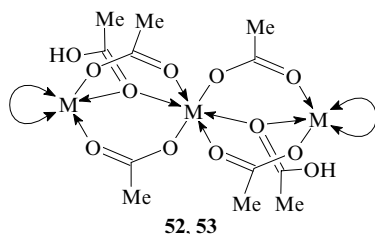
$\curvearrowright = 2,2'\text{-bipy}$ (**48**, **49**), 1,10-phen (**50**), 2-bepy (**51**);

$\text{R} = \text{Me}$ (**48**, **50**), CH_2Cl (**49**), Ph (**51**).

It was shown^{70–73} that the chelating properties of a carboxylate group depend upon steric features of the terminal ligand that can hinder the chelating process. For instance, the reaction with 2-benzoylpyridine (2-bepy) or 1,10-phenanthroline instead of

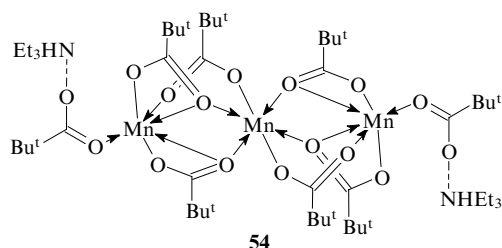
[†]Such interactions are also typical of binuclear nickel and cobalt carboxylates.^{57,61–63}

2,2'-bipyridyl results in the formation of complexes **50** and **51** similar to **48** and **49**. At the same time, bis(1-methylimidazol-2-yl)(methoxy)phenylmethane (biphme) blocks chelation of the carboxylate group due to increase in the N–Mn–N(O) bond angle from $\sim 72.3^\circ$ in complexes **48–51** [72.2° (in **48**), 73.2° (in **49**), 73.4° (in **50**), 70.5° (in **51**)] up to 81.9° in complex **52**.



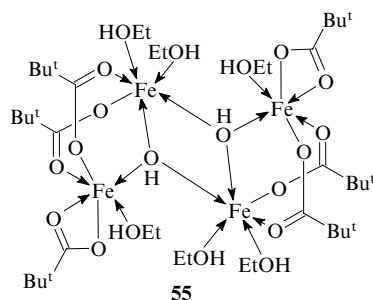
M = Mn (**52**), Fe (**53**); $\curvearrowright$ = biphme.

The change in the conditions of synthesis affects the structures of the final products. Thus the above-described binuclear complex **33** with four bridging carboxylate groups was obtained in hexane at room temperature. However, heating of the starting reaction mixture in heptane to the solvent boiling point affords the trinuclear complex $[\text{Mn}_3(\mu, \eta^2\text{-OOCBu}^t)_4(\mu\text{-OOCBu}^t)_2(\text{Bu}^t\text{COO} \cdot \text{HNEt}_3)_2]$ (**54**). In this complex, two carboxylate groups are bridging and four others are chelating-bidging groups.⁵²



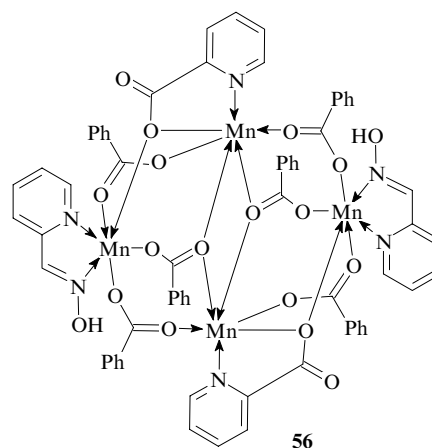
The change in the conditions of synthesis of complex **46**, namely, the use of EtOH instead of acetonitrile and the removal of pivalic acid from the reaction mixture results in the tetranuclear hydroxopivalate complex $[\text{Fe}_4(\mu_3\text{-OH})_2(\mu\text{-OOCBu}^t)_4(\eta^2\text{-OOC} \cdot \text{Bu}^t)_2(\text{EtOH})_6]$ (**55**).⁶⁰

The metal core of this complex consists of two $\{\text{Fe}_2(\mu\text{-OOCBu}^t)_2(\eta^2\text{-OOCBu}^t)(\text{EtOH})_3\}$ fragments linked by two $\mu_3\text{-OH}$ -groups. All metal atoms of complex **55** lie in the same plane. Cobalt and nickel isostructural analogues of complex **55** are also known.^{74, 75}



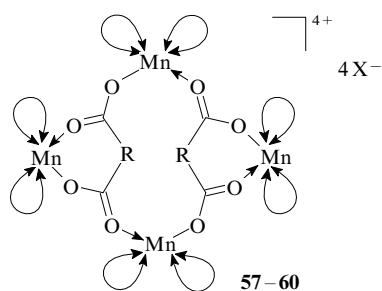
The magnetic properties of these isostructural complexes are different. Thus the antiferromagnetic exchange interactions exist between paramagnetic sites in iron and cobalt complexes, while in the nickel derivative, these interactions are ferromagnetic.

The tetranuclear manganese complex $[\text{Mn}_4(\text{O}_2\text{CPh})_6 \cdot 2(\text{OOCCH}_2\text{CH}_2\text{N})_2 \cdot 2(\text{HON}=\text{C})\text{C}_3\text{H}_4\text{N} \cdot 0.6 \text{CHCl}_3]$ (**56**) was obtained by reaction of manganese benzoate with 2-pyridinaldoxime in MeCN.⁷⁶



The metal core of complex **56** is planar and the metal atoms form a rhomb. Manganese atoms are linked by six μ_3 -bridging benzoate groups and two chelating-bridging (2-pyridyl)carboxylate groups resulting from hydrolysis of the oxime and oxidation.

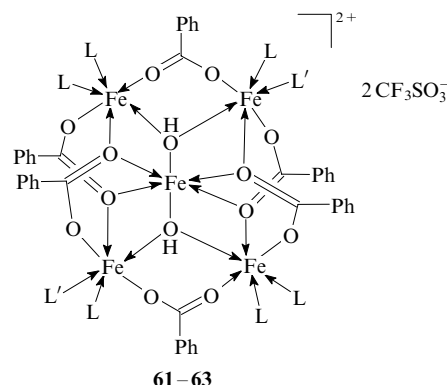
Tetranuclear manganese carboxylate complexes with a planar metal core are also formed in reactions of manganese salts with dicarboxylic acids [maleic (H_2male) or phthalic (H_2phth)] and N-donating ligands (2,2'-bipyridyl or 1,10-phenanthroline). The manganese complexes $\{\text{Mn}_4[(\text{OOC})_2\text{R}]_2\text{L}_8\}\text{X}_4$ (**57–60**) were obtained in this way.^{77, 78}



R = CH=CH (**57, 58**), $\text{C}_6\text{H}_4\text{-o}$ (**59, 60**);
 $\curvearrowright$ = 2,2'-bipy (**57, 60**), 1,10-phen (**58, 59**);
 X = ClO_4 (**57, 58, 60**), PF_6 (**59**).

The manganese atoms in these complexes form a parallelogram and are linked by four bridging carboxylate groups of two molecules of doubly deprotonated acids.

Unusual antiferromagnetic pentanuclear systems $[\text{Fe}_5(\mu_3\text{-OH})_2(\text{OOCPh})_6\text{L}_6\text{L}'_2](\text{CF}_3\text{SO}_3)_2$ (**61–63**) were obtained in the reactions of $\text{Fe}(\text{CF}_3\text{SO}_3)_2 \cdot 2 \text{MeCN}$, N-donors [pyridine, butyronitrile or ethylenediamine (en)], benzoic acid and triethylamine in acetonitrile in the presence of small amount of water. The metal cores of these complexes are formed of two triangular fragments sharing a vertex.⁷⁹



L = L' = py (**61**); L = py, L' = PrCN (**62**); L–L' = en (**63**).

Unfortunately, the chemistry of manganese(II) and iron(II) carboxylates is still insufficiently explored. Only hypothetically, the existence of hexa-, hepta- and octa-nuclear molecules, similar to the known cobalt and nickel derivatives, can be imagined. So far, the range of synthesised polynuclear molecular structures of iron derivatives is limited to the nonanuclear (II) complex ‡ $[\text{Fe}_9(\mu_4\text{-N}_3)_2(\mu\text{-OAc})_8(\mu_5\text{-L})_4]$ [$\text{H}_2\text{L} = (2\text{-C}_5\text{H}_4\text{N})_2\text{C}(\text{OH})_2$] (**64**) (Fig. 1 a).⁸⁰ At present, this is the only known representative of polynuclear iron(II) carboxylate complexes with molecular magnets properties (the ground spin state is $S = 14$ at 2 K). It was obtained by the reaction of iron(II) acetate with bis(2-pyridyl) ketone in acetonitrile and treatment of the reaction product with sodium azide. In this process, bis(2-pyridyl) ketone is converted into a *gem*-diol, which binds five metal atoms simultaneously (Fig. 1 b).

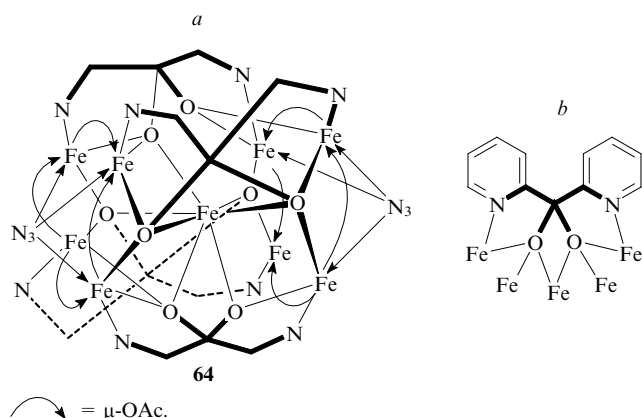
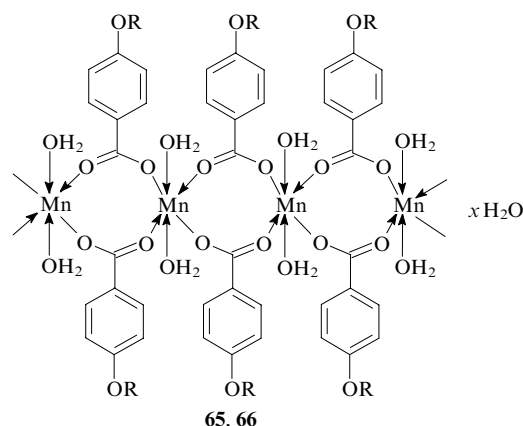


Figure 1. The schematic representation of the structure of complex **64** (a) [the non-coordinated atoms of $(2\text{-C}_5\text{H}_4\text{N})_2\text{COO}^{2-}$ moiety are not shown] and coordination of the *gem*-diol form of bis(2-pyridyl) ketone in complex **64** (b).

IV. Polymeric carboxylate complexes

Most of the so-called 'dicarboxylates' of divalent transition metals with the composition $\text{M}(\text{OOCR})_2 \cdot x\text{H}_2\text{O}$ [$\text{M} = \text{Mn}(\text{II}), \text{Fe}(\text{II})$ and others, $x = 3\text{--}8$] are mononuclear aqua-complexes,^{83–88} however some of them are polymeric. Usually, the latter are stable only in a solid state and are easily converted to monomers when dissolved in water. Complexes $[\text{M}(\text{dmba})_2(\text{H}_2\text{O})_3]_n$ ($\text{M} = \text{Mn}, \text{Co}, \text{Ni}, \text{Zn}$), containing 2,6-dimethoxybenzoic acid (Hdmba) anions, represent this type of polymers. Upon action of a hot aqueous solution of 2,6-dimethoxybenzoic acid on aqueous solutions of metal acetates or sulfates (pH 4–5) followed by cooling, crystalline polymeric complexes are formed.⁸⁹ The polymeric chains in these complexes consist of square-planar *trans*- $\{\text{M}(\text{dmba})_2(\text{H}_2\text{O})_2\}$ units linked by axial bridging water molecules.

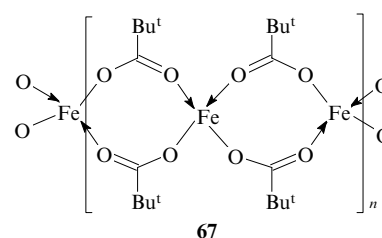
In addition to the metalopolymers linked in chains by bridging water molecules, metalopolymers with bridging carboxylate anions are known. Thus polymeric products $[\text{Mn}(\text{OOC} \cdot \text{C}_6\text{H}_4\text{OR-}p)_2(\text{H}_2\text{O})_2 \cdot x\text{H}_2\text{O}]_n$ (**65**, **66**) were obtained in the reaction of sodium *para*-hydroxy- or *para*-methoxybenzoate with a Mn(II) salt. In these compounds, octahedral coordination of metal atoms is formed by four oxygen atoms of bridging carboxylate anions and two oxygen atoms of terminal water molecules in *trans*-configuration.^{90, 91}



65: $\text{R} = \text{H}$, $x = 0$; **66:** $\text{R} = \text{Me}$, $x = 1$.

In aqueous medium, it is possible to obtain polynuclear structures devoid of water molecules in the coordination sphere of the metal atoms. For instance, the ionic polymer $[\text{Mn}(\mu\text{-OOCCH}_2\text{NMe}_3)_3]_n \cdot n\text{MnCl}_4$ has been synthesised by the reaction of manganese chloride with betaine $\text{Me}_3\text{N}^+\text{CH}_2\text{COO}^-$ in water.⁹² The metal atoms in this compound are linked by three carboxylate groups. The complex $\{[\text{Mn}_3(\mu\text{-OOC}(\text{CH}_2)_2\text{NH}_3)_8] \cdot 6\text{ClO}_4 \cdot 2\text{H}_2\text{O}\}_n$ is formed upon action of manganese perchlorate on β -alanine. This crystallises as a linear polymer the repeating unit of which consists of three manganese atoms linked by two bridging and one chelating-bridging carboxylate groups.⁹³

Pivalate complexes crystallise most easily as linear polymers since the *tert*-butyl groups provide a high solubility of these compounds. Thus the polymer $[\text{Fe}(\mu\text{-OOCBu}^t)_2]_n$ (**67**) devoid of neutral ligands was obtained by refluxing the tetranuclear complex $[\text{Fe}_4(\mu_3\text{-OH})_2(\mu\text{-OOCBu}^t)_4(\eta^2\text{-OOCBu}^t)_2(\text{EtOH})_6]$ (**55**) in acetonitrile.⁶⁰



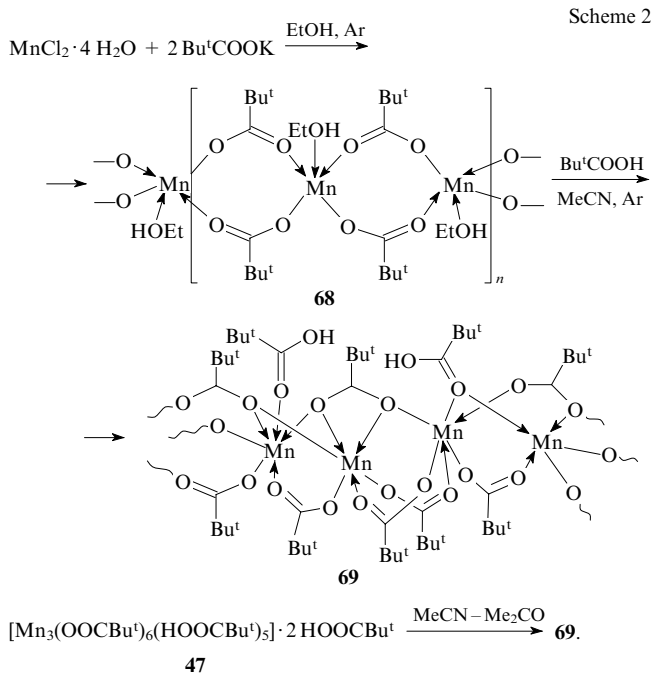
Ferromagnetic exchange interactions are observed in this compound. Polymer **67** undergoes phase transition into magnetic-ordered state at $T_c = 3.8\text{ K}$ and becomes a 'soft magnet'. It should be noted that dissolution of polymer **67** in oxygen-free (but not anhydrous) ethanol results in the formation of the original tetranuclear complex **55**.

Antiferromagnetic manganese(II) pivalate polymer $[(\eta^1\text{-HOEt})\text{Mn}(\mu\text{-OOCBu}^t)_2]_n$ (**68**) can be obtained by reaction of $\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$ with potassium pivalate in ethanol under argon (Scheme 2).

Polymer **68** consists of $\text{Mn}(\text{HOEt})$ fragments linked by two carboxylate groups.⁵⁹ Surprisingly, an isostructural analogue of compound **68**, *viz.*, the polymer $[(\text{HOEt})\text{Fe}(\mu\text{-OOCBu}^t)_2]_n$ is formed from tetranuclear complex **55** in the presence of *o*-phenylenediamine.⁶⁰

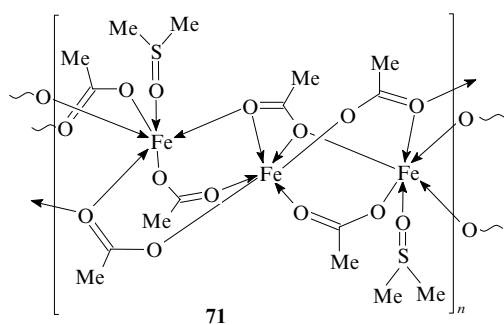
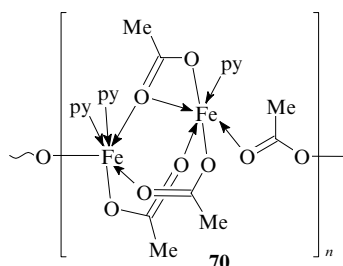
The structure of polymeric chain can be made more complicated by changing the number of metal atoms in the repeating unit. For instance, the polymeric product $[\text{Mn}_4(\text{OOC} \cdot \text{Bu}^t)_8(\text{HOOCBu}^t)_2]_n$ (**69**) is obtained in the reaction of complex **68** with an excess of pivalic acid in acetonitrile.⁹⁴ It can also be obtained by recrystallisation of the trinuclear complex $[\text{Mn}_3(\text{OOCBu}^t)_6(\text{HOOCBu}^t)_3] \cdot 2\text{HOOCBu}^t$ (**47**) from an acetonitrile–acetone mixture.¹⁶ Thus, the substitution of a carboxylic

‡ Analogous cobalt and nickel complexes have been prepared.^{81, 82}



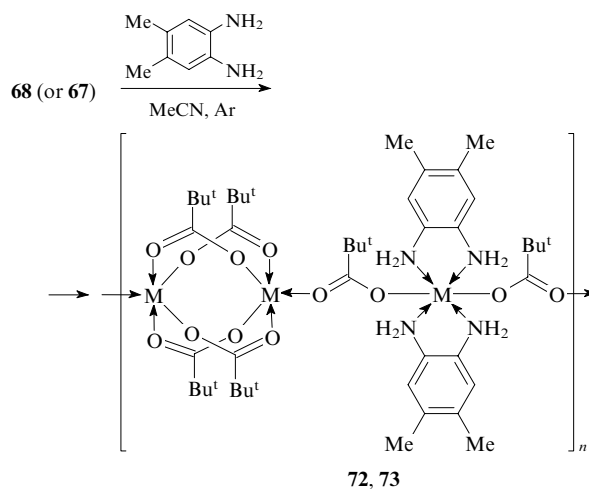
acid in polymeric complex **68** for ethanol resulted in the structural changes of the polymeric chain due to the ability of pivalate anions to coordinate metal in different modes. The pivalate groups easily pass from O,O-bridging to O-bridging ones (see Scheme 2).

The number of metal atoms in a repeating unit can be controlled by selecting conditions of synthesis. For example, the polymeric structures $[\text{Fe}_2(\text{OAc})_4(\text{py})_3]_n$ (**70**) and $[\text{Fe}_3(\text{OAc})_6(\text{DMSO})_2]_n$ (**71**), containing bi- and trinuclear fragments, were obtained from the same starting mononuclear complex $[\text{Fe}(\text{OAc})_2(\text{py})_4]$ (**72**), but under different conditions. Compound **70** is obtained upon dissolution of complex **72** in diethyl ether, while compound **71**, upon dissolution of complex **72** in DMSO.^{17,95}



Further complication of repeating units of a polymeric chain is also possible by combining bi- and mononuclear fragments, which was demonstrated on an example of manganese and iron pivalate derivatives. *o*-Phenylenediamine ligands have been chosen as the components that control the polymer chain formation. Isostruc-

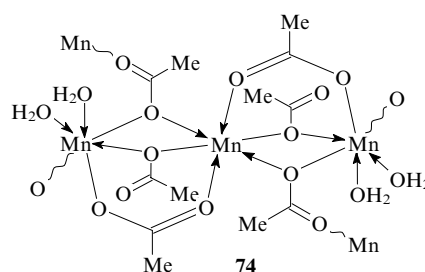
tural polymeric compounds $\{[(\eta^2-(\text{NH}_2)_2\text{C}_6\text{H}_2\text{Me}_2)_2\text{M}(\mu\text{-OOC}\cdot\text{Bu}^t)]_2[\text{M}_2(\mu\text{-OOCBu}^t)_4]\}_n$ [$\text{M} = \text{Mn}$ (**72**), Fe (**73**)] were obtained by reactions of polymers **68** and **67** with 4,5-dimethyl-1,2-phenylenediamine in acetonitrile.⁶⁰



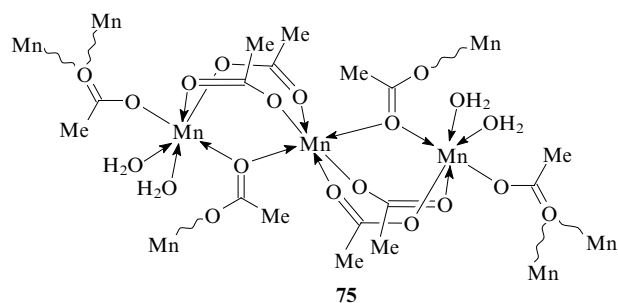
$\text{M} = \text{Mn}$ (**68**, **72**), Fe (**67**, **73**).

Complexes **72** and **73** are magnetically different: intra- and intermolecular exchange interactions in complex **72** are antiferromagnetic, while in the iron complex **73**, ferromagnetic interactions were observed at low temperature.

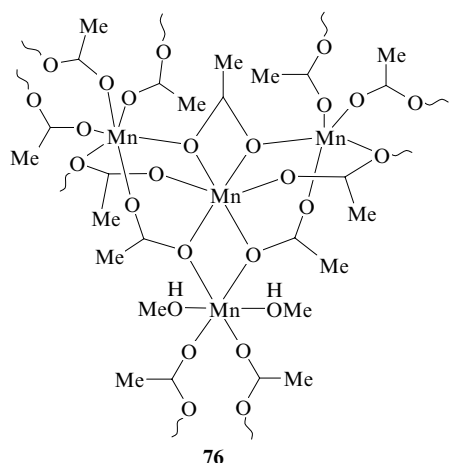
A carboxylate group can bind three or even four metal atoms; therefore, the existence of two- or three-dimensional polymers is possible. Thus high-temperature (230 °C) treatment of Mn_3O_4 with acetic acid yields the polymeric complex $\{[\text{Mn}_3(\mu\text{-OAc})_6(\text{H}_2\text{O})_4] \cdot 2 \text{H}_2\text{O}\}_n$ (**74**) of a layered structure.⁹⁶ The crystallisation water molecules in crystals of this compound form the interlayer hydrogen bonds.



The commercially available $\text{Mn}(\text{OAc})_2 \cdot 4 \text{H}_2\text{O}$ widely used in carboxylate synthesis is in fact a layered polymer $\{[\text{Mn}_3(\text{OAc})_6(\text{H}_2\text{O})_4] \cdot 8 \text{H}_2\text{O}\}_n$ (**75**) in which the crystallisation water molecules take part in linking the layers by hydrogen bonds.⁹⁷



Dissolution of $\text{Mn}(\text{OAc})_2 \cdot 4 \text{H}_2\text{O}$ in anhydrous methanol leads to the formation of the polymer $[\text{Mn}_4(\text{OAc})_8(\text{MeOH})_2]_n$ (**76**). The repeating unit of this polymer consists of four Mn atoms linked by acetate bridges.⁹⁸



The increase in the number of metal atoms in a repeating unit up to four results in their distorted non-planar Y-shaped arrangement. Non-planarity of the metal core together with the decrease in the number of neutral molecules in the repeating unit results in the formation of three-dimensional structure (in contrast to layered structures of complexes **74** and **75**). Antiferromagnetic exchange interactions between high spin manganese(II) atoms exist in this compound.

Three-dimensional manganese acetate $[\text{Mn}(\text{OAc})_2]_n$ (**77**) devoid of neutral molecules was obtained by dehydration of $\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ in acetonitrile under elevated pressure at 150 °C.⁹⁹ A 3D-system of polymer **77** is built of trinuclear fragments in which the coordination number of one of the manganese atoms is as high as 7 (Fig. 2*a*).

A variety of the carboxylate group coordination modes can be exemplified in complex **77** (Fig. 2*b*). Besides, the dependence of the Mn...Mn distances on the bridging group type is observed in this structure. Thus, while the distance between Mn(1) and Mn(2) atoms linked by three monoatomic carboxylate bridges is 3.202 Å, the distance between Mn(1) and Mn(3) linked by two monoatomic and one triatomic carboxylate bridges increases to 3.373 Å. The Mn...Mn distances between the atoms linked by two triatomic

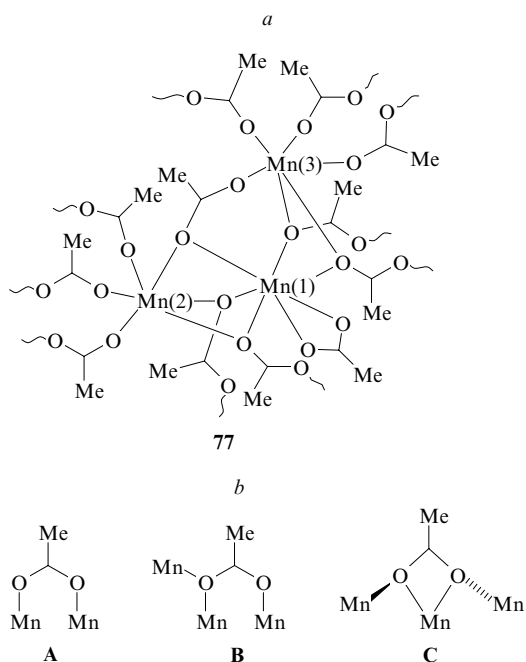
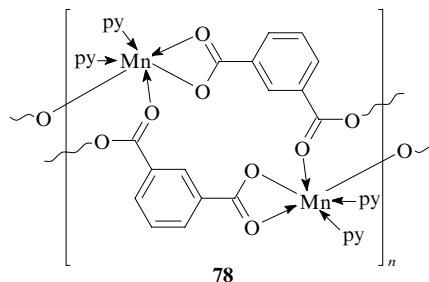


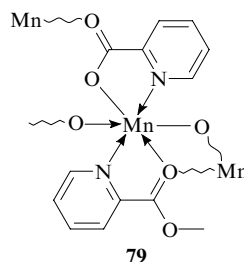
Figure 2. The structure of a fragment of polymer **77** (*a*) and the coordination types of bridging carboxylate groups in it (*b*).

and one monoatomic carboxylate bridges increase to 3.816 and 3.887 Å. At temperatures below 15 K, compound **77** exists in an ordered antiferromagnetic state.

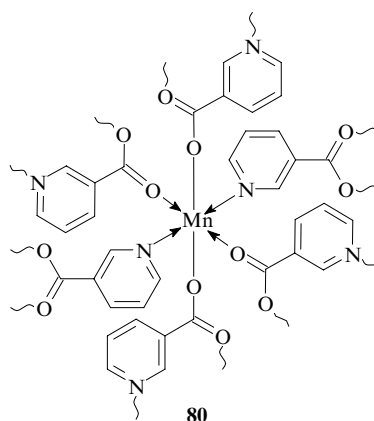
The use of polycarboxylic acids favours the formation of polymeric carboxylate complexes, the arrangement of the carboxy groups in the acid molecule being very important. For instance, the reaction of manganese chloride with isophthalic acid $[m\text{-(HOOC)}_2\text{C}_6\text{H}_4]$ in the presence of pyridine in aqueous methanol yields the linear polymer $[\text{Mn}\{m\text{-(OOC)}_2\text{C}_6\text{H}_4\}(\text{py})_2]_n$ (**78**) with the binuclear fragment as a repeating unit.¹⁰⁰



The presence of other functional groups in the carboxylic acid molecule also induces the formation of polymeric structures that depend on the geometrical parameters of the ligand. Thus the structure of isomers of pyridinecarboxylic acid determines the type of a carboxylate complex formed. For example, the layered polymeric complex $[\text{Mn}(2\text{-OOCCH}_2\text{CH}_2\text{N})_2]_n$ (**79**) containing no water molecules is formed in the reaction of $\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$ with α -picolinic acid in aqueous methanol at 145 °C (Ref. 102).⁸

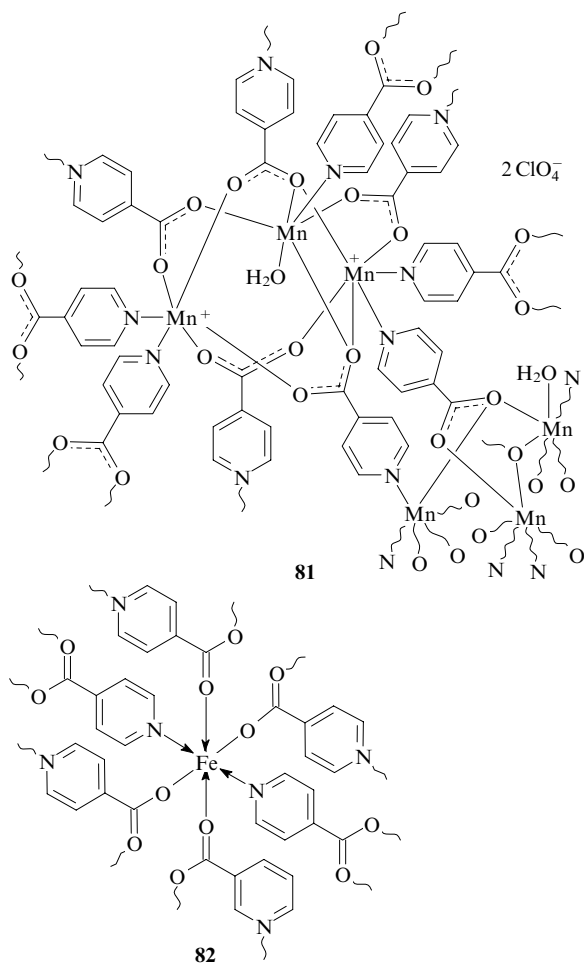


In the case of β -picolinic acid, the three-dimensional polymeric complex $[\text{Mn}(3\text{-OOCCH}_2\text{CH}_2\text{N})_2]_n$ (**80**) is formed.^{100, 103}



Manganese(II) perchlorate reacts with γ -picolinic acid in aqueous ethanol yielding the three-dimensional ionic polymer $[\text{Mn}_6(4\text{-OOCCH}_2\text{CH}_2\text{N})_{10}(\text{H}_2\text{O})_2](\text{ClO}_4)_2$ (**81**),¹⁰⁴ while the reaction of iron(II) perchlorate with γ -picolinic acid results in the formation of 3D-polymer with a different structure $[\text{Fe}(4\text{-C}_5\text{H}_4\text{NCOO})_2]_n$ (**82**).¹⁰⁵

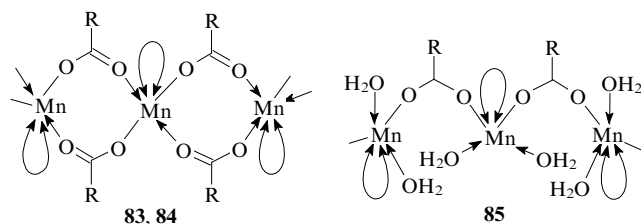
§ At room temperature, the mononuclear complex $[\text{Mn}(\eta^2\text{-2-OOCCH}_2\text{CH}_2\text{N})_2(\text{H}_2\text{O})_2]$ is formed.¹⁰¹



Polyfunctional ligands of various denticity and geometry (for example, linear or angular bidentate, planar or pyramidal tridentate, planar or tetrahedral tetradentate ligands) are used for the targeted synthesis of polymeric carboxylate complexes of different dimensionality.[†] The maintenance of a correct balance between such ligands and metal sites is very important in this case, because an excess of the ligand brings about smooth formation of mono- and binuclear compounds.

The complex $[\text{Mn}(\text{OOCCH}_2\text{Cl})_2(1,10\text{-phen})]_n$ (**83**) is formed in the reaction of $\text{Mn}(\text{OOCCH}_2\text{Cl})_2$ with 1,10-phenanthroline in the ratio 1 : 1. The manganese atoms in this complex are arranged into infinite chains in which two adjacent metal atoms are linked by two carboxylate groups.^{69,107} Similar linear polymer $[\text{Mn}(\text{OOC}_6\text{H}_4\text{Cl-}m)_2(2,2'\text{-bipy})]_n$ (**84**) was obtained by reaction of manganese *m*-chlorobenzoate with bipyridyl.⁴⁸

In the reaction of 1,10-phenanthroline with a salt of a dicarboxylic acid, *e.g.*, manganese phthalate, instead of a salt of a monocarboxylic acid, the linear polymer $\{\text{Mn}[o\text{-(OOC)}_2\text{C}_6\text{H}_4](1,10\text{-phen})(\text{H}_2\text{O})_2\}_n$ (**85**) is also formed, but its manganese atoms are linked by only one bridging carboxylate group.¹⁰⁸

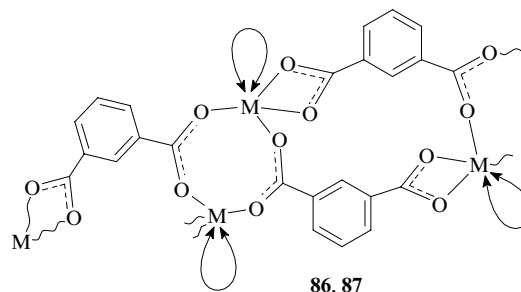


$\curvearrowright = 1,10\text{-phen}$ (**83**, **85**), $2,2'\text{-bipy}$ (**84**);

$\text{R} = \text{CH}_2\text{Cl}$ (**83**), $\text{C}_6\text{H}_4\text{Cl-}m$ (**84**), $\text{C}_6\text{H}_4\text{COO-}o$ (**85**).

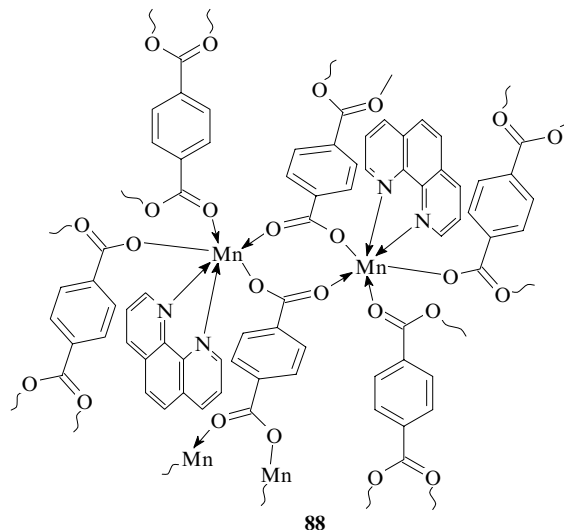
[†]The examples of carboxylate complexes of 3d-metals are given in a review.¹⁰⁶

The reactions of complexes $\text{Mn}(2,2'\text{-bipy})_2\text{Cl}_2$ and $\text{Fe}(1,10\text{-phen})_2\text{Cl}_2$ with isophthalic acid salts yield the corresponding helical polymeric structures $\{\text{Mn}[m\text{-(OOC)}_2\text{C}_6\text{H}_4](2,2'\text{-bipy})\}_n$ (**86**) and $[\text{Fe}(m\text{-(OOC)}_2\text{C}_6\text{H}_4)(1,10\text{-phen})]_2$ (**87**) due to coordination of the second carboxylate group of the acid anion and stacking interactions of aromatic rings.^{109,110}



$\text{M} = \text{Mn}$ (**86**), Fe (**87**); $\curvearrowright = 2,2'\text{-bipy}$ (**86**), $1,10\text{-phen}$ (**87**).

The terephthalic acid dianion obtained upon hydrolysis of 1,4-dicyanobenzene reacts with manganese chloride and 1,10-phenanthroline also to yield the polymer $\{\text{Mn}[p\text{-(OOC)}_2\text{C}_6\text{H}_4](1,10\text{-phen})\}_n$ (**88**) in which this dianion links four manganese atoms at once.¹¹¹



Thus, various *n*-dimensional systems can be obtained by modifying the structure (denticity, functionality and geometry) of carboxylate ligands. Usually, the paramagnetic sites in such polymers are in a high spin state and the predominant exchange interactions between them are antiferromagnetic.

V. Mixed-valence complexes containing manganese(II) and iron(II)

Manganese(II) and iron(II) carboxylate complexes are highly liable to oxidation yielding Mn(III) and Fe(III) derivatives. In the case of polynuclear compounds, these processes usually proceed *via* mixed-valence systems, which are often quite stable. Such compounds containing high spin metal sites are definitely of interest, because even if all the metal atoms in the complex are of the same kind, the molecule turns out to be of a hetero-spin type.

Binuclear mixed-valence systems are usually formed as a result of oxidation of M(II) complexes. The controlled oxidation of iron and manganese binuclear complexes, for example, complexes **17** and **19**, results in the oxidation of one out of two metal atoms and affords complexes $[\text{M}_2(\mu\text{-O})(\mu\text{-OOCR})_2(\text{Me}_3\text{tacn})_2]\text{ClO}_4$ [$\text{M} = \text{Fe}$, $\text{R} = \text{Me}$ (**89**); $\text{M} = \text{Mn}$, $\text{R} = \text{Bu}^t$ (**90**)].^{41,43} Oxidation of binuclear complex **20** by atmospheric oxygen also yields green mixed-valence complex $[\text{Fe}_2(\mu\text{-O})(\mu\text{-OOCPh})_2(\text{Me}_3\text{tacn})_2] \cdot \text{BPh}_4$. Further oxidation of this complex by H_2O_2 results in the

formation of stable orange iron(III) complex $[\text{Fe}_2(\mu\text{-O})(\mu\text{-OOCPh}_3)_2(\text{Me}_3\text{tacn})_2](\text{BPh}_4)_2$.⁴⁴

Mixed-valence systems can also be obtained starting from ordinary manganese(II) and iron(II) salts. For example, the reaction of 2,6-bis[bis[(1-methylimidazol-2-yl)methyl]amino-methyl]-4-methylphenol (Hbimp) with sodium acetate and magnesium(II) or iron(II) perchlorate in methanol results in the formation of dimers $[\text{M}^{\text{II}}\text{M}^{\text{III}}(\text{bimp})(\text{OOCR})_2](\text{ClO}_4)_2$ ($\text{M} = \text{Mn, Fe}$).^{112, 113}

Mixed-valence cationic complexes with a 'Chinese lantern' structure $[\text{Fe}_2(\mu\text{-OOCR})_4(\text{py})_2]\text{PF}_6$ (**93**) and $[\text{Fe}_2(\mu\text{-OOCR})_4.(4\text{-Bu}^t\text{C}_5\text{H}_4\text{N})_2]\text{CF}_3\text{SO}_3$ (**94**) were obtained by single-electron oxidation of iron(II) binuclear complexes **26** and **34** with $[\text{FeCp}_2]\text{PF}_6$ and AgCF_3SO_3 , respectively (Scheme 3).^{114, 115} Oxidation of compounds **26** and **34** by atmospheric oxygen yields complexes $[\text{Fe}_2(\mu\text{-OH})_2(\mu\text{-OOCR})_2(\text{OOCR})_2\text{L}_2]$ [$\text{L} = \text{py}$ (**95**), 4-Bu^tC₅H₄N (**96**), Scheme 3]. In these complexes, the iron(III) atoms are in a different ligand environment and their coordination number increases up to 6.

Manganese and iron oxocarboxylate triangular complexes $[\text{M}_3(\mu_3\text{-O})(\mu\text{-OOCR})_6\text{L}_3]^{n+}$ are well studied by magnetic methods.^{116–119} These compounds play an important role in bioinorganic systems because they may be regarded as models of active sites of metalloproteins and as structural models of oxygen-containing centres in the photosystem II.^{120–122} There are very few neutral ($n = 0$) iron and manganese M(II) and M(III) mixed-valence oxocarboxylate trinuclear complexes. These complexes are interesting as hetero-spin systems with potentially highly variable metal sites.^{7, 123}

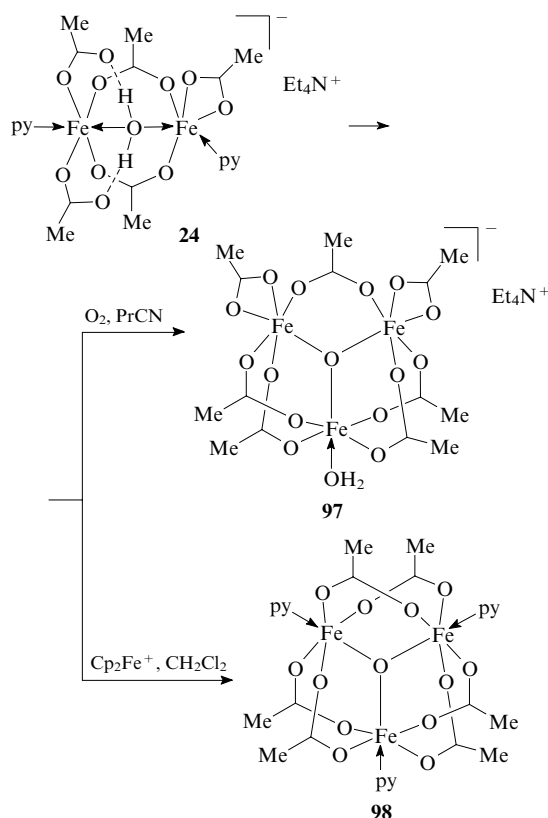
Iron mixed-valence trinuclear complexes are obtained by either direct reaction of iron powder with an acid {synthesis of $[\text{Fe}_3\text{O}(\text{OOCBu}^t)_6(\text{HOOCBu}^t)_3]$ }¹²⁴ or reactions of inorganic salts with acids {synthesis of $[\text{Fe}_3\text{O}(\text{OOCCH}_2\text{Cl})_6(\text{H}_2\text{O})_3]$ }.¹²⁵ Terminal ligands in such systems can be replaced by various N-donating molecules, *e.g.*, pyridine. The oxocomplex $[\text{Fe}_3\text{O}(\text{OOCBu}^t)_6(\text{py})_3]$ was obtained from $[\text{Fe}_3\text{O}(\text{OOCBu}^t)_6(\text{HOOCBu}^t)_3]$ by this method.¹²⁴

Manganese acetate is typically used as a starting material in the synthesis of neutral manganese mixed-valence trinuclear oxocarboxylates. Oxidation of a solution of $\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ by tetrabutylammonium perchlorate in a mixture of glacial acetic acid and pyridine yields the complex $[\text{Mn}_3\text{O}(\text{OAc})_6(\text{py})_3]$,¹¹⁹ while the oxidation in the presence of benzoic acid in a mixture of ethanol and pyridine results in the substitution of acetate groups and formation of mixed-valence complex $[\text{Mn}_3\text{O}(\text{OOCPh})_6]$.

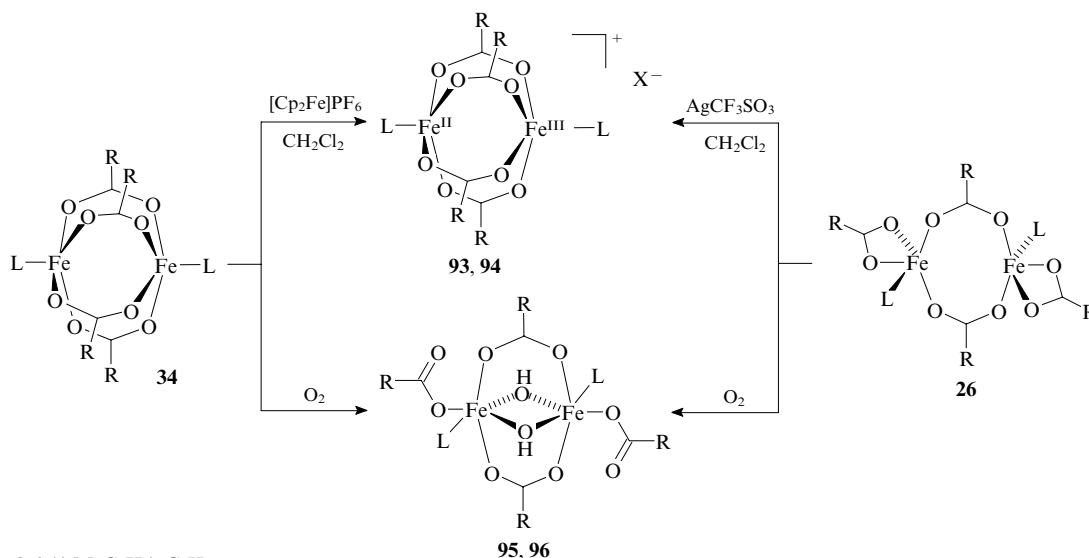
$(\text{py})_2(\text{H}_2\text{O})$.¹¹⁹ Treatment of the latter with a solution of 2,2'-bipyridyl-3,3'-dicarboxylic acid and triethylamine in acetonitrile affords trinuclear complex $[\text{Mn}_3\text{O}(\text{OOCPh})_6(\text{py})_3]$ with similar structure, but with three terminal pyridine molecules.¹²⁶

More complex starting reagents can also be used for the synthesis of trinuclear complexes. Thus the decomposition of the dodecanuclear complex $[\text{Mn}_8^{\text{III}}\text{Mn}_4^{\text{IV}}\text{O}_{12}(\text{OAc})_{16}(\text{H}_2\text{O})_4] \cdot 2\text{HOAc} \cdot 4\text{H}_2\text{O}$ in trichloroacetic or trifluoroacetic acid is accompanied by partial reduction of manganese atoms and the formation of the mixed-valence complex $[\text{Mn}^{\text{II}}\text{Mn}_2^{\text{III}}\text{O}(\text{OOCR})_6(\text{H}_2\text{O})_3]$ ($\text{R} = \text{CCl}_3$ or CF_3).^{127, 128}

Yet another type of trinuclear systems, *viz.*, asymmetric triangular oxocarboxylate $(\text{Et}_4\text{N})[\text{Fe}_3\text{O}(\text{OAc})_7(\text{OH}_2)]$ (**97**), was obtained by reaction of atmospheric oxygen with the complex $(\text{Et}_4\text{N})[\text{Fe}_2(\mu\text{-OH}_2)(\mu\text{-OAc})_2(\text{py})_4(\text{OAc})_3]$ (**24**).¹²⁹ It was noted



Scheme 3

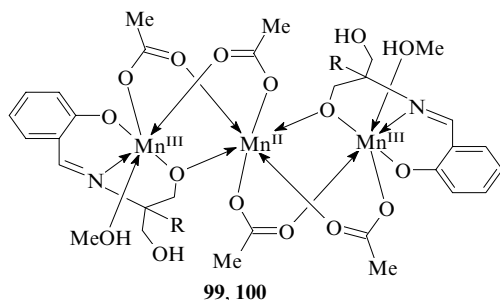


$\text{R} = 2,6\text{-(4-MeC}_6\text{H}_4)_2\text{C}_6\text{H}_3$;

$\text{L} = \text{py}$ (**26**, **93**, **95**), 4-Bu^tC₅H₄N (**34**, **94**, **96**).

that the oxidation of compound **24** with ferrocenyl cation affords the symmetrical mixed-valence complex $[\text{Fe}_3\text{O}(\text{OAc})_6(\text{py})_3]$ (**98**).

Trinuclear linear complexes of general formula $[\text{Mn}^{\text{II}}\text{Mn}^{\text{III}}\text{L}_2(\mu\text{-OAc})_4(\text{MeOH})_2]$ [**99**: H_2L is 1,3-dihydroxy-2-methyl-2-(salicylidenamino)propane, **100**: H_2L is tris(hydroxymethyl)(salicylidenamino)methane] were obtained by reaction of salicylaldehyde with 2-amino-2-methylpropane-1,3-diol [or tris(hydroxymethyl)aminomethane] and manganese acetate in methanol.¹³⁰ Manganese(II) atom in the obtained complexes occupies the central position and the Mn(III)–Mn(II)–Mn(III) bond angle is equal precisely to 180° . Coordinated methanol molecules in complexes **99** and **100** are labile and can be replaced by other donating ligands, e.g., H_2O or 2-pyridone.

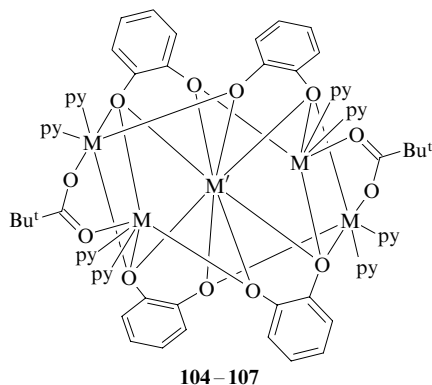


99, 100

$\text{R} = \text{Me}$ (**99**), CH_2OH (**100**).

Mixed-valence tetranuclear complexes of the 'butterfly' geometry are known only for manganese. The ratio of two- and three-valence metals in such complexes may be equal to 1 : 1 as in the complex $[\text{Mn}_2^{\text{II}}\text{Mn}_2^{\text{III}}(\mu_3\text{-O})_2(\mu\text{-OAc})_6 \cdot (2,2'\text{-bipy})_2]$ (**101**), or 1 : 3 as in compounds $[\text{Mn}^{\text{II}}\text{Mn}_3^{\text{III}}(\mu_3\text{-O})_2(\mu\text{-OOCCH}_2\text{X})_7(2,2'\text{-bipy})_2]$ [$\text{X} = \text{Cl}$ (**102**), Br (**103**)].^{131, 132} Complex **101** is formed in the reaction of the trinuclear complex $[\text{Mn}^{\text{II}}\text{Mn}_2^{\text{III}}\text{O}(\text{OAc})_6(\text{py})_3]$ with 2,2'-bipyridyl in acetonitrile and compounds **102**, **103** are formed in the reaction of the complexes $[\text{Mn}_3^{\text{II,III}}\text{O}(\mu\text{-OOCCH}_2\text{X})_7(2,2'\text{-bipy})_2]$ [$\text{X} = \text{Cl}$, Br] with 2,2'-bipyridyl in CH_2Cl_2 . The metal atoms in complexes **101**–**103** are 'butterfly'-shaped, the Mn(II) atoms in compound **101** being located in the 'wings' of the 'butterfly', while in complexes **102** and **103** the 'wings' are formed by one Mn(II) and one Mn(III) atom.

Pentanuclear mixed-valence complexes $[\text{M}_5(\text{OOCBu}^t)_2 \cdot (\text{C}_6\text{H}_4\text{O}_2\text{-}o)_4(\text{py})_8]^+$ [$\text{M} = \text{Mn}$ (**104**), Fe (**105**)] are obtained in reactions of metal pivalates and chlorides with tetrabutylammonium catecholate $(\text{Bu}_4\text{N})_2(\text{C}_6\text{H}_4\text{O}_2\text{-}o)$ in pyridine.¹³³ They were isolated as salts with outer-sphere anions Cl^- , Br^- , PF_6^- . The only three-valence metal atom is located in the central position and can be replaced by another metal. Thus the partial replacement of MnCl_2 by FeCl_3 in the starting reagents ($\text{Mn} : \text{Fe} = 4 : 1$) results in the formation of the heterometallic complex $[\text{Mn}_4\text{Fe}(\text{OOC} \cdot \text{Bu}^t)_2(\text{C}_6\text{H}_4\text{O}_2\text{-}o)_4(\text{py})_8]\text{Cl}$ (**106**). The heterometallic complex



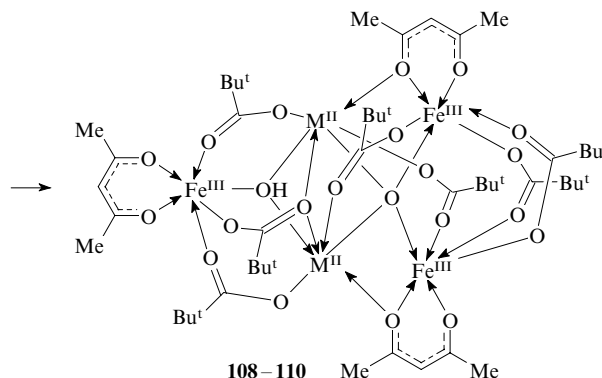
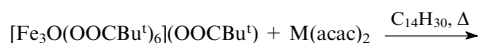
104–107

104: $\text{M} = \text{M}' = \text{Mn}$; **105**: $\text{M} = \text{M}' = \text{Fe}$;

106: $\text{M} = \text{Mn}$, $\text{M}' = \text{Fe}$; **107**: $\text{M} = \text{Mn}$, $\text{M}' = \text{Tb}$.

$[\text{Mn}_4\text{Tb}(\text{OOCBu}^t)_2(\text{C}_6\text{H}_4\text{O}_2\text{-}o)_4(\text{py})_8]\text{NO}_3$ (**107**) was obtained by the same method.¹³⁴

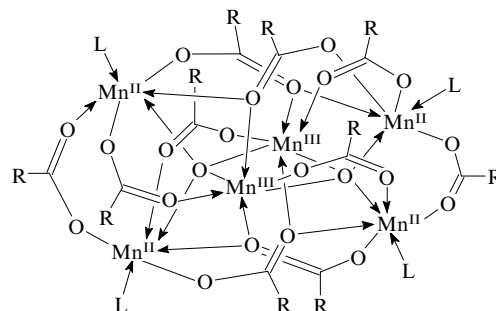
Refluxing of $[\text{Fe}_3^{\text{III}}\text{O}(\text{OOCBu}^t)_6](\text{OOCBu}^t)$ and $\text{M}(\text{acac})_2$ in pentadecane yields pentanuclear complexes $[\text{Fe}_3\text{M}_2(\mu_4\text{-O})(\mu_3\text{-OH})(\mu_3\text{-OOCBu}^t)(\mu_2\text{-OOCBu}^t)_6(\mu, \eta^2\text{-acac})_2(\eta^2\text{-acac})][\text{M} = \text{Mn}$ (**108**), Co (**109**), Ni (**110**)].¹³⁵



108–110

$\text{M} = \text{Mn}$ (**108**), Co (**109**), Ni (**110**).

Unlike iron(II) carboxylates, which are easily oxidised by atmospheric oxygen producing iron(III) derivatives, the oxidation of manganese(II) carboxylates affords stable mixed-valence hexanuclear complexes $[\text{Mn}_6(\mu_4\text{-O})_2(\text{OOCR})_{10}\text{L}_4]$ (**111**–**117**). The metal core of these complexes $\text{Mn}_4^{\text{II}}\text{Mn}_2^{\text{III}}\text{O}_2$ is surrounded by six μ_2 -bridging, four μ_3 -bridging carboxylate groups and four N- or O-donating terminal monodentate ligands.^{16, 136–141} Four manganese(II) atoms in these complexes occupy peripheral positions.



111–117

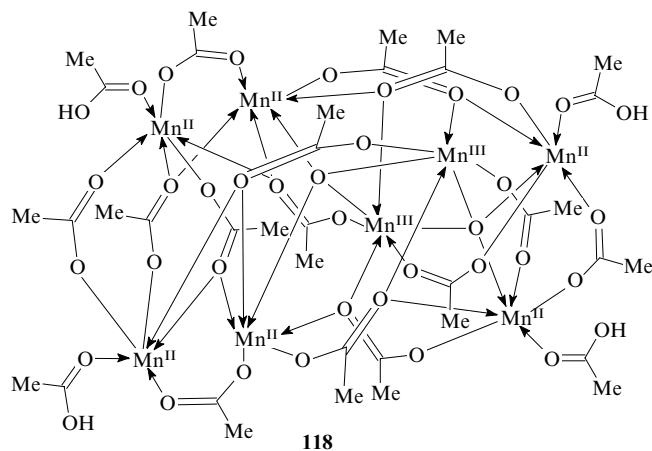
111: $\text{R} = \text{Me}$, $\text{L} = \text{py}$; **112**: $\text{R} = \text{Ph}$, $\text{L} = \text{py}$; **113**: $\text{R} = \text{Ph}$; $\text{L} = 1/2 \text{ py}$, $1/2 \text{ MeCN}$; **114**: $\text{R} = \text{Bu}^t$, $\text{L} = \text{HO}_2\text{CBu}^t$; **115**: $\text{R} = \text{Bu}^t$,

$\text{L} = \text{py}$; **116**: $\text{R} = \text{Bu}^t$, $\text{L} = \text{THF}$; **117**: $\text{R} = \text{Bu}^t$, $\text{L} =$

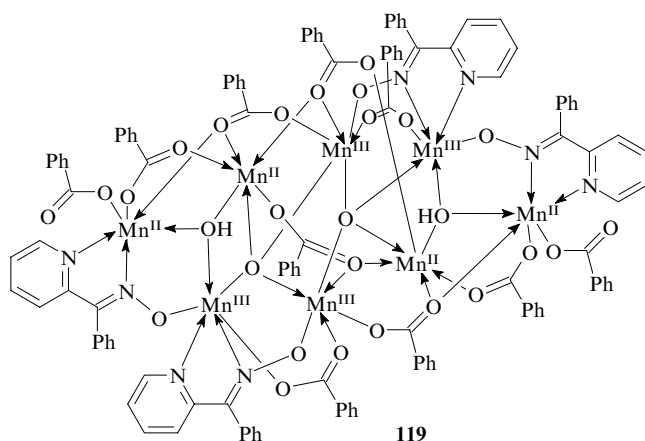
The methods of synthesis of such complexes are quite diverse. For example, complex **114** is obtained by refluxing $\text{Mn}(\text{NO}_3)_2 \cdot x\text{H}_2\text{O}$ ($x = 4\text{--}6$) with an excess of pivalic acid in dioxane, while complex **115**, by reaction of complex **114** with pyridine in chloroform, whereupon the terminal pivalic acid molecules are replaced by pyridine molecules. Complex **116** can be obtained either by oxidation of a mixture of $\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$ and NaOOCBu^t in methanol and recrystallisation of the reaction product from THF or by oxidation of the complex $[\text{Mn}_3(\text{OOC} \cdot \text{Bu}^t)_6(\text{HOOCBu}^t)_3]$ (**47**) in THF.

Among octanuclear complexes, compounds $[\text{Mn}_6^{\text{II}}\text{Mn}_2^{\text{III}}(\mu_4\text{-O})_2(\mu\text{-OOCCH}_2\text{Bu}^t)_{14}(\text{HO}_2\text{CCH}_2\text{Bu}^t)_4]$ (**118**) and $[\text{Mn}_4^{\text{II}}\text{Mn}_4^{\text{III}} \cdot \text{O}_2(\text{OH})_2(\text{OOCPh})_{10}(\text{L})_4]$ (**119**, L is phenyl 2-pyridyl ketone oxime) have to be noted.^{142, 143} Complex **118** was obtained by reduction of the dodecanuclear cluster $[\text{Mn}_8^{\text{III}}\text{Mn}_4^{\text{IV}}\text{O}_{12}(\text{OOCCH}_2 \cdot \text{Bu}^t)_{16}(\text{H}_2\text{O})_4]$ (**120**) with pyridine-2,6-dimethanol. The metal-fragment $[\text{Mn}_2^{\text{III}}\text{Mn}_4^{\text{II}}(\mu_4\text{-O})_2]^{10+}$ in this complex is identical to

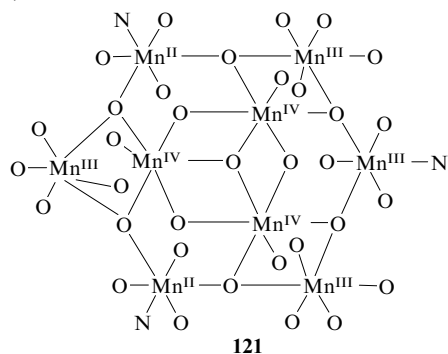
those in compounds **111**–**117**. The build-up of the metal core $\text{Mn}_2^{\text{III}}\text{Mn}_4^{\text{II}}(\mu_4\text{-O})_2$ occurs upon linking of two adjacent bridging carboxylate ligands with two Mn(II) atoms.



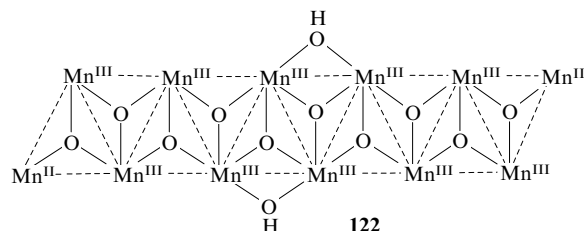
Complex **119** obtained by oxidation of $\text{Mn}(\text{OOCPh})_2 \cdot 2\text{H}_2\text{O}$ with tetrabutylammonium permanganate in the presence of phenyl 2-pyridyl ketone oxime also contains metallofragment $[\text{Mn}_4^{\text{III}}\text{Mn}_2^{\text{II}}(\mu_4\text{-O})_2]^{12+}$ but with four Mn(III) and two Mn(II) atoms. In this case, the build-up of the metal core proceeds from the opposite sides of the metal moiety.



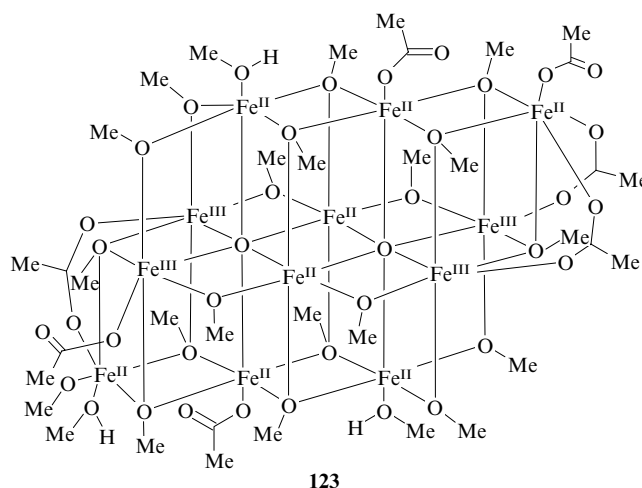
In contrast to iron derivatives, mixed-valence manganese complexes are known that contain simultaneously bi-, tri- and tetra-valent manganese ions. For example, the reaction of mixed-valence acetate complex $[\text{Mn}_3\text{O}(\text{OAc})_6(\text{py})_3]$ with 1,1,1-tris(hydroxymethyl)ethane (H_3L) results in the formation of nonanuclear complex $[\text{Mn}_2^{\text{II}}\text{Mn}_4^{\text{III}}\text{Mn}_3^{\text{IV}}\text{O}_7(\text{OAc})_{11}\text{L}(\text{py})_3(\text{H}_2\text{O})_2]$ (**121**).¹⁴⁴



However, the reaction of similar triphenylacetate complex $[\text{Mn}^{\text{II}}\text{Mn}_2^{\text{III}}(\mu\text{-O})(\text{OOCPh})_6(\text{py})_2(\text{H}_2\text{O})]$ with 1,1,1-tris(hydroxymethyl)ethane yields the dodecanuclear complex $[\text{Mn}_2^{\text{II}}\text{Mn}_{10}^{\text{III}}\text{O}_4(\text{OH})_2(\text{OOCPh})_{12}(\text{L})_4(\text{py})_2]$ (**122**). The metal core of this complex consists of ten triangular fragments $\{\text{Mn}_3(\mu_3\text{-O})\}$ with nine common sides.¹⁴⁵ The Mn(II) atoms occupy the peripheral positions in this system.



The dodecanuclear complex $[\text{Fe}_8^{\text{II}}\text{Fe}_4^{\text{III}}(\text{O})_2(\text{OMe})_{18}(\text{OAc})_6 \cdot (\text{MeOH})_{4.67}]$ (**123**) is obtained by controlled oxidation of a methanolic solution of iron acetate in the presence of lithium methoxide.¹⁴⁶ In this compound, six Fe(II) and four Fe(III) atoms are linked by two μ_6 -oxo-bridges.

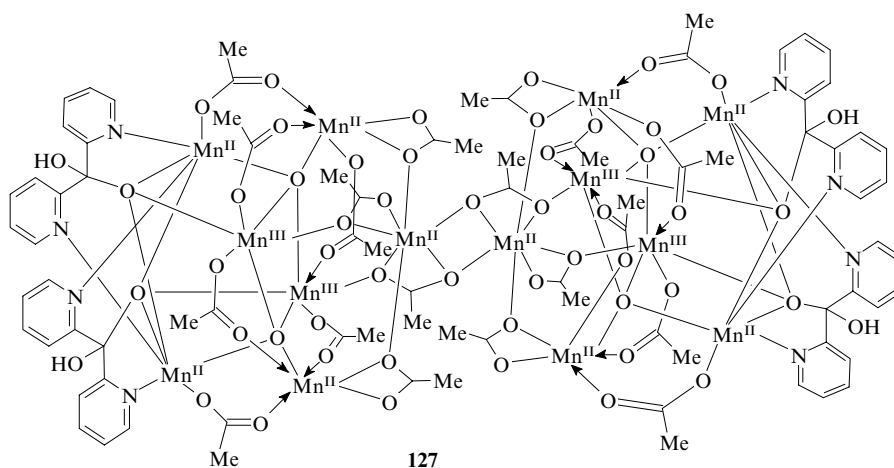


If a $\text{FeCl}_2\text{-ClCH}_2\text{COOH}$ mixture is used instead of iron acetate, the reaction with LiOMe and atmospheric oxygen results in a similar dodecanuclear complex with a part of carboxylate groups replaced by chlorine atom: $[\text{Fe}_8^{\text{II}}\text{Fe}_4^{\text{III}}(\text{O})_2(\text{OMe})_{18} \cdot (\text{OOCCH}_2\text{Cl})_{5.3}\text{Cl}_{0.7}(\text{MeOH})_4]$ (**124**).¹⁴⁷ More profound oxidation yields the Fe(III) cyclic complex $[\text{Fe}(\text{OMe})_2(\text{OOCCH}_2\text{Cl})]_{10}$ known as a molecular ‘iron ring’.¹⁴⁷

The reaction of manganese dodecanuclear complexes with reducing agents not always results in their decomposition. For instance, one-electron reduction of the complex $[\text{Mn}_8^{\text{III}} \cdot \text{Mn}_4^{\text{IV}}\text{O}_{12}(\text{OOCR})_{16}(\text{H}_2\text{O})_4]$ ($\text{R} = \text{Et}, \text{C}_4\text{H}_3\text{S}$) with tetraphenylphosphonium iodide produces the corresponding ionic molecular magnets $[\text{PPh}_4][\text{Mn}^{\text{II}}\text{Mn}_7^{\text{III}}\text{Mn}_4^{\text{IV}}\text{O}_{12}(\text{OOCR})_{16}(\text{H}_2\text{O})_x]$ [$\text{R} = \text{Et}, x = 4$ (**125**), $\text{R} = \text{C}_4\text{H}_3\text{S}, x = 2$ (**126**)], in which just one manganese atom is in the oxidation state +2 (see Refs 9, 148).

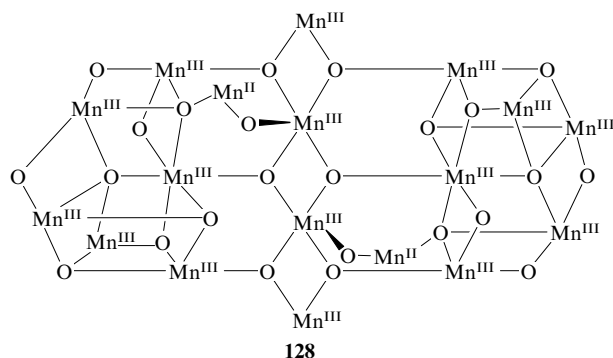
As was mentioned above, the use of polyfunctional ligands in the reactions with metal carboxylate increases the possibility of formation of polynuclear complexes. Thus the tetradecanuclear carboxylate complex $[\text{Mn}_{10}^{\text{II}}\text{Mn}_4^{\text{III}}\text{O}_4(\text{OAc})_{20}(\text{HL})_4]$ (**127**, $\text{H}_2\text{L} = (2\text{-C}_5\text{H}_4\text{N})_2\text{C}(\text{OH})_2$) is the reaction product of manganese acetate with bis(2-pyridyl) ketone, which can exist as a *gem*-diol when coordinated by metal ions, in acetonitrile in air.¹⁴³

The reaction of two triangular complexes $[\text{Mn}_3^{\text{III}}\text{O}(\text{OAc})_6 \cdot (\text{py})_3]\text{ClO}_4$ and $[\text{Mn}_3\text{O}(\text{OAc})_6(\text{py})_3]$ with 2-(2-hydroxyethyl)pyridine (HL) in acetonitrile results in the formation of polynuclear ionic complex $[\text{Mn}_2^{\text{II}}\text{Mn}_{16}^{\text{III}}\text{O}_{14}(\text{OAc})_{18}\text{L}_4(\text{HL})_2(\text{H}_2\text{O})_2](\text{ClO}_4)_2$



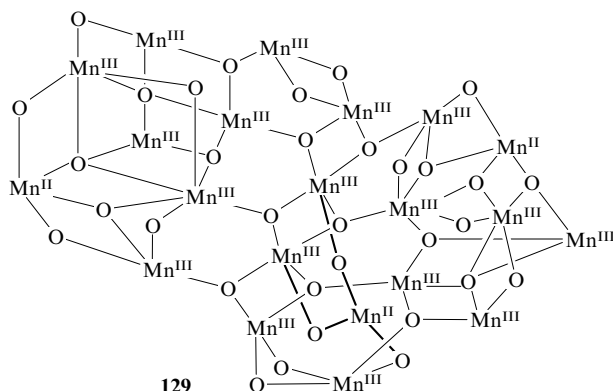
127

(128) in which the linear fragment $[\text{Mn}_4^{\text{III}}\text{O}_6]$ is linked to two heptanuclear fragments $[\text{Mn}^{\text{II}}\text{Mn}_6^{\text{III}}\text{O}_9]$.¹⁴⁹



128

The complex $[\text{Mn}_3^{\text{II}}\text{Mn}_{18}^{\text{III}}\text{O}_{14}(\text{OH})_2(\text{OAc})_{16}\text{L}_8(\text{pic})_2(\text{py}) \cdot (\text{H}_2\text{O})](\text{ClO}_4)_4$ (129, Hpic is α -picolinic acid) is formed in the reaction of $[\text{Mn}_{10}^{\text{III}}\text{O}_4(\text{OH})_2(\text{OAc})_8\text{L}_8](\text{ClO}_4)_4$ [HL is 2-(hydroxymethyl)pyridine] and $[\text{Mn}_3^{\text{II}}\text{O}(\text{OAc})_6(\text{py})_3]\text{ClO}_4$ in MeCN.¹⁵⁰ It should be noted, that partial reduction of manganese atoms proceeds due to the oxidation of 2-(hydroxymethyl)pyridine anions to anions of α -picolinic acid. Thus, starting from manganese(III) complex, it is possible to obtain a mixed-valence complex with the $[\text{Mn}_{21}(\mu_4\text{-O})_4(\mu_3\text{-O})_{12}(\mu\text{-O})_{16}]$ metal core. In this metal core, the linear fragment $[\text{Mn}_4^{\text{III}}\text{O}_6]$ is surrounded by two octanuclear fragments $[\text{Mn}^{\text{II}}\text{Mn}_7^{\text{III}}\text{O}_{12}]$ and one mononuclear $[\text{Mn}^{\text{II}}\text{O}_3]$ fragment (marked with bold lines).



129

Recrystallisation of the complex $[\text{Mn}_8^{\text{III}}\text{Mn}_4^{\text{IV}}\text{O}_{12}(\text{OOC} \cdot \text{CH}_2\text{Bu}^t)_{16}(\text{H}_2\text{O})_4]$ (120), which can be obtained by oxidation of manganese(II) acetate with potassium permanganate in the presence of $\text{Bu}^t\text{CH}_2\text{COOH}$, from $\text{CH}_2\text{Cl}_2\text{--MeNO}_2$ affords the complex $[\text{Mn}_3^{\text{II}}\text{Mn}_{26}^{\text{III}}\text{Mn}^{\text{IV}}\text{O}_{24}(\text{OH})_8(\text{OOCCH}_2\text{Bu}^t)_{32}(\text{H}_2\text{O})_2 \cdot (\text{MeNO}_2)_4]$.^{151, 152} This compound has a virtually linear

$[\text{Mn}_4\text{O}_6]$ core, which is fixed between two $[\text{Mn}_{13}\text{O}_9(\text{OH})_4]$ fragments. The quantum tunnelling of magnetisation (QTM) was reported for this compound as well as for not numerous polynuclear complexes 64, 121, 122, 125, 126, 128 and 129. The QTM is possible in polynuclear systems with several states of different multiplicity and a hysteresis at low temperature, thus these compounds belong to a unique class of molecular magnets (SMMs, Single Molecular Magnets).^{8, 9, 153} It should be noted, that the complexes containing eight and more metal atoms are exceptional for such carboxylate systems, rather unique and do not have analogues among carboxylate complexes of other transition metals.

VI. Conclusion

In conclusion, an exceptional diversity of structures of Mn(II) and Fe(II) carboxylates discussed — from relatively simple binuclear complexes up to highly complicated 30-nuclear hetero-spin compounds — is worth noting. Undoubtedly, these compounds with unique magnetic properties, which should be a subject of another review, are extremely important blocks for the creation of molecular electronic devices in the nearest future. The first synthetic strategies of the targeted production of high spin bi- and trinuclear systems with required structure and magnetic properties, already exist. However, the approaches to the synthesis of structures more complicated and probably more interesting as molecular magnets are obviously yet to be developed.

This review has been written with the financial support of the Russian Foundation for Basic Research (Project Nos 04-03-32880, 04-03-32883, 05-03-32767), of the Chemistry and Materials Section of the Russian Academy of Sciences (the Target basic research programme 'Chemistry and Physical Chemistry of Supramolecular Systems and Atomic Clusters'), of the Presidium of Russian Academy of Sciences [Project 'Molecular Design of Magnetoactive Compounds and Materials (Molecular Magnets)'] and of the INTAS (Grant 03-51-4532).

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^d — *Russ. J. Inorg. Chem. (Engl. Transl.)*

^e — *J. Struct. Chem. (Engl. Transl.)*

The chemistry of 3-cyanopyridine-2(1*H*)-chalcogenones

V P Litvinov

Contents

I. Introduction	577
II. Methods of synthesis	577
III. Reactivity and chemical transformations	588
IV. Applications	595
V. Conclusion	595

Abstract. The data on the methods of synthesis and chemical properties of 3-cyanopyridine-2(1*H*)-chalcogenones published over the last 20 years are systematised and analysed. Special attention is given to the use of these compounds as building blocks in the synthesis of fused *O,N,S*-heterocycles. The bibliography includes 277 references.

I. Introduction

Pyridine derivatives and their fused analogues have been in the centre of attention of researchers over many years due to the high practical value of these compounds, in the first place, the unusually broad spectrum of biological activities. In a paper by Lukevits¹ devoted to the 150th anniversary of pyridine chemistry, it was noted that more than 10% of the 1500 therapeutic agents most popular to that period contain the pyridine ring in their active components. These include vitamins (B₃, B₆, PP), analgetics, analeptics, antiarrhythmic drugs, antiseptics, antidepressants, spasmolytics, neuroleptics, tranquilisers and other medicines manifesting diverse pharmacological activities. This is why the expediency of improving the existing methods and a search for novel methods for the construction of pyridine-containing substrates as 'building blocks' for organic synthesis leaves no doubt. The synthetic potential of such compounds revealed from the analysis of their structures and reactivities will enable the development of convenient, cost-effective and environmentally safe methods for the preparation of novel pyridine derivatives possessing valuable biological properties.

Recently, functionalised pyridinechalcogenones have become the subject of intensive studies in the chemistry of heterocyclic compounds. This particular class of substances presents both theoretical and practical interest. Pyridinechalcogenone derivatives are used, *inter alia*, as substrates in the preparation of a medicine Bupiron, which possesses antidepressant and analgetic activities and prevents narcotic dependence, and some novel types of calcium antagonists and antioxidants. In addition, these compounds can be used as models for the redox coenzymes NAD and

NADP and as substrates for the synthesis of folic acid derivatives, vitamin B₆ and some other biologically active compounds. 3-Cyanopyridine-2(1*H*)-thione derivatives are used in the production of dyes, pigments, additives to fuels and lubricants, stabilisers for polymers and varnishes, acid–base indicators for titrimetric assays and as other important compounds.

The unfading interest in the chemistry of pyridinechalcogenones observed over the past two decades is reflected in numerous patents and papers that are partially systematised in the reviews^{2–14} and numerous theses (see, *e.g.*, those presented over the past two years^{15–19}).

The topicality of this line of research and the lack of comprehensive reviews on the state-of-the-art and future outlooks in heterocyclic chemistry served as a reason for preparing the present review. Here, an attempt is made at systematisation and analysis of modern data (predominantly those obtained in the past two decades) on the chemistry of 3-cyanopyridine-2(1*H*)-ones (thiones, selones).[†] These compounds contain, along with the nitrile group, an amide, a thioamide or a selenoamide group with the endocyclic nitrogen atom in the vicinal position and represent convenient synthons of a vast array of annelated heterocyclic systems (including those hardly obtainable by other methods). The main attention in the review is focused on the methods for the synthesis of 3-cyanopyridine-2(1*H*)-chalcogenones and their applications as building blocks in the synthesis of biologically active compounds. Aromatic, di- and tetrahydro-forms of these compounds, hydrated derivatives as well as enol tautomers are considered. The physicochemical properties and general regularities of the reactivities of this class of compounds have been discussed earlier (see, for example, Ref. 8) and are beyond the scope of the present review.

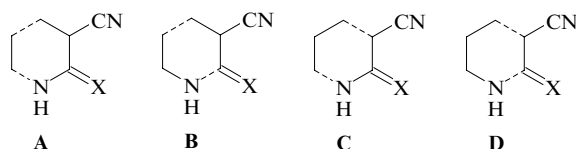
II. Methods of synthesis

Systematisation of the methods for the synthesis of heterocyclic compounds is based on different principles (*e.g.*, type of reactants, reaction mechanisms, *etc.*). The formally logical retrosynthetic classification based on the topology of the bonds formed is especially popular. The formation of any heterocyclic system is represented as the formation of specific bonds in preformed structural blocks, which enables comparison and estimation of the value of each approach and the development of novel, hitherto

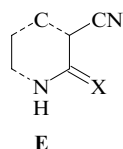
V P Litvinov N D Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky prosp. 47, 119991 Moscow, Russian Federation. Fax (7-495) 135 53 28, tel. (7-495) 135 88 37, e-mail: vpl@ioc.ac.ru

[†] According to the IUPAC Nomenclature, these compounds should be termed as 2-oxo(thioxo,selenoxo)-1,2-dihydropyridine-3-carbonitriles; however, in this work we shall adhere to the historic names.

unexplored trends. In the framework of this approach, all the methods for the synthesis of 3-cyanopyridine-2(1*H*)-chalcogenones are classified into six groups. Examples of methods for the introduction or modification of substituents in the preformed pyridine substrates and for cyclisation of a five-carbon fragment with formation of the N–C bond are few in number. Most of the data available refer to different methods for the synthesis of the pyridine ring from two fragments. Information on the cyclisation of three- and two-carbon fragments (3 + 2) is especially abundant as can be judged from the number of relevant papers. In this case, the formation of the N–C bond is accompanied by the formation of a new carbon–carbon bond, *viz.*, C(5)–C(4) (structures **A** and **B**) or C(3)–C(4) (structures **C** and **D**).



In addition to a small chapter devoted to the synthesis of the pyridine ring from three fragments (1 + 2 + 2) (structure **E**), some examples of the formation of the pyridine system based on ring transformation reactions are considered.

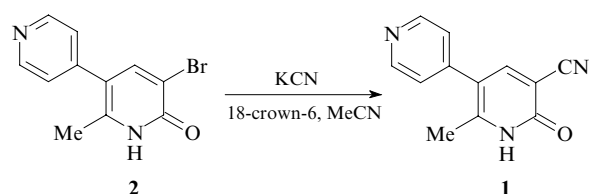


It is of note that the most promising procedures for the synthesis of pyridinechalcogenones based on cyclisation of several fragments are usually performed as one-pot synthesis. A chain of sequential conversions of functional groups, elongation of the carbon chain and its cyclisation without any additional reagent or a catalyst and without any change in the reaction temperature has got the name cascade heterocyclisation. Such a methodology of the synthesis of 3-cyanopyridine-2(1*H*)-chalcogenones has been discussed in detail.²

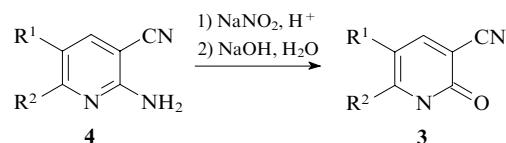
1. Introduction or modification of a substituent in a preformed pyridine substrate

Introduction or modification of a substituent in a preformed pyridine substrate is the most direct approach to the synthesis of 3-cyanopyridine-2-chalcogenones. Only a few examples of this approach are known, since the starting compounds for such syntheses are difficult to obtain.

Thus substitution of the cyano group for the bromine atom was employed in a facile preparation of a phosphodiesterase inhibitor drug Milrinone (**1**). The reaction of 3-bromopyridin-2(1*H*)-one **2** with potassium cyanide in acetonitrile proceeds smoothly in the presence of 18-crown-6.²⁰

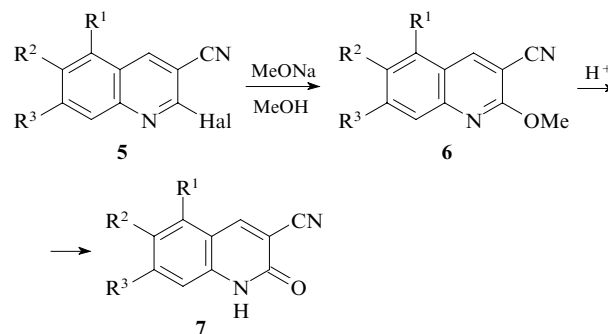


In some cases, the starting compounds contain a nitrile group in the pyridine (quinoline) ring. For example, 3-cyanopyridin-2(1*H*)-ones **3** were prepared from substituted 2-amino-3-cyanopyridines **4** by diazotisation and subsequent hydrolytic elimination of dinitrogen.^{21, 22}



$R^1 = \text{Ar, Het}; R^2 = \text{Alk, OAlk, SAlk, OPh.}$

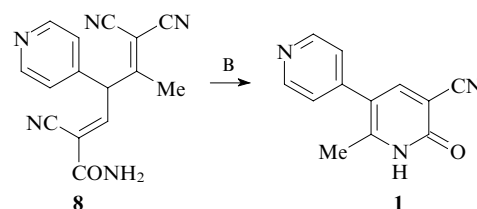
Methoxylation of 3-cyano-2-haloquinolines **5** was used for an access to a broad series of 2-methoxy derivatives **6**; their acid hydrolysis resulted in 3-cyanoquinolinones **7**.^{23–27}



$R^1 = \text{H, Alk, CN, NO}_2, \text{Hal}; R^2 = \text{H, Alk, Het, Hal, SO}_3\text{H}; R^3 = \text{Het.}$

2. Cyclisation of a five-carbon fragment with formation of the N–C(6) bond

Only one example of a conversion of an acyclic precursor (*viz.*, polyfunctional alkene) into 3-cyanopyridin-2-one is documented. Synthesis of the aforementioned drug Milrinone (**1**) by cyclisation of tricyanohexa-1,4-dienamide **8** with elimination of malononitrile in EtOH in the presence of a base (**B**) (NaOH, Na₂CO₃ or EtONa) has been patented.²⁸ The yield of the target product was not indicated.

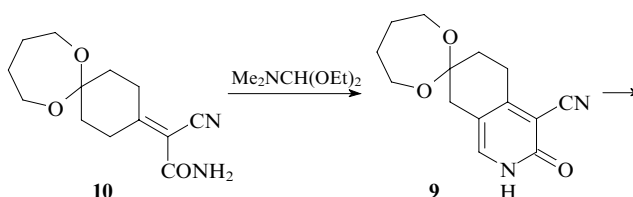


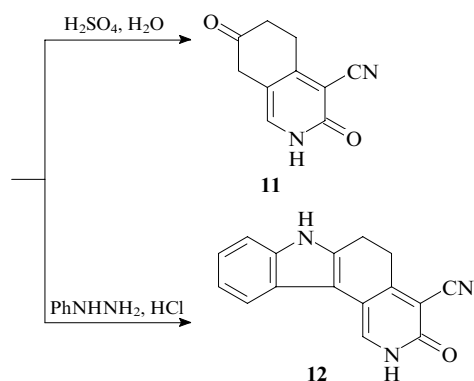
3. Synthesis of the pyridine ring from two fragments

a. Cyclisation of four- and single-carbon fragments with formation of the N–C(6) and C(5)–C(6) bonds

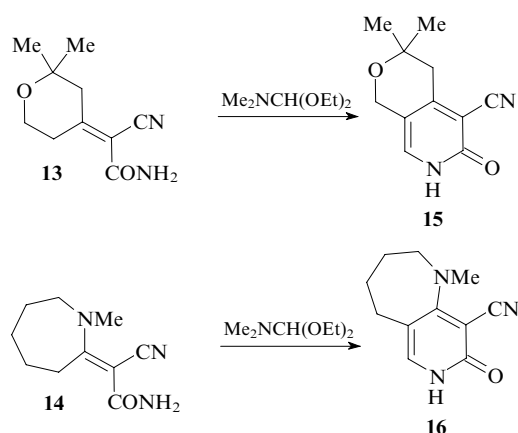
The first, within the given classification, variant of the assembly of the 3-cyanopyridine-2-chalcogenone molecule from two fragments includes cyclisation of four- and one-carbon units. Such reactions result in the formation of the C(5)–C(6) and N–C(6) bonds of the pyridine ring. This approach is exemplified by a single type of reactions, *viz.*, condensation of unsaturated cyanoamides with dimethylformamide acetal.

A non-trivial synthesis of tetrahydroisoquinolinone **9** from cyanoamide **10** and dimethylformamide diethyl acetal has been described.²⁹ This was converted into both isoquinolinedione **11** and pyrido[3,4-*c*]carbazole **12**.





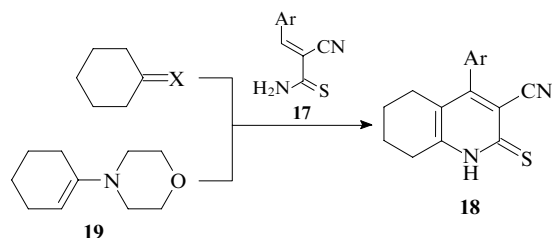
A similar reaction of cyanoamides **13** and **14** with dimethylformamide diethyl acetal was employed in the synthesis of pyrano[3,4-*c*]pyridin-3-one **15**³⁰ and pyrido[4,3-*a*]azepin-3-one **16**,³¹ respectively:



b. Cyclisation of three- and two-carbon fragments with formation of the C(5)–C(4) and N–C bonds

The construction of the pyridine molecule from two- and three-carbon fragments with simultaneous (or consecutive) formation of the C(4)–C(5) and N–C(6) bonds is often used in the synthesis of 3-cyanopyridine-2-chalcogenones. Arylmethylidene(cyano)thioacetamides **17** are usually employed as the principal components to which a two-carbon fragment is attached.

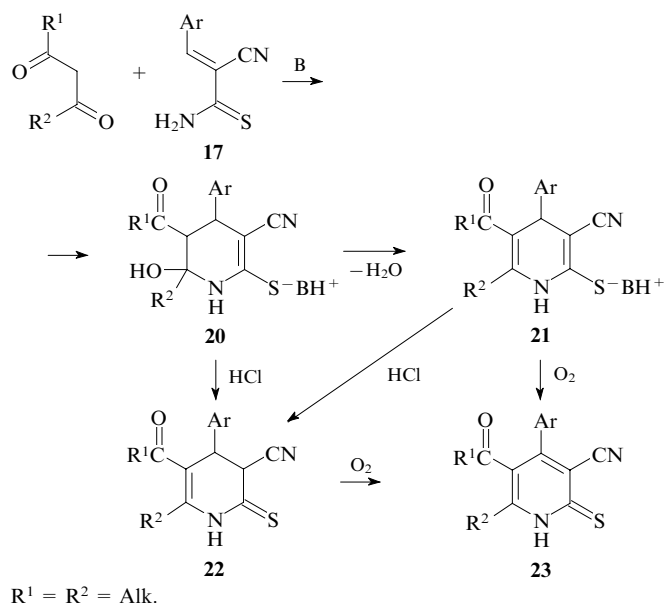
Synthesis of tetrahydroquinolinethiones **18** from (thio)cyclohexanone or enamine **19** is the simplest example of such a reaction.³² This is carried out in methanol at room temperature; the yields are 78%–86%.



X = O, S; Ar = RC₆H₄ (R = H, 2-F, 4-F, 4-Cl, 4-Br, 4-MeO), 3-Py.

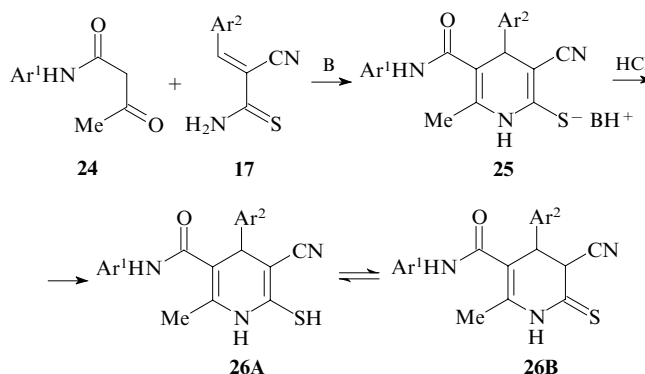
Diketones and the corresponding enamines react similarly with arylmethylidene(cyano)thioacetamides **17** to yield partially hydrogenated 3-cyanopyridine-2(1*H*)-thiones or their salts (Refs 11, 33–51). The intermediate thiolates **20** can be isolated; their subsequent dehydration results in 3-cyano-1,4-dihydropyridine-2-thiolates **21**. Upon acidification, the salts **20** and **21** are converted into 3-cyano-3,4-dihydropyridine-2-thiolates **22** which

undergo dehydrogenation in solution to afford 3-cyanopyridine-2(1*H*)-thiones **23**. Enamines derived from diketones react with amides **17** in the absence of basic catalysts; the corresponding 1,4-dihydropyridine-2-thiolates are formed in high yields.

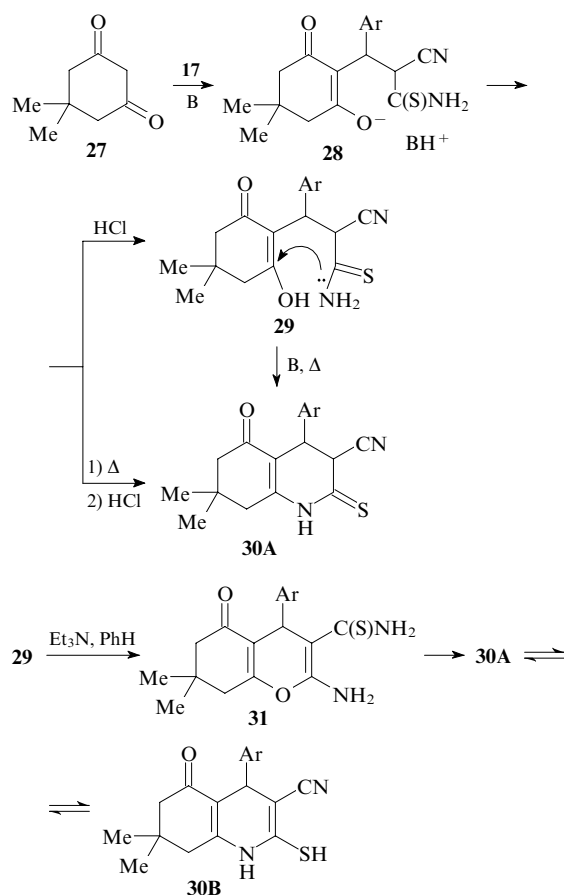


R¹ = R² = Alk.

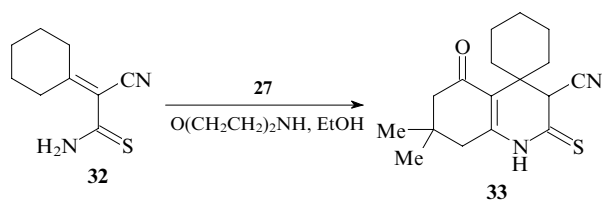
This type of reactions includes also the condensation of (het)arylmethylidene(cyano)thioacetamides **17** with acetoacetanilides.^{52, 53} Amides **17** enter easily into the Michael reaction with anilides **24** due to the presence of an activated double bond; subsequent cyclisation yields 1,4-dihydropyridine-2-thiolates **25**. The latter are converted into thiols by treatment with HCl; in DMSO, thiols exist as a mixture of tautomers **26A** and **26B**.



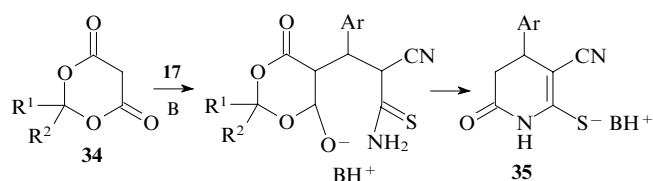
Cyclic 1,3-dicarbonyl compounds, in particular, dimedone, are also widely and successfully used in the synthesis of 3-cyanopyridine-2-chalcogenones (**27**). The use of dimedone made it possible to elucidate some peculiarities of the mechanism of its reaction with arylmethylidene(cyano)thioacetamides **17** (see, for example, Refs 7, 52, 54 and 55). In some cases, intermediate Michael adducts **28** were isolated as rather stable salts, which enabled studies of their properties. Thus acidification of salts **28** yielded compounds **29**; heating of the latter in the presence of organic bases (or direct heating of salts **28** with subsequent acidification) resulted in dihydropyridine-2-thiones **30A**. It is of note that compounds **29** are converted into substituted tetrahydro-4*H*-benzo[*b*]pyrans **31** in the presence of triethylamine. These represent the products of kinetic control, which are converted into thermodynamically controlled dihydropyridine-2-thiones **30A** existing in a tautomeric equilibrium with the thiol form **30B** in polar solvents (e.g., ethanol).



Dimedone (**27**) was successfully used in the synthesis of spirofused 3-cyanopyridine-2(1H)-thione from cyclohexylidene(cyano)thioacetamide **32**. The reaction in ethanol in the presence of morpholine afforded 3,4,5,6,7,8-hexahydroquinoline-4-spiro-1'-cyclohexane-2(1H)-thione (**33**) in high yield.^{52, 56}



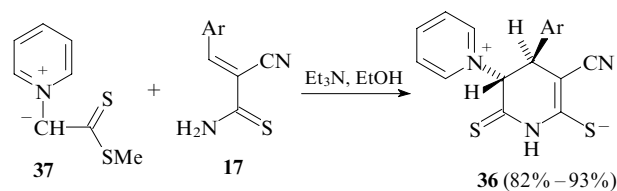
The reaction of arylmethylidene(cyano)thioacetamides **17** with Meldrum's acids **34** is an example of the use of other cyclic 1,3-diketones in the synthesis of pyridinechalcogenones by this method. This is carried out in ethanol in the presence of a base (e.g., piperidine, *N*-methylmorpholine); under these conditions, 4-aryl-3-cyano-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolates **35** are formed in 85% yields. If the reaction is carried out in benzene, the yields of the products drop down to 30%.⁵⁷



$\text{R}^1 = \text{R}^2 = \text{Me}$, $\text{R}^1 - \text{R}^2 = (\text{CH}_2)_5$; Ar = 2- ClC_6H_4 , 4- BrC_6H_4 .

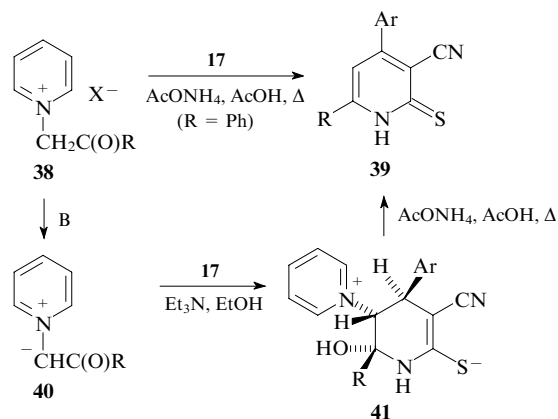
Pyridinium ylides also play the role of two-carbon fragments.^{58–66} Synthesis of *trans*-6-thioxo-1,4,5,6-tetrahydropyridine-2-thiolates **36** by the reaction of pyridinium ylide **37** with

arylmethylidene(cyano)thioacetamides **17** can serve as an example.^{51, 58, 59, 61}



Ar = 4- XC_6H_4 (X = HO, MeO, F, Cl, Br), 3-Py.

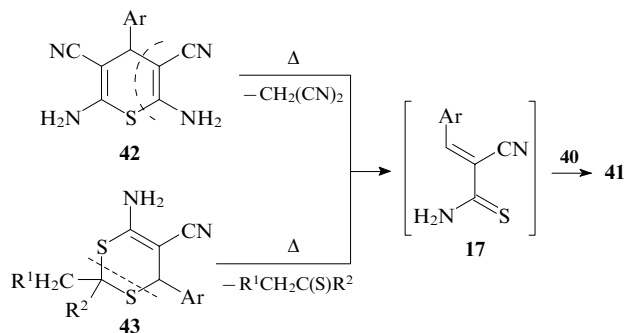
In this reaction, the effect of conditions on the nature of the products formed was observed. Thus heating of amides **17** with *N*-phenacylpyridinium salts **38** in the presence of ammonium acetate in acetic acid yielded 4,6-diaryl-3-cyanopyridine-2(1H)-thiones **39**.⁵⁸ However, reactions of pyridinium ylides **40** generated from the salts **38** with the same amides **17** in ethanol in the presence of triethylamine proceeded with high regio- and stereo-selectivity and gave *trans,trans*-1,4,5,6-tetrahydropyridine-2-thiolates **41**.^{62–64} The latter were converted into thiones **39** by heating in acetic acid in the presence of ammonium acetate.



R = Me, Ph, cyclo- C_3H_5 ; Ar = XC_6H_4 (X = H, 4-MeO, 4- NO_2 , 2-F, 4-F, 4-Br), 3-Py.

Isoquinolinium ylides were also used in the synthesis of thiolates **41**.⁶³

It is noteworthy that the three-carbon fragment (unsaturated thioamide) of the target pyridinechalcogenone is often cut out upon ring transformation of six-membered cyclic enaminonitriles, derivatives of 4*H*-pyran, 4*H*-thiopyran, 4*H*-selenopyran and 1,3-dithiacyclohexene.^{7, 8, 32, 35, 54, 67–81} Thus it was found that heating of 4*H*-thiopyran **42** with pyridinium salt **38** results in the breakdown of the thiopyrane ring.¹¹ Subsequent reaction (formally, cross-ring transformation) of thioacetamide **17** and pyridinium ylide **40** formed thereupon yielded stable 1,4,5,6-tetrahydropyridine-2-thiolates **41**.

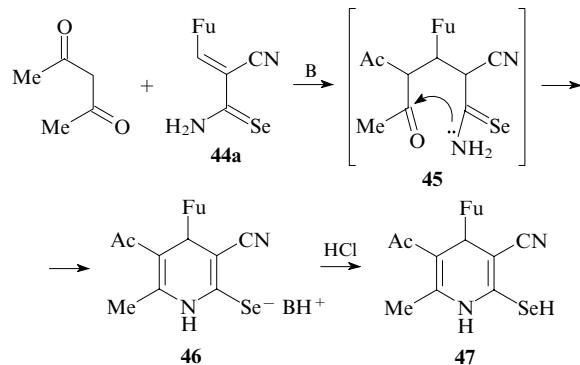


$\text{R}^1, \text{R}^2 = \text{Alk}, (\text{CH}_2)_n$; Ar = Ph, 3- FC_6H_4 , 4- FC_6H_4 , 4- ClC_6H_4 .

The reaction of 1,3-dithiacyclohex-4-enes **43** with salt **38** proceeds in a similar manner. Upon elimination of a thioketone,¹¹

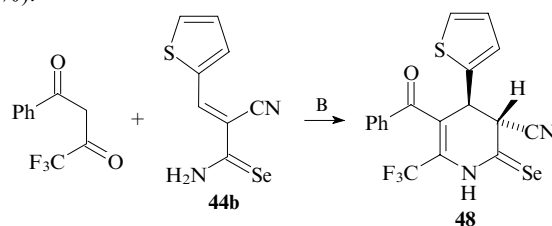
pyridinium ylides **40** react with *in situ* generated thioamides **17** to yield stereoselectively thiolates **41**.

The use of selenium analogues of thioamides **17** is documented. The reaction of acetylacetone with 2-furfurylidene(cyano)selenoacetamide **44a** affords, *via* the intermediate Michael adduct **45** and stable salt **46**, 5-acetyl-3-cyano-4-(2-furyl)-6-methyl-1,4-dihydropyridine-2-selenol (**47**) (yield 80%).^{52, 82}

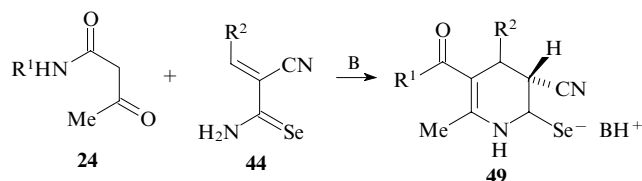


Fu is 2-furyl.

A method for the synthesis of *trans*-5-benzoyl-3-cyano-4-(2-thienyl)-6-trifluoromethyl-3,4-dihydropyridine-2(1*H*)-selenone (**48**) was developed, which consists of treatment of benzoyltrifluoroacetone with 2-thienylmethylidene(cyano)selenoacetamide (**44b**) in the presence of *N*-methylmorpholine (yield 78%).⁴⁰

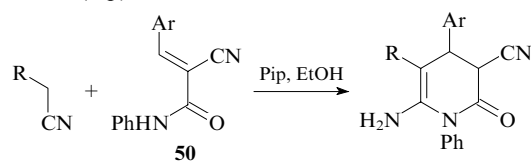


Condensation of hetaryl(methylidene)(cyano)selenoacetamides **44** with acetoacetanilide (**24**, R¹ = Ph) or acetoacetamide (**24**, R¹ = H) also occurs in a regioselective mode and yields 1,4-dihydropyridine-2-selenolates **49**.^{83, 84}



R¹ = H, Ph; R² = Het, B is morpholine.

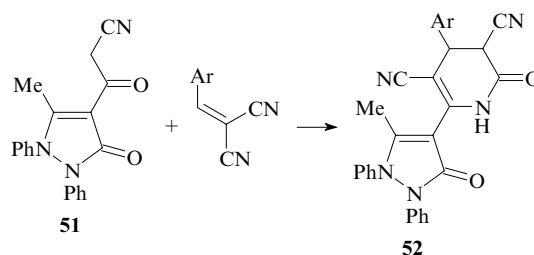
In addition to the above-mentioned fragment CH–C(O), the role of a two-carbon component can be played by the CH₂CN group. Thus the reaction of anilides of cinnamic and other 3-aryl-2-cyanoacrylic acids **50** with this type of CH-acids was successfully used in the synthesis of 3,4-dihydropyridine-2(1*H*)-ones. These reactions are carried out in boiling ethanol in the presence of piperidine (Pip).⁸⁵



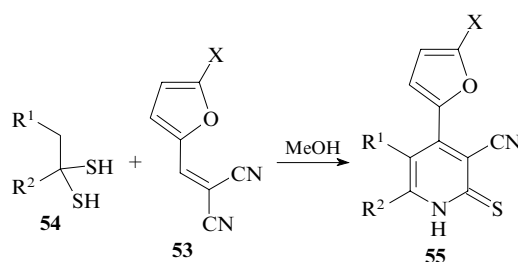
R = NC, EtO₂C, PhHNC(O), 4-ClC₆H₄C(O).

In conclusion, we mention some interesting examples of the use of unsaturated dinitriles as three-carbon and one-nitrogen atom donors for the pyridine ring. Reactions of dinitriles of the

styrene type with 4-(cyanoacetyl)pyrazolinone **51** give substituted 3,4-dihydropyridine-2(1*H*)-thiones **52** in up to 75% yields.⁸⁶

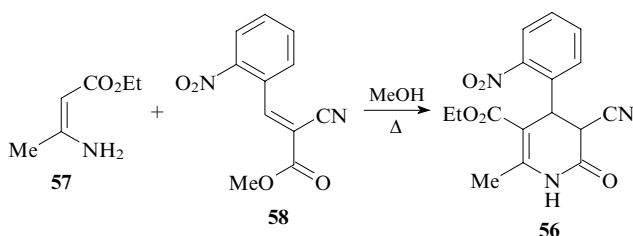


Reactions of substituted furfurylidene malononitriles **53** with alicyclic and aliphatic *gem*-dithiols **54** were also reported.^{68, 70} Contrary to benzylidenemalononitriles, these reactions directly yielded substituted tetrahydroquinolinethiones **55** rather than the corresponding 1,3-dithiacyclohexenes (see Section II.5).



R¹ = H, Me; R² = Me, Et; R¹–R² = (CH₂)_n (n = 3–5); X = H, 2,4-Cl₂C₆H₃, 3,4-Cl₂C₆H₃; B is morpholine,⁶⁸ Et₂NH.⁷⁰

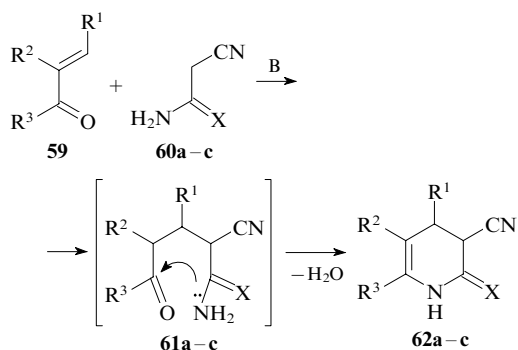
The synthesis of substituted pyridone **56** is the only example of construction of 3-cyanopyridine-2-chalcogenones from two- and three-carbon fragments; this involves the formation of the C(4)–C(5) and N–C(2) bonds. Nucleophilic addition of enamine **57** to unsaturated nitrile **58** yields the final product.⁸⁷



c. Cyclisation of one- and three-carbon fragments with formation of the C(3)–C(4) and N–C bonds

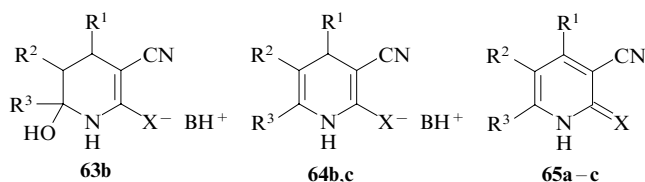
The construction of a pyridine system from two fragments with formation of the C(3)–C(4) and N–C(6) bonds is the most popular approach to the synthesis of 3-cyanopyridine-2(1*H*)-chalcogenones. Such conversions follow the cascade heterocyclisation mechanism and begin with the addition of 1,3-bis-nucleophile, *viz.*, cyanoacetamide, its thio- or selenium derivative, to a three-carbon fragment. The role of the latter can be played by 1,3-bis-electrophiles, *e.g.*, different forms of α,β-unsaturated carbonyl and 1,3-dicarbonyl compounds, such as aldehydes, ketones and their enols as ethers and salts, as well as by enamines and carboxylic acid derivatives (esters, amides, nitriles).

The majority of published data are devoted to the synthesis of 3-cyanopyridine-2(1*H*)-chalcogenones by the reaction of α,β-unsaturated carbonyl compounds **59** with cyano(thio,seleno)acetamides **60a–c**. This reaction occurs in the presence of organic bases as catalysts; the intermediate Michael adducts **61a–c** undergo cyclisation into 3-cyanodihydropyridine-2(1*H*)-chalcogenones **62a–c** in fairly high yields.



$R^1 - R^3 = \text{H, Alk, Ar, Het; X = O (a), S (b), Se (c); B}$ is a base.

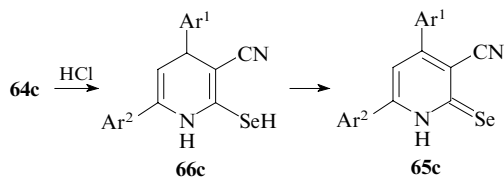
For the first time, this method was used for the preparation of 4,6-diaryl- (Refs 88 and 89) and 4-aryl-3-cyanopyridine-2(1H)-thiones.⁹⁰ Either stable intermediates, *viz.*, salts **63** (for $X = \text{S}$), or salt derivatives of compounds **62**, *viz.*, dihydropyridines **64** (for $X = \text{S, Se}$) or dehydrogenation products **65**, can be isolated depending on the reaction conditions and the nature of the reactants. In the course of isolation, compounds **61** (or **63**) are oxidised (dehydrogenated) by atmospheric oxygen into salts **64**.



In the reactions of cyanoacetamide (**60a**) with unsaturated (hetero)aromatic ketones (**59**, $R^1, R^3 = \text{Ar, Het; } R^2 = \text{H}$), the Michael adducts (amides **61a**) can be isolated in a pure state.^{91,92} Heating of the latter in acetic acid in the presence of ammonium acetate brings about their cyclisation into pyridones **62a**, which are further dehydrogenated into pyridones **65a**.

The reaction conditions and the nature of the base (catalyst) were varied in the synthesis of 3-cyanopyridine-2(1H)-thione derivatives (see, for example, Refs 93–98). Thus the use of sodium alkoxides in boiling alcohol afforded pyridinethiones **65b**,^{89,99–101} while the use of an equimolar amount of an organic base (in ethanol at 20 °C) that served as both the catalyst and a stabilising reagent resulted in salts **63b** and **64b**.^{90,93,95–98,102} Acidification of salts **64b** with hydrochloric acid afforded 3,4-dihydropyridine-2(1H)-thiones **62b**, which were oxidised by atmospheric oxygen to thiones **65b**.

The reaction of chalcones **59** ($R^1, R^3 = \text{Ar, } R^2 = \text{H}$) with cyanoselenoacetamide **60c** in the presence of excess *N*-methylmorpholine under similar conditions gave exclusively 1,4-dihydropyridine-2-selenolates **64c** (yield 90%).^{52,103,104} Treatment of the latter with HCl afforded 1,4-dihydropyridine-2-selenols **66c**, which represent tautomers of dihydropyridine-2(1H)-selenones **62c**; the latter are easily oxidised in the air into the corresponding pyridineselones **65c**.

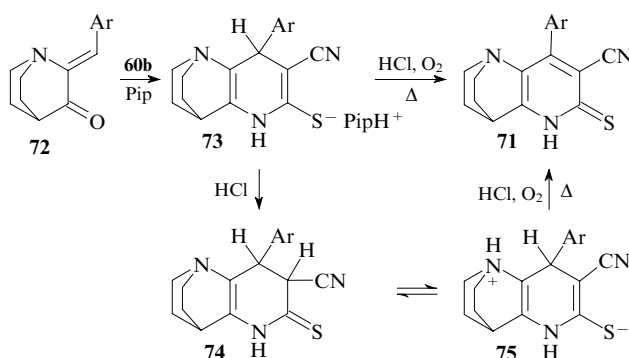


These data suggest that the nature of the substrate and the reagent should be taken into consideration in each particular case.

Examples of the synthesis of different 3-cyanopyridine-2-chalcogenone derivatives are given in Table 1. In all these cases, the role of the two-carbon component is played by cyano(thio, seleno)acetamide **60**, while a broad range of original 1,3-bis-electrophiles demonstrates the prospects of this approach. The versions of this reaction given in Table 1 are discussed below.

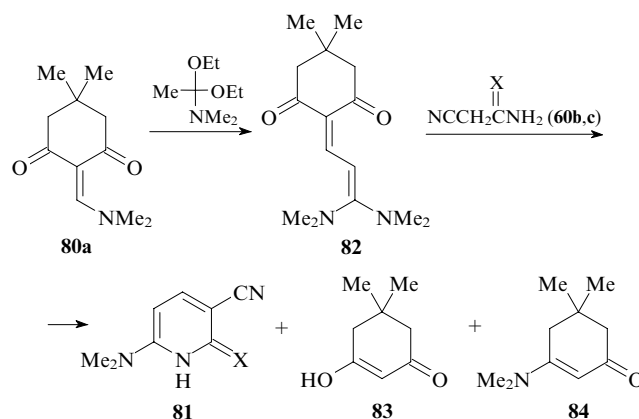
Hetero- and carbocycles (including steroids) can be annelated to α,β -unsaturated carbonyl fragments. No intermediate 3,4-dihydropyridines could be isolated in the reaction of cyclic unsaturated ketone **67** with cyanothioacetamide (**60b**) in methanol in the presence of sodium methoxide (see Table 1, entry 1).^{105–108} However, the structurally similar isochroman-4-one **68** and amide **60a** gave 3-cyano-3,4-dihydroisochromano[3,4-*b*]pyridine-2(1H)-ones **69**, which were further dehydrogenated into compounds **70** (entry 2).¹⁰⁹

Naphthyridinethiones **71** were prepared from 2-aryl-methylidenequinclidin-3-ones **72** and (cyano)thioacetamide (**60b**) (Table 1, entry 3).^{110,111} After treatment with hydrochloric acid, the primary reaction products, *viz.*, piperidinium 4-aryl-3-cyano-5,8-ethano-1,4,5,6,7,8-hexahydro-1,5-naphthyridine-2-thiolates **73**, were converted into 4-aryl-3-cyano-5,8-ethano-1,4,5,6,7,8-hexahydro-1,5-naphthyridine-2(1H)-thiones (**74**), which exist in a tautomeric equilibrium with betaines **75**. Heating of salts **73** or betaines **75** in ethanol in the presence of HCl resulted in their dehydrogenation and formation of compounds **71**.



Steroid derivatives **76** and **77** were obtained by similar reactions of ketones **78** and **79** with (cyano)thioacetamide **60b**,^{112,113} in the former case, saponification of the acetoxy group took place (entries 4 and 5).

The three-carbon fragment used in the synthesis of pyridine-chalcogenones according to the (3 + 2)-scheme can represent a component of a more complex conjugated system. In such a case, compounds containing different functional groups are formed. For instance, dimethylaminomethylidenedimedone **80a** was employed in the synthesis of 3-cyano-6-dimethylamino-pyridine-2(1H)-chalcogenones (**81**).¹¹⁴ Its reaction with *N,N*-dimethylacetamide diethyl acetal afforded diaminodienodione **82** in high yield. Reactions of the latter with cyanothio(seleno)-acetamides **60b,c** resulted in a mixture of pyridine **81** (entry 6), dimedone (**83**) and its derivative **84**.



Reactions of cyanoacetamides with cyclic and acyclic pentadien-3-ones also yielded cyanopyridinechalcogenone derivatives (see Table 1, entries 7 and 8). The reaction of dibenzylidenecyclopentanone **85** with thioamide **60b** in the presence of sodium

Table 1. Synthesis of 3-cyanopyridine-2-chalcogenone derivatives using cyanoacetamides NCCH₂C(=X)NH₂ (**60a–c**).

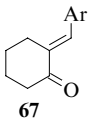
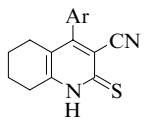
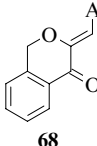
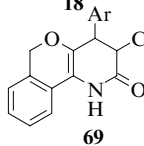
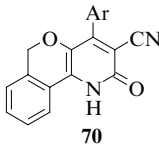
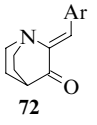
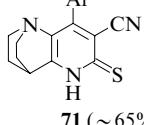
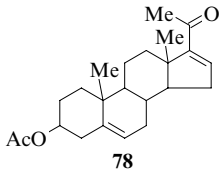
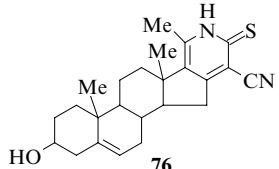
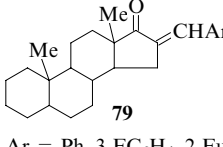
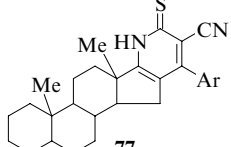
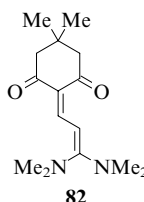
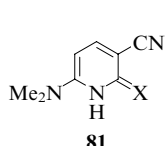
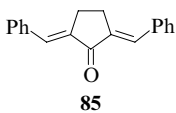
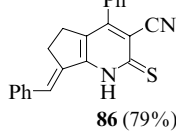
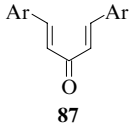
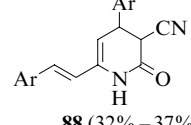
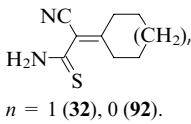
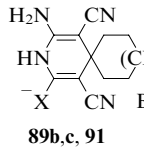
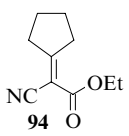
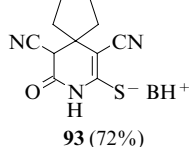
Entry	1,3-Bis-electrophile	X	Reaction conditions	Intermediates and products (yields)	Ref.
1	 67	S	MeONa, MeOH	 18	105–108
2	 68	O	Pip, EtOH, Δ	 69 $\xrightarrow[\Delta]{\text{Se}}$  70	109
3	 72	S	Pip	 71 (~65%)	110, 111
4	 78	S	EtONa, EtOH	 76	112, 113
5	 79 Ar = Ph, 3-FC ₆ H ₄ , 2-Fu, 3-Py.	S	EtONa, EtOH	 77	112, 113
6	 82	S, Se	EtOH	 81 X = S (76%), Se (43%).	114
7	 85	S	EtONa, EtOH, Δ	 86 (79%)	83, 115
8	 87	O	170 °C in a sealed tube	 88 (32%–37%)	116
9	 92 $n = 1$ (32), 0 (92).	S ($n = 0, 1$), Se ($n = 1$)	<i>N</i> -methylmorpholine (B), EtOH	 89b,c, 91 $n = 1$ (89b,c, 90b,c), 0 (91).	52, 117–120
10	 94	S	<i>N</i> -methylmorpholine (B), EtOH	 93 (72%)	121

Table 1 (continued).

Entry	1,3-Bis-electrophile	X	Reaction conditions	Intermediates and products (yields)	Ref.
11		Se	<i>N</i> -methylmorpholine, EtOH	89c → 90c	52, 117–120
12		O	Pip, Δ		86
13		S	Et ₃ N		122
14		S	morpholine		123
15		S	AcOH, EtOH		83
16		S	AcOH, EtOH, Δ		124
17		S, Se	Et ₃ N, EtOH		34, 89, 125–127
18		S, Se	Et ₃ N, EtOH		93, 128, 129
19		S	Et ₃ N, EtOH, Δ		53, 83, 130–134
20		S	1) KOH, EtOH 2) 60b , HCl		53, 83, 130–134

Table 1 (continued).

Entry	1,3-Bis-electrophile	X	Reaction conditions	Intermediates and products (yields)	Ref.
21	115 R¹, R² = H, Alk, Ar, Het.	S	AcOH, EtOH, Δ	110 (< 98%)	30
22	116	S	Pip, EtOH	117	45
23	118 Ar = 3-NO₂C₆H₄, 4-ClC₆H₄	S	Pip (B), EtOH	119 → 120 (60%–61%)	97
24	80 R¹ = H, Me; R² = H, Me, Ph.	O	NaOH, THF	121 (14%–91%)	135

ethoxide at room temperature gave pyridine-2(1*H*)-thione **86** annelated with the cyclopentane ring.^{83, 115} The reaction of acyclic symmetrical pentadienone **87** performed under more drastic conditions (heating of reactants at 170 °C in a sealed tube without a solvent) afforded substituted 3-cyano-3,4-dihydropyridine-2(1*H*)-ones **88**.¹¹⁶

Amides and esters of cycloalkylidenecyano(thio)acetic acid are also used as 1,3-bis-electrophiles in reactions with amides **60**. Thus the reaction of cyclohexylidenecyanothioacetamide **32** with cyanothio(seleno)acetamides **60b,c** in ethanol in the presence of *N*-methylmorpholine gave salts **89**, which were further converted into 6-amino-3,5-dicyano-1,4-dihydropyridine-4-spiro-1'-cyclohexane-2-thione (**90b**) or -selone (**90c**), respectively, upon treatment with HCl (entry 9).^{52, 117–119} Similar spiro-fused 6-aminothiolates **91** were prepared from ethyl cyclopentylidenecyanothioacetamide (**92**);¹²⁰ 6-oxothiolates **93** were obtained from ethyl cyclopentylidenecyanoacetate (**94**) (entry 10).¹²¹

Mention should also be made of α,β-unsaturated nitriles, which, by virtue of their high availability and high reactivity, are widely employed in the synthesis of pyridinechalcogenones, of their spiro-fused derivatives, in particular. Thus compounds **89c** and **90c** were obtained from cyclohexylidenemalononitrile (**95**) and selenoacetamide **60c** (Table 1, entry 11).^{52, 117–119} Refluxing of cyanoacetamide (**60a**) and dicyanomethylidenecoumarin **96** in ethanol in the presence of piperidine gave the adduct **97**, which underwent intramolecular cyclisation *in situ* into spiropyridine-chalcogenone **98** (Table 1, entry 12).⁸⁶

Regioselective syntheses of isomeric 3-cyano-4(6)-methyl-6(4)-phenylpyridine-2(1*H*)-thiones are documented.^{122, 123} The isomer containing a phenyl group at position 4 (compound **99**) is formed in the reaction of (cyano)thioacetamide (**60b**) with acetylenic ketone **100** (entry 13). However, the reaction with enamino ketone **101** derived from alkyne **100** gave 6-phenylpyridinethione **102** (entry 14). Similarly, enamino ketone **103** gave tetrahydroquinolinethione **104** (example 15).³⁵

1,3-Dicarbonyl compounds and their derivatives, *e.g.*, the above-mentioned enamino ketones **101** and **104**, are successfully employed in the synthesis of 3-cyanopyridine-2(1*H*)-chalco-

genones. Reactions of cyanothioacetamide (**60b**) with sodium enolates of 2-formylcycloalkanones are known to yield pyridine-2(1*H*)-thiones **105** and **106** (Table 1, entry 16).¹²⁴ Reactions of 1,3-diketones **107** with cyanothio(seleno)acetamides (**60b,c**) gave high yields of substituted 3-cyanopyridine-2(1*H*)-thiones (**65b**) and -selones (**65c**) (entry 17).^{34, 89, 125–127} In the presence of bases, a similar reaction of cyclic diketones **108** occurs with high regioselectivity and affords 4,5-polymethylene-3-cyanopyridine-2(1*H*)-thiones(selones) **109** (Table 1, entry 18).^{93, 128, 129}

Different approaches to the synthesis of substituted isomeric trifluoromethylpyridine-2(1*H*)-thiones **110** (Table 1, entry 19) and **111** (entry 20) have been developed. These included the reaction of trifluoromethyl derivatives **112** with (cyano)thioacetamide (**60b**) or the reaction of 4-methoxy-1,1,1-trifluoropent-3-enone (**113**) first with EtONa and then with amide **60b**.^{53, 83, 130–134} The yields reach 90% in both cases.

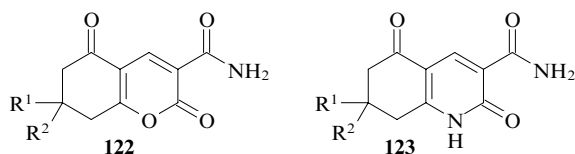
It is of note that the range of substituents in pharmacologically promising 3-cyano-4-trifluoromethylpyridine-2(1*H*)-thiones is limited by the availability of the starting 1,3-dicarbonyl compounds carrying a trifluoromethyl group. To overcome this limitation, it has recently been proposed to synthesise substituted 3-cyano-4-trifluoromethylpyridine-2(1*H*)-thiones **110** from sodium enolates of trifluoromethyl-1,3-diketones **114** (Table 1, entry 21).³⁰ The latter were prepared by coupling of methylene ketones **115** with ethyl trifluoroacetate; the free 1,3-diketone was introduced without isolation into the reaction with (cyano)thioacetamide (**60b**). The role of the starting methylene ketones was played by dialkyl-, alkylaryl-, hetaryl ketones and five–eight-membered cycloalkanones; in some cases, the yields of pyridine-thiones **110** reached 98%.¹⁷

The reaction of (cyano)thioacetamide (**60b**) with 3-benzylidenecoumarin (**116**) was studied.⁴⁵ It was thiol **117** that was the condensation product (Table 1, entry 22), although no such prototropic tautomer is known for other compounds of this series.⁸

The reaction of 3-arylideneacetylacetone **118** with amide **60b** in ethanol in the presence of piperidine yielded thiolates **119**;

treatment of the latter with HCl resulted in their conversion into thiones **120** possessing neurotropic activity (entry 23).⁹⁷

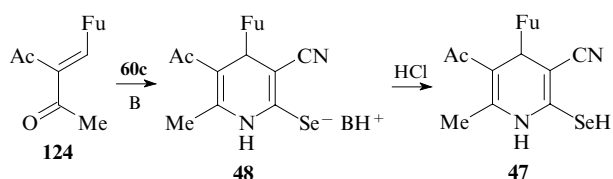
Reactions of 2-dimethylaminomethylidenecyclohexane-1,3-diones **80** with cyanoacetamide (**60a**) in THF in the presence of NaOH yielded a mixture of quinolinecarbonitriles **121** (entry 24) and benzopyrancarboxamides **122**.¹³⁵ Only quinoline-3-carboxamides **123** were obtained in high yields upon change in the solvent (refluxing of the reaction mixture in absolute ethanol).



$R^1 = \text{H, Me}; R^2 = \text{H, Me, Ph.}$

Thus, numerous examples of the use of cyano(thio,seleno)-acetamides in the synthesis of 3-cyanopyridinechalcogenones listed in Table 1 illustrate the versatility of this approach.

In some cases, the same compounds can be prepared by varying the reactants. For example, the reaction products of acetylacetone with 2-furfurylideneacyanoselenoacetamide **44a** considered above (see Section II.3.b) were also synthesised under mild conditions (abs. EtOH, 20 °C) from 2-furfurylideneacetylacetone (**124**) and (cyano)selenoacetamide (**60c**) in the presence of *N*-methylmorpholine.^{52, 82} Ethyl benzylidene- and 2-furfurylideneacetoacetates react similarly with amide **60c**.^{52, 136–138}

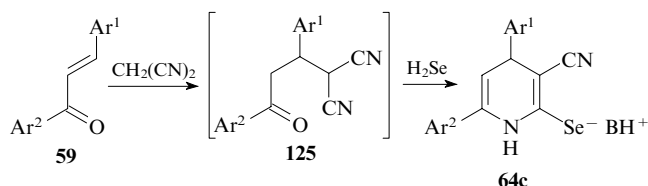


3,5-Dicyano-6-oxo-1,4,5,6-tetrahydropyridine-4-spiro-1'-cyclopentane-2-thiolate (**93**) is formed in the reaction of cyclopentylidene(cyano)thioacetamide **92** with amide **69b** (see Table 1) or ethyl cyanoacetate.¹²¹

Reactions of bis-nucleophiles with bis-electrophiles were described in the foregoing sections. However, each of the reactants

undergoing cyclisation to give the pyridine system can simultaneously contain electrophilic and nucleophilic sites. In this case, the role of a two-carbon fragment is played by CH-acids (*e.g.*, malononitrile, ethyl cyanoacetate, acetoacetanilide, *etc.*).

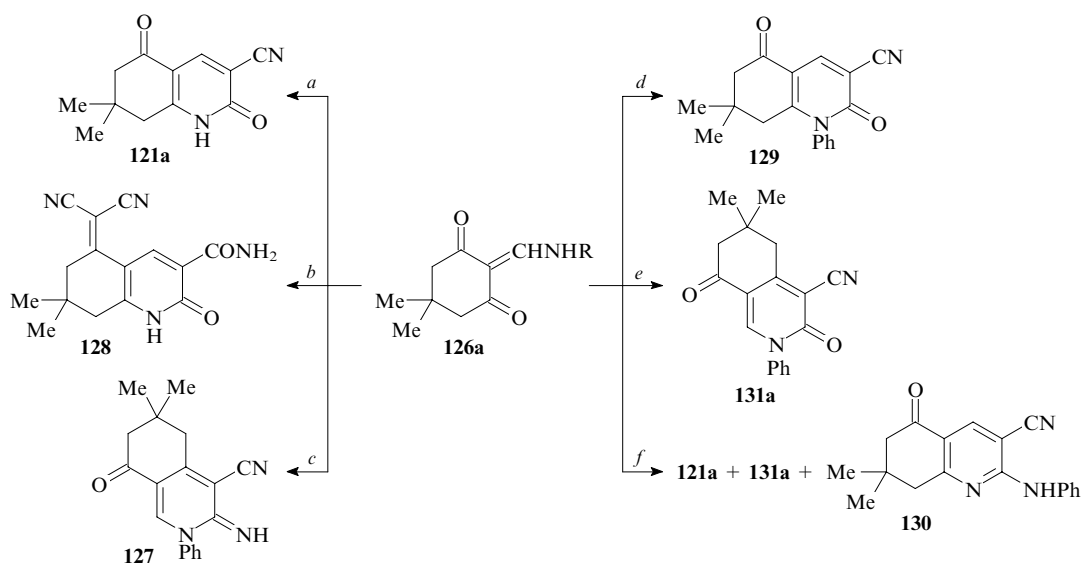
Several examples of the use of malononitrile in the formation of the pyridine ring have been described. Reactions of chalcones **59** with malononitrile yield δ -keto dinitriles **125**, which give selenolates **64c** upon treatment with hydrogen selenide. The latter can further be converted into compounds **65c** and **66c** (see above).



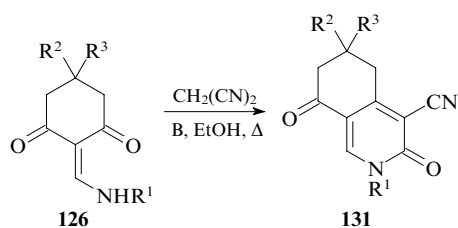
The synthesis of hydrogenated 3-cyanoquinolin-2-ones by the reaction of malononitrile with 2-aminomethylidenecyclohexane-1,3-diones was studied in detail. It is of note that the direction of this reaction strongly depends on the reactant ratio and the nature of the catalyst and the solvent. Thus refluxing of 2-anilinomethylidene-5,5-dimethylcyclohexane-1,3-dione (**126a**) with an equimolar amount of malononitrile in ethanol in the presence of KOH gave 3-cyano-7,7-dimethyl-1,2,5,6,7,8-hexahydroquinoline-2,5-dione (**121a**)^{139, 140} (Scheme 1), while the reaction in the presence of a two-fold excess of malononitrile yielded 4-cyano-3-imino-6,6-dimethyl-2-phenyl-2,3,5,6,7,8-hexahydroisoquinolin-8-one (**127**) under identical conditions.^{139, 141} The reaction with a two-fold excess of malononitrile and piperidine as a catalyst in ethanol afforded 3-carbamoyl-5-dicyanomethylidenequinolin-2-one (**128**),¹³⁹ while the reaction in DMF in the presence of KOH resulted in *N*-phenyl-substituted 3-cyanoquinolin-2-one **129**.¹⁴² With equimolar amounts of the reactants in the presence of an excess of morpholine, compounds **121a**, **130** and **131a** were obtained in yields of 46%, 25% and 17%, respectively.¹¹⁴ In the absence of a catalyst, this reaction yielded exclusively quinolinone **121a**.

Reactions of compounds **126** bearing other substituents with a small excess of malononitrile were carried out by 1-hour refluxing in ethanol in the presence of catalytic amounts of morpholine to yield exclusively isoquinolinones **131**.¹¹⁴

Scheme 1

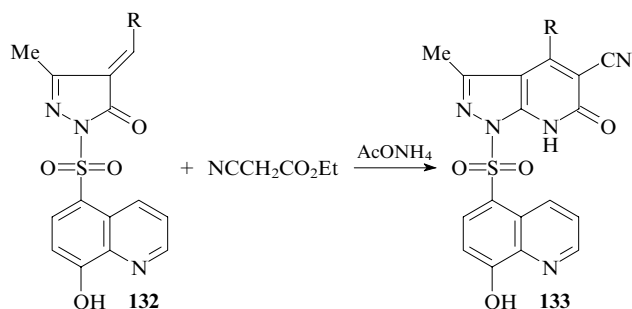


(a) $\text{CH}_2(\text{CN})_2$ (1 equiv.), KOH, EtOH, Δ ; (b) $\text{CH}_2(\text{CN})_2$ (2 equiv.), KOH, EtOH, Δ ; (c) $\text{CH}_2(\text{CN})_2$ (2 equiv.), Pip, EtOH; (d) $\text{CH}_2(\text{CN})_2$ (2 equiv.), KOH, DMF; (e) $\text{CH}_2(\text{CN})_2$ (excess), morpholine (cat.), EtOH, Δ , 1 h; (f) $\text{CH}_2(\text{CN})_2$ (1 equiv.), morpholine (excess), EtOH, Δ , 1 h.



$\text{R}^1 = \text{Me, Ph; R}^2, \text{R}^3 = \text{H, Me, Ph; B}$ is morpholine.

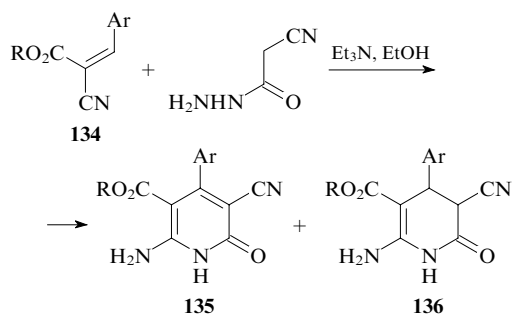
Let us consider a non-trivial example of a reaction of 5-hetarylsulfonyl-8-hydroxyquinolines **132** with ethyl cyanoacetate in the presence of ammonium acetate, which afforded a new heterocyclic system **133**.¹⁴³



$\text{R} = \text{Alk.}$

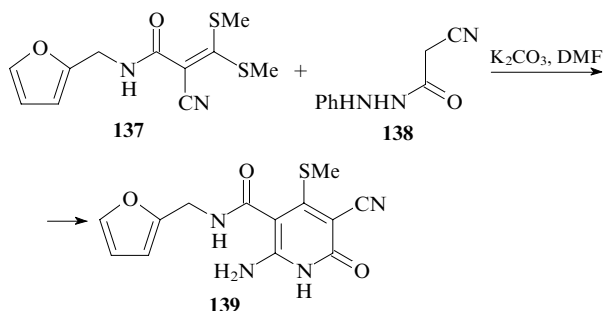
A method for the synthesis of 3,4-dihydropyridine-4-spiro-1'-cyclohexane-2(1*H*)-thione by the reaction of amide **32** with acetoacetanilide in ethanol in the presence of *N*-methylmorpholine (yield 87%) has been described.^{52, 144}

Alkylarylidencyanoacetates **134** reacted with cyanoaceto-hydrazide in boiling ethanol in the presence of triethylamine or piperidine to give pyridones **135** in > 80% yields.¹⁴⁵ However, at room temperature this reaction gave, along with pyridones **135**, 3,4-dihydropyridin-2(1*H*)-ones **136**.^{146–148}



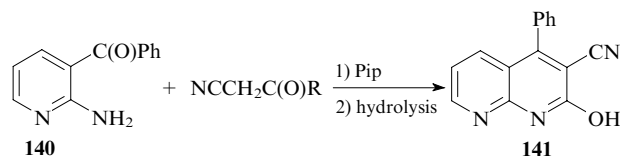
$\text{Ar} = 4\text{-XC}_6\text{H}_4$ ($\text{X} = \text{H, Me, Cl, NO}_2$).

The reaction of *N*-furfurylacrylamide **137** with *N*'-phenylcyanoaceto-hydrazide **138** gave functionalised 3-cyanopyridone **139**.¹⁴⁹



In all the above-cited reactions of the pyridine ring closure, the N–C(6) bond was formed along with the C(3)–C(4) bond.

However, there is only one example of the formation of the N–C(2) bond, *viz.*, condensation of 2-amino-3-benzoylpyridine (**140**) with cyanoacetic acid derivatives. Subsequent hydrolysis gives 3-cyano-2-hydroxy-1,8-naphthyridine **141**.¹⁵⁰



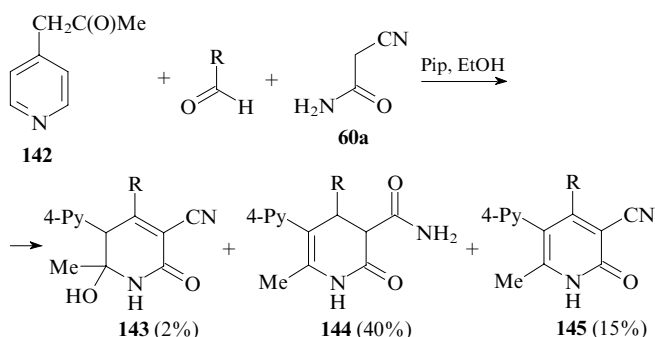
$\text{R} = \text{NH}_2, \text{OMe, OEt.}$

Thus, this method for the preparation of 3-cyanopyridine-2-chalcogenones is represented by the largest number of examples. Presumably, it is the most efficient approach to the synthesis of this class of compounds.

4. Synthesis of the pyridine ring from three fragments

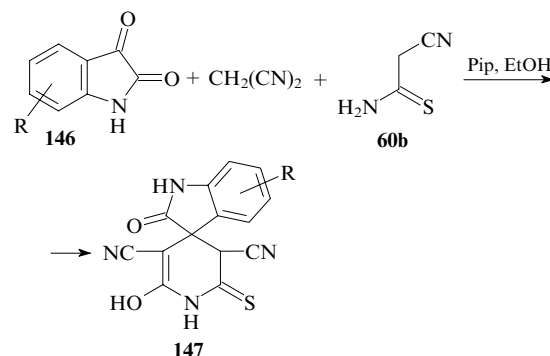
Among other approaches to the synthesis of pyridine chalcogenones, multicomponent condensations (cascade heterocyclisation) have recently gained increasing popularity. For example, three-component condensation (1 + 2 + 2), which consists of reactions of aliphatic, aromatic or heteroaromatic aldehydes with 1,3-dicarbonyl compounds and cyano(thio,seleno)acetamides **60a–c**, is often used in the synthesis of substituted 3-cyanopyridine-2(1*H*)-thiones.^{7, 8, 17, 22, 125, 151–154} In this section, aldehydes and isatins are considered as examples of one-carbon fragments, while substituted acetone, malononitrile and pyridinium ylides, as fragments forming the C(5)–C(6) bond in the pyridine ring. In all these cases, cyanoacetamides **60a,b** were used as nitrogen, C(2) and C(3) sources.

Thus condensation of 4-pyridylacetone (**142**) with aldehydes and cyanoacetamide (**60a**) gave a mixture of pyridones **143–145**, which were separated by crystallisation.¹⁵⁵



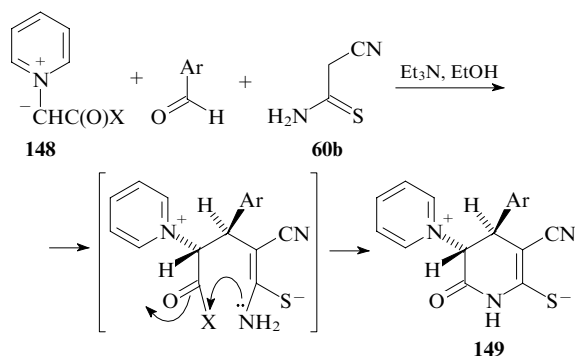
$\text{R} = \text{Ar, Het.}$

Substituted isatins **146** reacted with malononitrile and (cyano)thioacetamide **60b** in ethanol in the presence of piperidine. This afforded spiro derivatives **147**, which represent the hydrolysis products of the intermediate 6-iminopyridine-2-thiones and which are difficult to prepare by other methods.¹⁵⁶



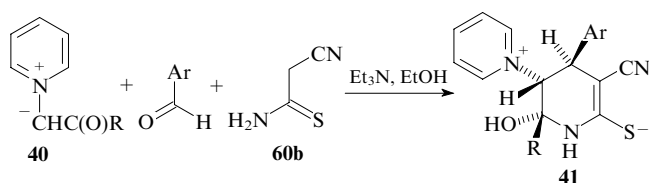
As is known, pyridinium ylides generated *in situ* from quaternised pyridines are widely and successfully employed in organic

synthesis,^{155–158} particularly for the preparation of substituted 3-cyanopyridine-2(1*H*)-thiones. Simple procedures for their synthesis were developed on the basis of the three-component coupling methodology.^{17, 51, 58–62, 64–66, 159–163} Thus reactions of pyridinium ylides **148** with aromatic aldehydes and cyanothioacetamide (**60b**) in ethanol in the presence of triethylamine proceeded in a regio- and stereoselective manner and afforded hydrogenated *trans*-4-aryl-3-cyano-5-pyridiniumpyridine-2-thiolates **149** in high yields.^{51, 58–61}



X = NH₂, OAlk; Ar = 4-YC₆H₄ (Y = HO, MeO, F, Cl, Br), 3-Py.

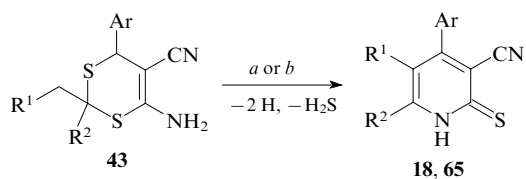
The synthesis of the aforementioned thiolates **41** (see Section II.3.b) was also accomplished using three-component condensation of pyridinium ylides **40**, (cyano)thioacetamide (**60b**) and aromatic aldehydes.^{58, 64, 160}



R = Me, Ph, cyclo-C₃H₅; Ar = XC₆H₄ (X = H, 4-MeO, 4-NO₂, 2-F, 4-F, 4-Br), 3-Py.

5. Ring transformation reactions

The formation of the pyridine ring from other heterocycles represents a non-trivial approach to the synthesis of 3-cyanopyridine-2(1*H*)-thiones. Originally, this method was used for the preparation of pyridines annulated with a five- or six-membered ring at positions 5 and 6.^{67, 69} Thus 4-amino-6-aryl-5-cyano-1,3-dithiacyclohex-4-enes **43** spiro-fused with cycloalkanes [R¹–R² = (CH₂)_n, n = 3, 4] were used in the synthesis of the corresponding 5,6-polymethylene-3-cyanopyridine-2(1*H*)-thiones **18**. This transformation occurs upon short-term heating of the reactants in pyridine or DMF (conditions *a*). This reaction follows a complex mechanism⁷¹ and is accompanied by a loss of two hydrogen atoms and H₂S. Later, this reaction was extended⁷² to non-spirocyclic 1,3-dithiacyclohex-4-enes **43** (R¹ = H, Me; R² = Me), which underwent ring transformation into pyridine-thiones **65** upon heating in methanol or DMF in the presence of a base [diethylamine or morpholine (conditions *b*)]. The yields were moderate in all cases.

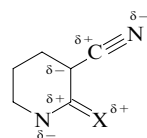


R² = Me: R¹ = H, Me (**65**); R¹–R² = (CH₂)_n (n = 3, 4) (**18**);
Ar = RC₆H₄ (R = H, 2-F, 4-F, 4-Cl, 4-Br, 4-MeO), 3-Py.

Thus, the above-cited examples of the construction of 3-cyanopyridine-2-chalcogenone derivatives demonstrate the high promise in the development of novel approaches to their synthesis, on the one hand, and enable the prediction of novel trends in this branch of heterocyclic chemistry, on the other hand.

III. Reactivity and chemical transformations

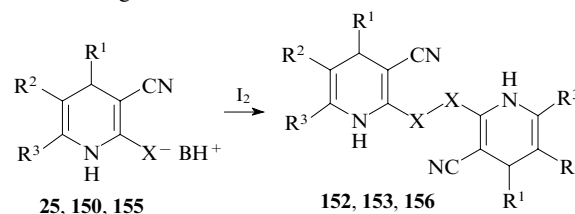
Chemical properties of 3-cyanopyridine-2-chalcogenones have been the subject of intensive studies over the last 15–20 years. Their main fragment [NC–C–C(X)N–] contains four nucleophilic and two electrophilic sites.



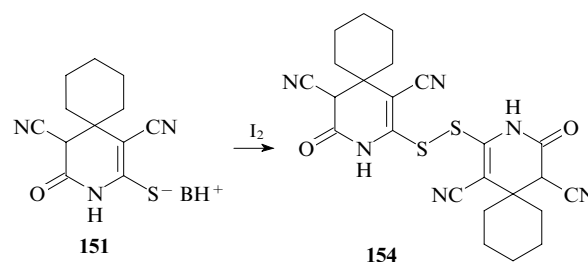
Two vicinal reactive functional groups (the nitrile group and the thio(seleno)amide group incorporating an endocyclic nitrogen atom) possess different properties: addition reactions are characteristic of the former, while the latter reacts with electrophilic reagents. The interest in such systems is caused by two main reasons: the possibility of their transformations into functionalised pyridines possessing valuable characteristics and their use as building blocks in the synthesis of fused heterocycles. 3-Cyanopyridine-2-chalcogenones are promising synthons for complex heterocyclic systems containing a pyridine fragment, *e.g.*, furo-(pyrazolo, thieno, selenopheno)pyridines, pyridothienopyridines, pyridothienopyrimidines and other annulated heterocycles manifesting a broad range of biological activities. The chemical transformations of some 3-cyanopyridine-2-chalcogenones are described below. The primary attention is given to reactions of partially hydrogenated derivatives with halogens and alkylating reagents as well as to heterocyclisation reactions. Dehydrogenation reactions were considered in the previous section in relation to discussion of the methods for the synthesis of these compounds.

1. Reactions with halogens

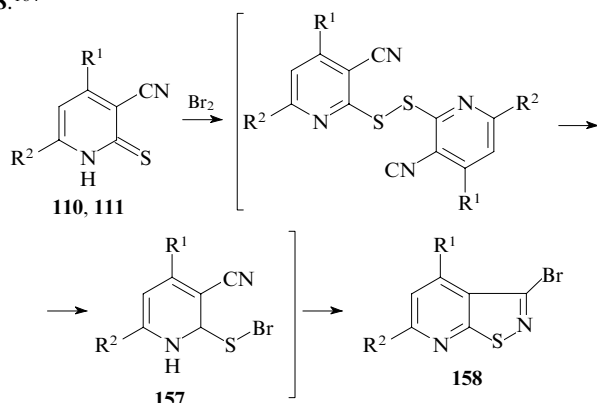
Reactions of some thiolates with elemental iodine have been studied.^{52, 72, 151} It was found that treatment of salts **25** and **150** and the spiro-fused 6-oxothiolate **151** with iodine in ethanol in the presence of alkali afforded the corresponding disulfides **152–154** in high yields together with small amounts of dehydrogenation products. Such disulfides are usually formed upon oxidation of the corresponding thiones by atmospheric oxygen. Similarly, selenolate **155** gave diselenide **156**.



X = S: R¹ = 2-ClC₆H₄, R² = NC, R³ = H₂N (**150, 153**);
R¹ = 2-ClC₆H₄, 2-Fu; R² = PhNHC(O), R³ = Me (**25, 152**);
X = Se, R¹ = 2-ClC₆H₄, R² = EtO₂C, R³ = Me (**155, 156**).



Bromination of trifluoromethyl-substituted 3-cyanopyridine-2(1*H*)-thiones **110** and **111** also proceeded *via* the corresponding disulfides. However, under the reaction conditions the latter were converted into bromides **157**, which cyclised into isothiazoles **158**.¹⁶⁴

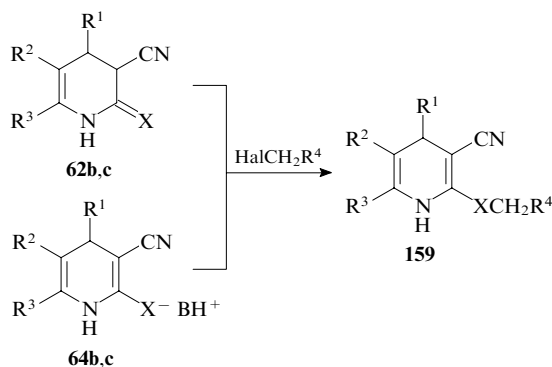


$\text{R}^1 = \text{CF}_3$, $\text{R}^2 = \text{Me}$ (**110**); $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{CF}_3$ (**111**).

2. Alkylation

Numerous recent publications on the reactivities of 3-cyanopyridine-2(1*H*)-chalcogenones deal with different aspects of alkylation of sulfur- and selenium-containing derivatives. Reactions with alkylating reagents may involve two nucleophilic sites due to ambident character of the $\text{HN}-\text{C}(\text{X})$ fragment ($\text{X} = \text{S}, \text{Se}$) of these heterocycles. As a rule, reactions with alkyl halides and activated halides (α -halogenocarbonyl compounds) in the presence of bases involve the chalcogen atom.

Numerous studies have shown (see, for example, Refs 7, 15, 43, 48, 50–52, 103–106, 165–176) that the alkylation of 3,4-dihydropyridinechalcogenones **62b,c** or their salts **64b,c** with alkyl



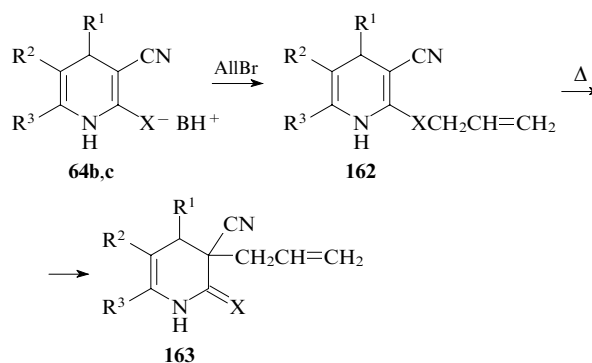
$\text{R}^1, \text{R}^2, \text{R}^3 = \text{H}, \text{Alk}, \text{Ar}, \text{Het}$; $\text{R}^4 = \text{Alk}$; $\text{X} = \text{S}, \text{Se}$;

B is *N*-methylmorpholine.

halides is regioselective and results in 2-alkylthio(seleno)-1,4-dihydropyridines **159**.

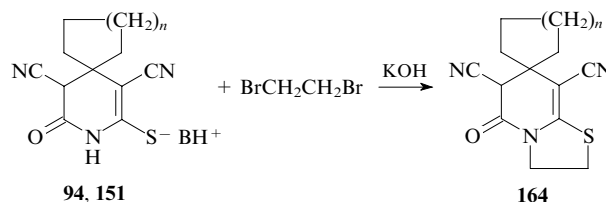
Reactions of betaines **41** with alkyl halides in ethanol or DMF (in the absence of bases) gave 6-alkylthiotetrahydropyridine salts **160**.^{47, 51} However, heating of betaines **41** with allyl bromide in ethanol and subsequent prolonged storage of the reaction mixture at room temperature gave a [3,3]-sigmatropic rearrangement product, *viz.*, compound **161** as a mixture of two epimers (Scheme 2).

A [3,3]-sigmatropic rearrangement of 2-allylthio(seleno)-1,4-dihydropyridines **162** into 3-allyl-3,4-dihydropyridinechalcogenones **163** also occurred in the alkylation of salts **64b,c** with allyl bromide.^{7, 52, 57, 120, 136, 177–179} However, in contrast with analogous transformations of aromatic allyloxy(thio)pyridines and -quinolines,^{180–182} this reaction was regioselective: the yields of compounds **163** reached 98%.



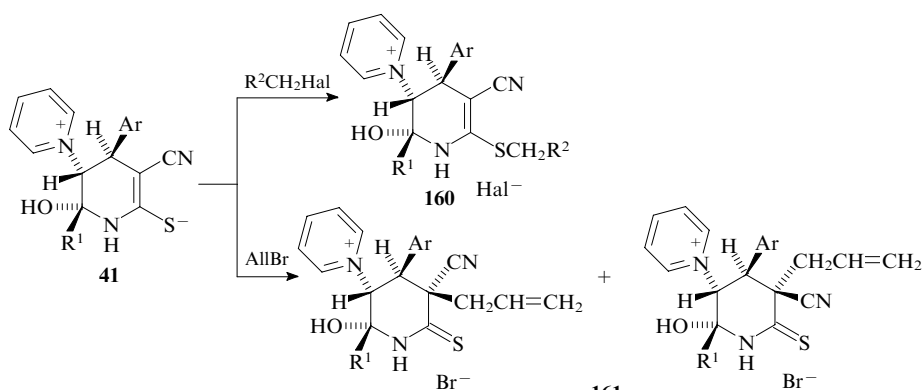
$\text{R}^1, \text{R}^2, \text{R}^3 = \text{H}, \text{Alk}, \text{Ar}$; $\text{X} = \text{S}, \text{Se}$.

A convenient method for the synthesis of hitherto unknown spiro-fused heterocyclic systems (6,8-dicyano-5-oxo-2,3,6,7-tetrahydro-5*H*-thiazolo-[2,3-*a*]pyridine-7-spiro-1'-cycloalkanes, **164**) has been developed.^{52, 118, 121, 183} It includes alkylation of thiolates **94** and **151** with 1,2-dibromoethane in DMF at room temperature.



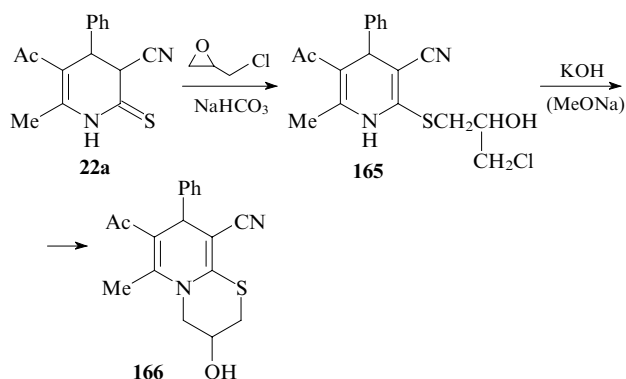
$n = 1$ (**94**), 2 (**151**).

Reaction of sulfide **22a** with epichlorohydrin yielded thione **165**, which underwent cyclisation into pyridothiazine **166** upon treatment with ethanolic KOH or MeONa .¹⁸⁴

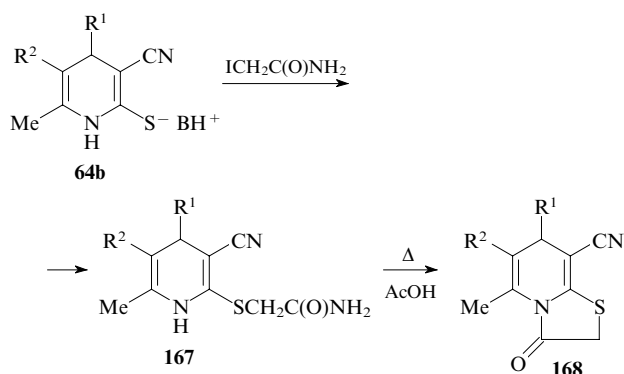


$\text{R}^1, \text{R}^2 = \text{Alk}$; $\text{Ar} = \text{Ph}, 2\text{-NO}_2\text{C}_6\text{H}_4$.

Scheme 2

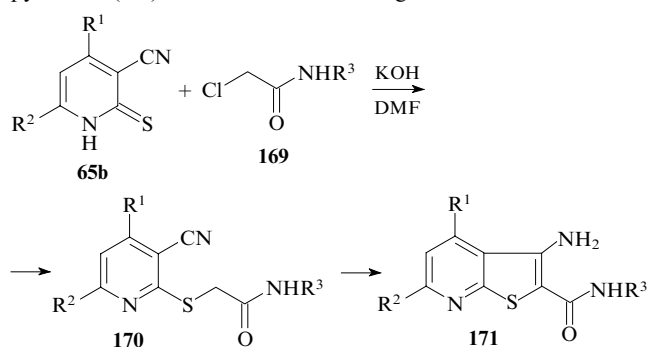


Haloacetic acid derivatives (amides and chlorides) were also studied as alkylating agents. Thus salts **64b** ($R^3 = \text{Me}$) reacted with iodoacetamide in ethanol to give sulfides **167**. The latter underwent intramolecular cyclisation into 3-oxo-2,3-dihydro-7H-thiazolo[3,2-a]pyridines **168** upon refluxing in acetic acid. The yields depended on the nature of the substituent at position 4 of the pyridine ring: for $R^1 = 4\text{-Py}$, the yields were 70%–85%, while its replacement by the aryl substituent ($R^1 = 4\text{-ClC}_6\text{H}_4$) resulted in a significant reduction of the product yield (down to 25%).¹⁸⁵

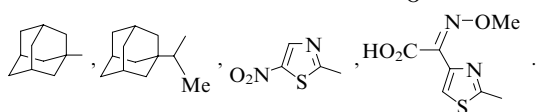


$R^1 = 4\text{-Py}$, $4\text{-ClC}_6\text{H}_4$; $R^2 = \text{Ar}$, Het.

N-Substituted chloroacetamides **169** are currently successfully employed as alkylating agents in the synthesis of novel 3-cyanopyridine-2(1*H*)-thiones.¹⁶⁴ A broad range of such derivatives were

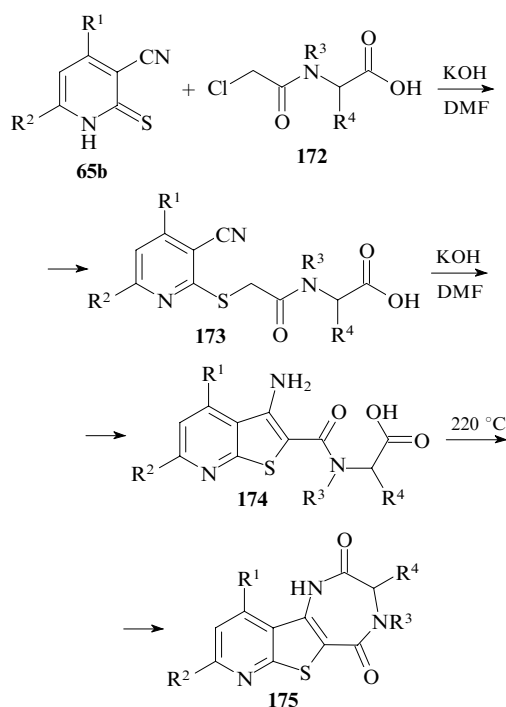


$R^1, R^2 = \text{Alk}$, Ar, Het; $R^3 = \text{Pr}^i$, cyclo- C_3H_7 , Bn, $\text{X}_n\text{C}_6\text{H}_{5-n}$ (X = 4-F, 3-F₃C, 3,4-(MeO)₂, 3,4-OCH₂O);



obtained by condensation of chloroacetyl chloride with pharmacologically active amines (*e.g.*, α -phenylethylamine, remantadine, *etc.*). Chloroacetamides **169** reacted with pyridinethiones **65b** in DMF or EtOH in the presence of KOH. Both compounds **170** and the respective intramolecular cyclisation products (substituted thienopyridines **171**) were obtained in high yields.

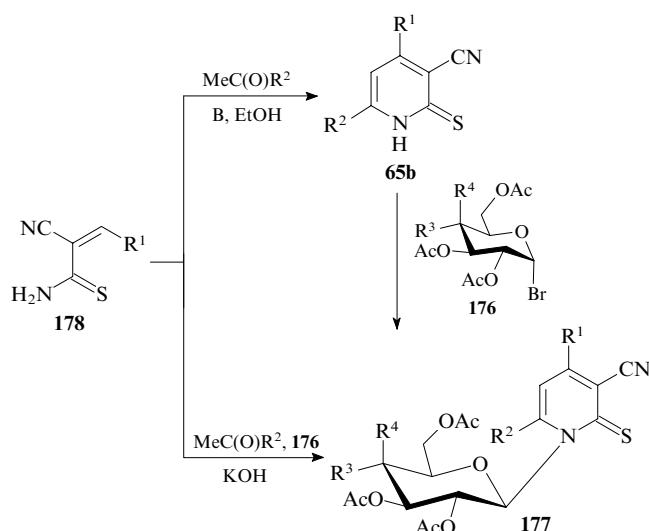
The alkylation reaction was used for the introduction of α -amino acid fragments into 3-cyanopyridine-2(1*H*)-thiones.¹⁶ Thus chloroacetamides **172** prepared by condensation of chloroacetyl chloride with amino acids reacted with pyridinethiones **65b** to give the alkylation products **173**. The latter cyclised under the reaction conditions into thienopyridines **174** analogous to the above-mentioned compounds **171**. However, thienopyridines **174** contained an ω -carboxy group at position 2 rather than the carbamide group, which enabled their intramolecular cyclisation into 4-dihydro-1*H*-pyrido[3',2':4,5]thieno[2,3-*e*][1,4]diazepine-2,5-diones **175** upon heating.



$R^1, R^2 = \text{Alk}$, Ar, Het; $R^3 = \text{H}$; $R^4 = \text{H}$, Me, Pr^i , Bn; $R^3-R^4 = (\text{CH}_2)_3$.

1-Bromomethylcarborane can also be used as an alkylating agent.^{186, 187}

All the reactions of 3-cyanopyridine-2(1*H*)-thiones with the above-considered electrophilic agents involve the chalcogen atom (sulfur or selenium); the alkylation at the nitrogen atom of the pyridine ring was described in only few cases (see Refs 188–190). This can be explained in terms of the hard and soft acids and bases theory. Whereas soft electrophiles react at the sulfur atom, reactions with harder reagents involve the nitrogen atom. In the presence of aqueous KOH, 2,3,4,6-tetra-*O*-acetyl- α -D-glucopyranosyl bromides **176** react with cyanopyridinechalcogenones **65b** to yield *N*-glycosides **177**. The latter can be prepared in one step starting from cyanothioacetamides **178**, glycosyl bromides **176** and ketones.¹⁹⁰



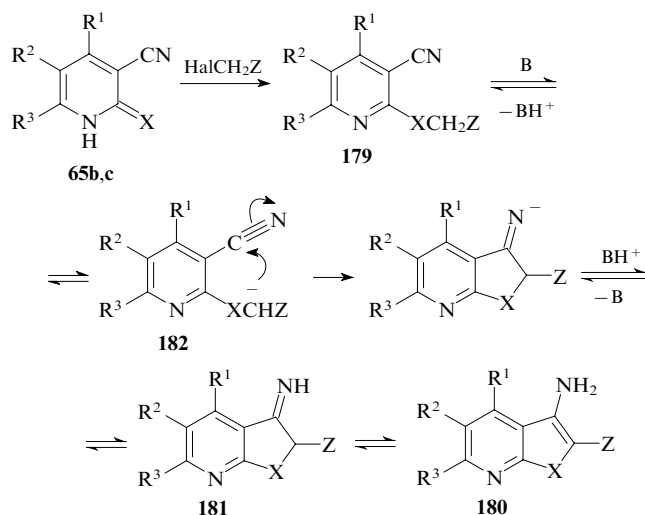
$R^1, R^2 = \text{Me, Et, Ph}; R^3 = \text{H}, R^4 = \text{OAc}; R^3 = \text{OAc}, R^4 = \text{H}.$

For other aspects of alkylation reactions of pyridinechalcogenones, see Refs 3, 5, 7 and 8.

3. Heterocyclisation

In addition to the aforementioned studies of chemical properties of pyridinechalcogenones, heterocyclisation of their functional derivatives is of the greatest interest as one of the most promising approaches to the synthesis of fused heterocyclic systems containing a pyridine fragment (see, for example, Refs 7, 20–22, 52, 83, 105, 108, 167, 173, 176, 178, 191–200).

Thus the Thorpe–Ziegler cyclisation of 2-alkylthio(seleno)-3-cyanopyridines **179** prepared by alkylation of 3-cyanopyridine-2-chalcogenones (**65**) in DMF or ethanol in the presence of a base gives thieno(selenopheno)-[2,3-*b*]pyridines **180**. The reaction mechanism can be presented by the following sequence:^{11, 201}



$R^1, R^2, R^3 = \text{Alk, Ar, Het}; X = \text{S, Se};$
Z is an electron-withdrawing group.

It was found that the equilibrium between the tautomeric forms $\mathbf{180} \rightleftharpoons \mathbf{181}$ is virtually completely shifted towards the amine **180**. The electron-withdrawing effect of the substituent Z, which determines the stability and the concentration of the carbanion **182**, is the rate-limiting factor of this cyclisation. The following order of activities of substituents Z was empirically established:^{8, 11} $\text{NO}_2 > \text{ArC(O)} > \text{CN} > \text{CO}_2\text{Alk} > \text{C(O)NH}_2 > \text{H}.$

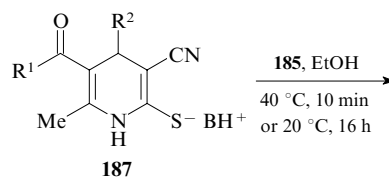
The substituent Z that imparts sufficiently high CH-acidity on the SCH_2Z fragment of compound **179** and stabilises anion **182** usually represents a π -acceptor; only one example of a reaction involving a σ -withdrawing group (the carborane fragment) is documented.¹⁸⁷

The cyclisation is usually carried out in the presence of bases; acid catalysis is used less often. Systems KOH–EtOH , $\text{K}_2\text{CO}_3\text{–EtOH}$, EtONa–EtOH , $\text{K}_2\text{CO}_3\text{–DMF}$, less often $\text{Na}_2\text{CO}_3\text{–EtOH}$, MeONa–EtOH , $\text{KOH–EtOH–H}_2\text{O}$, AcONa–EtOH (abs.) , $\text{Et}_3\text{N–EtOH}$, $\text{K}_2\text{CO}_3\text{–Me}_2\text{CO}$, $\text{Et}_3\text{N–dioxane}$, $\text{Et}_3\text{N–DMSO}$, are generally employed. Bases are used in both stoichiometric and catalytic amounts. Spontaneous formation of thienopyridines in the alkylation of thiones **65b** in the presence of equimolar amounts of the base has been observed in some cases; no intermediate products could be isolated. As a rule, the reaction is carried out at room temperature, although in some cases heating can be required. There are some examples of cyclisation in boiling ethanol^{202, 203} or under phase-transfer catalysis conditions with Bu_4NBr used as the catalyst.^{204, 205}

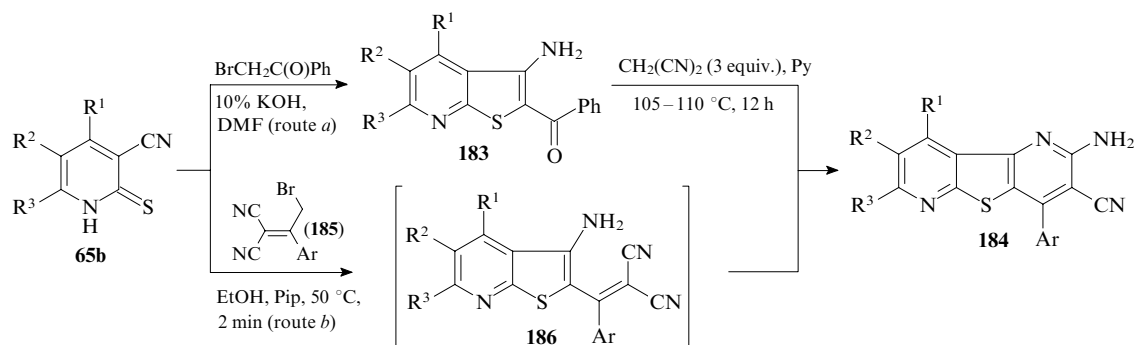
It is of note that the synthesis of thienopyridines is most often based on the cyclisation of 2-alkylthio-3-cyanopyridines that are conventionally prepared from 3-cyano-pyridine-2(1*H*)-thiones **65b** (or the corresponding thiolates) and an alkylating agent containing an electron-withdrawing substituent in the α -position relative to the halogen atom. This can also be achieved by multicomponent cascade heterocyclisation, which allows an access to pyridinechalcogenones from simple and readily available acyclic precursors in a one-pot procedure.² This strategy served as a basis for the synthesis of thienopyridines and related systems, *e.g.*, derivatives of quinoline, isoquinoline, benzo[*b*]quinoline, pyrano- and thiopyranopyridines, benzothiopyranopyridine, pyridopyridines (naphthyridines) and other fused heterocycles; the bibliography on the subject includes over 170 references (see the monograph¹⁹⁹).

Among numerous examples of this synthesis, special mention should be made of a successful solution of the problem of construction of substituted pyridothienopyridines which is based on the cascade conversions of some 3-cyanopyridine-2(1*H*)-thione derivatives.^{206, 207} On the whole, this type of heterocyclisation has a number of advantages over classical Friedlander annelation, since cascade reactions proceed faster and under less drastic conditions and ensure high yields of target products in one step. Thus the alkylation of thiones **65b** is accompanied by the Thorpe ring closure resulting in thienopyridines **183**; prolonged refluxing of the latter in the presence of the excess of malononitrile affords tricyclic Friedlander cyclocondensation products, *viz.*, compounds **184** (route *a*, yields 67%–75%). Compounds **184** can be prepared in 2 min from the same cyanopyridinethiones **65b** and 2-aryl-3-bromo-1,1-dicyanopropenes **185** (route *b*, yields 57%–95%); in the latter case, the intermediate thienopyridine **186** is not usually isolated from the reaction mixture, but is subjected to cyclisation *in situ* (Scheme 3).

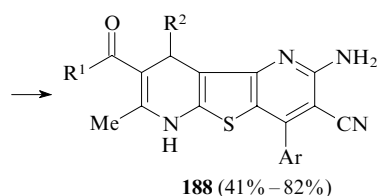
Later, the approach based on the use of bromides **185** was used in the synthesis of other dipyrrothiophenes.^{208, 209} For the first time, thiolates **187** were used as starting materials for the synthesis of 6,9-dihydropyrido [3',2':4,5]thieno[3,2-*b*]pyridines **188**. It is of note that in this case the cascade heterocyclisation occurs spontaneously in the absence of a basic catalyst.²⁰⁸



Scheme 3



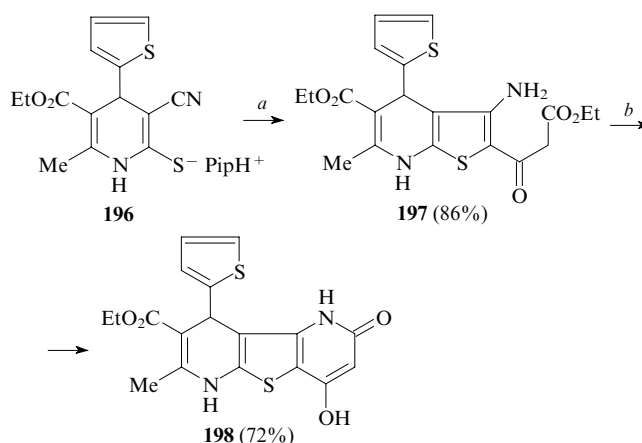
Ar = Ph, 4-BrC₆H₄; R¹ = H, Me, Ph; R² = H; R³ = Me, Ph; R²–R³ = (CH₂)_n (n = 3, 4).



R¹ = EtO, Me; R² = 4-MeOC₆H₄, 2-NO₂C₆H₄, 2-thienyl;
Ar = 4-BrC₆H₄.

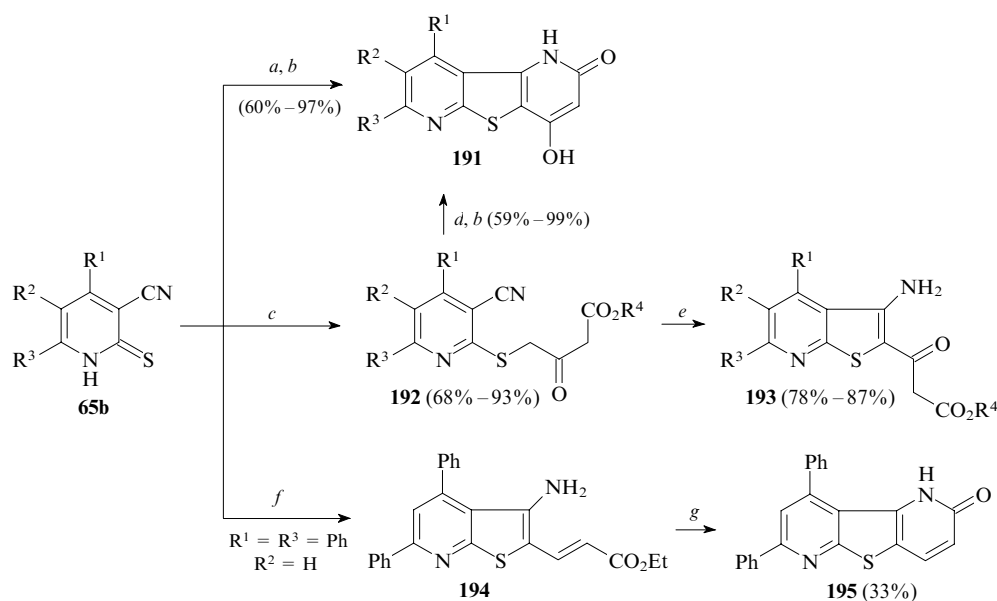
Among other alkylating agents used in heterocyclisation reactions that yield fused thienopyridine derivatives, alkyl γ -chloroacetoacetates **189**^{17, 210–213} and ethyl 4-bromocrotonate are worthy of mention (**190**).^{177, 208} Some aspects of the use of compounds **189** and **190** in the synthesis of heterocycles are detailed in the review.²¹⁴ The cascade heterocyclisation of substituted pyridine-2(1*H*)-thiones **65b** and γ -chloro β -oxo esters **189** in boiling ethanol in the presence of KOH or EtONa is the most efficient procedure for the preparation of dipyridothiophenes **191**. If the reaction is carried out under mild conditions, the intermediates, *i.e.*, pyridine **192** and thieno[2,3-*b*]pyridine **193**, can be isolated; they easily cyclise in the presence of bases into the target products **191**.²¹¹ Thienopyridine **194** prepared by the reaction of thione **65b** (R¹ = R³ = Ph, R² = H) with crotonate **190** was similarly converted into dipyridothiophene **195** (Scheme 4).¹⁷⁷

The reaction of piperidinium 1,4-dihydropyridine-2-thiolate **196** with the ester **189** (Alk = Et) gave the thienopyridine derivative **197**; the latter was converted into the corresponding dipyridothiophene **198** in good yield under more drastic conditions.²¹¹



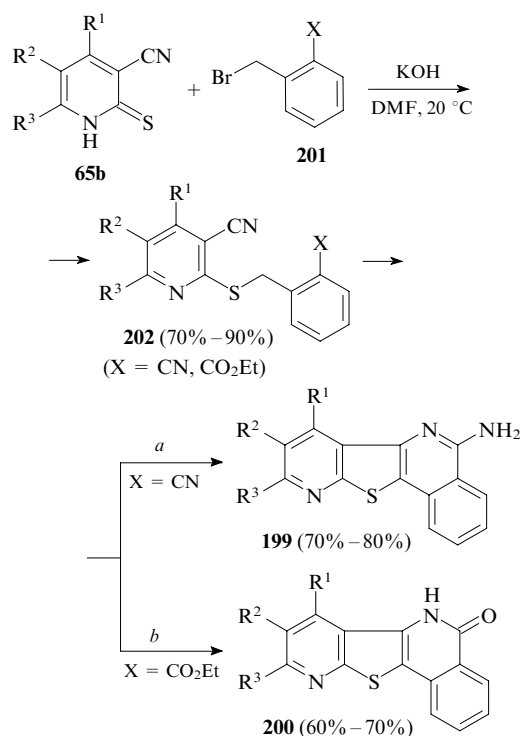
(a) **189**, KOH, EtOH, 40 °C; (b) (1) KOH, EtOH, Δ , 5 min; (2) 10% HCl.

Scheme 4



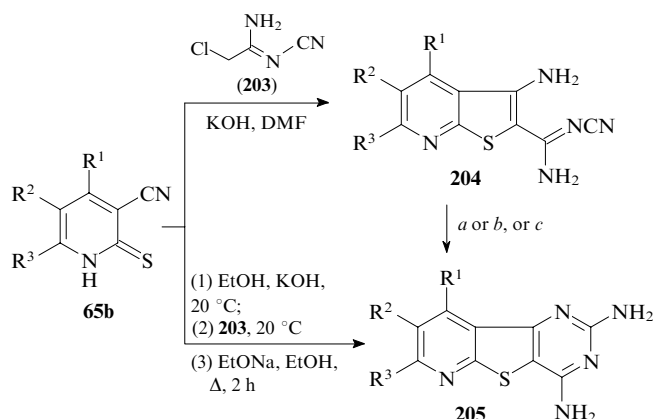
(a) $\text{ClCH}_2\text{C(O)CH}_2\text{CO}_2\text{Alk}$ (**189**) (R⁴ = Et, Prⁱ), KOH or EtONa, EtOH, Δ ; (b) 10% HCl; (c) **189**, 10% KOH, DMF; (d) KOH or EtONa, EtOH, Δ ; (e) Et₃N, EtOH, Δ ; (f) $\text{BrCH}_2\text{CH}=\text{CHCO}_2\text{Et}$ (**190**), KOH or EtONa, EtOH; (g) HCl, MeOH, Δ , 8 h;
R¹, R², R³ = H, Alk, Ar, Het.

The cascade synthesis of pyrido[3',2':4,5]thieno[3,2-*c*]isoquinolines **199** and **200** was accomplished using *o*-bromomethylbenzoic acid derivatives **201** as convenient precursors.^{215,216} This reaction is carried out either as a one-pot procedure or with isolation of intermediate benzylthiopyridines **202**.



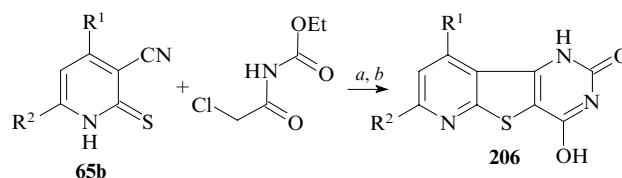
(a) KOH, DMF, Δ ; (b) Bu^tOK, DMF, Δ ; R¹, R², R³ = Alk, Ar, Het.

Two approaches to the synthesis of tricyclic pyridothienopyrimidine systems were developed. Reactions of 3-cyanopyridine-2(1*H*)-thione derivatives **65b** with *N*-cyano-chloroacetamide (**203**) afforded thienopyridines **204**,^{173, 208, 217, 218} which underwent cyclisation into pyridothienopyrimidines **205** (yields 60%–90%) under the action of basic or acidic catalysts. These compounds can also be synthesised directly from thiones **65b** and chloride **203**.



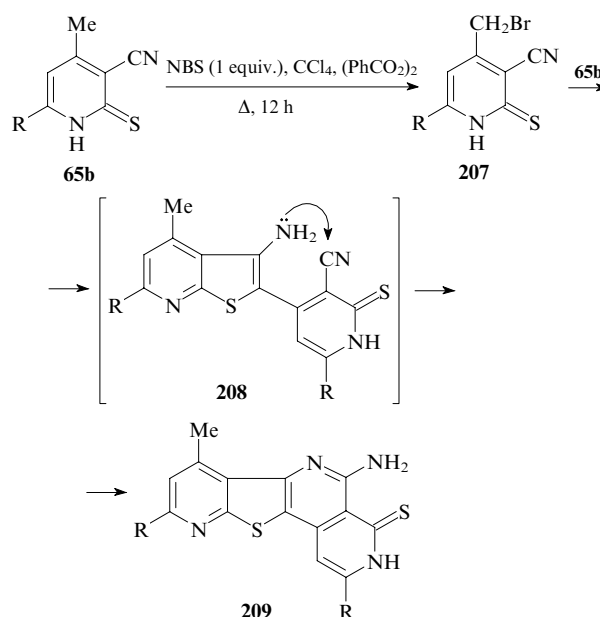
(a) EtONa, EtOH, Δ , 6 h; (b) 35% HCl, MeOH, 0.5–12 h; (c) Ac₂O, Δ , 6 h; R¹ = 4-MeOC₆H₄, 4-FC₆H₄, 2-NO₂C₆H₄, 2-thienyl; R² = MeCO, EtO₂C; R³ = Me.

The second approach, *viz.*, condensation of pyridinethiones **65b** with *N*-(ethoxycarbonyl)chloroacetamide, was used in the synthesis of pyridothienopyrimidines **206**.^{17, 213}



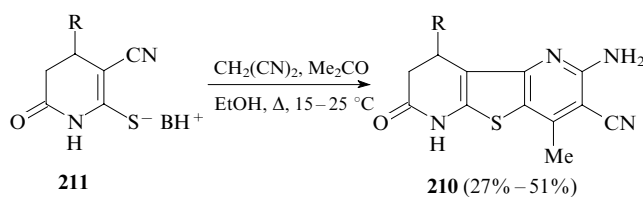
(a) EtONa, EtOH–DMF (1 : 1), Δ , 2 h; (b) 10% HCl, 20 °C; R¹ = Ph, 4-FC₆H₄, 4-MeOC₆H₄; R² = Ph, 2-thienyl.

A non-trivial procedure for the synthesis of fused thienoazines has been proposed.²¹⁹ It included radical bromination of pyridinethiones **65b** (R¹ = Me, R² = H) affecting the 4-methyl group with formation of bromides **207**. Reaction of the latter with the starting thiones first yielded intermediates **208** and then tetracyclic systems **209** containing annelated thienopyridine and naphthyridine fragments.



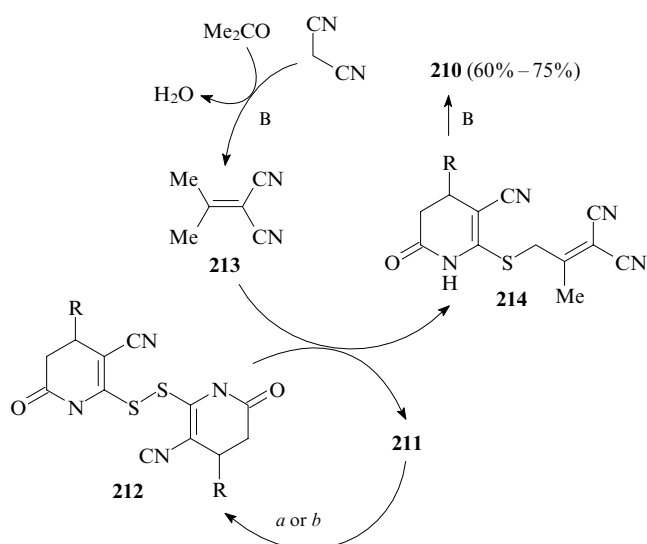
R = Me, Ph; NBS is *N*-bromosuccinimide.

Of note is the multicomponent approach to the synthesis of substituted 6,7,8,9-tetrahydropyrido[3',2':4,5]thieno[3,2-*b*]pyridines **210** based on the reaction of pyridinethiolates **211**, with malononitrile and acetone.^{16, 220–223}



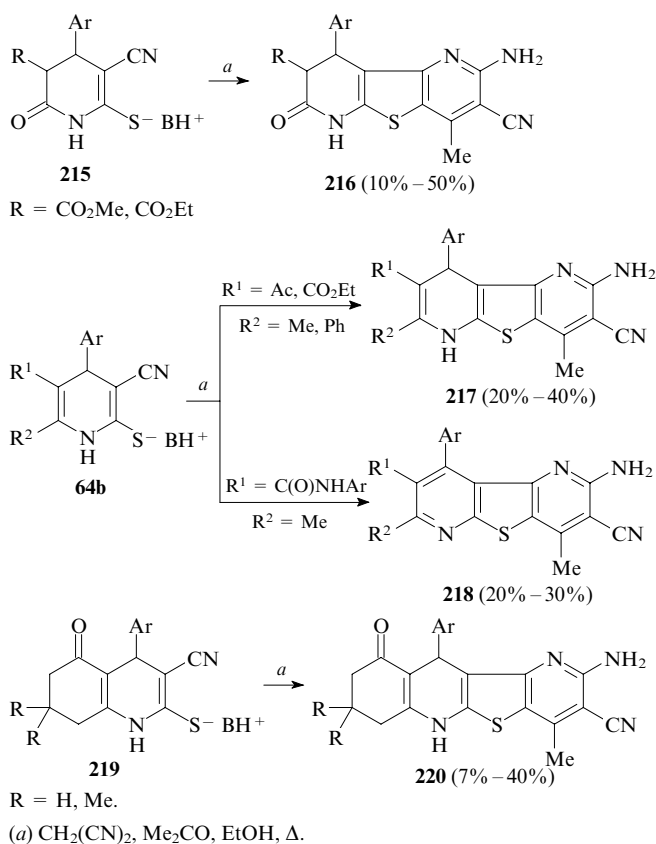
R = Ar, Het; B = *N*-methylmorpholine.

The following reaction mechanism has been proposed:^{16, 223, 224} the starting pyridinethiolate **211** is oxidised by atmospheric oxygen to the corresponding bis(2-pyridyl) disulfide **212**, which reacts with an anion derived from isopropylidene-malononitrile **213** generated *in situ* from malononitrile and acetone resulting in the cleavage of the S–S bond and the formation of dicyanoallyl sulfide **214** and thiolate **211**. The latter undergoes reoxidation into the disulfide, while compound **214** cyclises into dipyridothiophene **210**. The feasibility of this reaction mechanism was confirmed by the independent synthesis of compounds **210** from disulfides **212** formed upon mild oxidation of thiolates **211**. In the latter case, the target products were obtained with the highest yields (60%–75%).

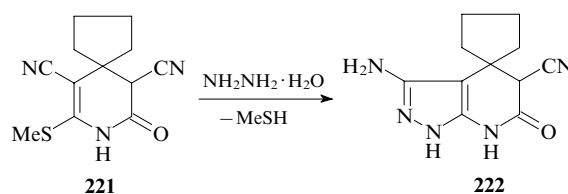


B is *N*-methylmorpholine; R = Ar, Het;
(a) O₂, EtOH, (b) I₂, EtOH–H₂O, 24 h (90%–100%).

A similar reaction of thiolates **215** and **64b** with malononitrile and acetone in boiling EtOH afforded partially hydrogenated pyridothienopyridines **216** and **217** or their dehydrogenated derivatives **218**.²²² Under analogous conditions, hexahydroquinoline-2-thiolates **219** yielded hexahydropyridothienoquinolines **220**.

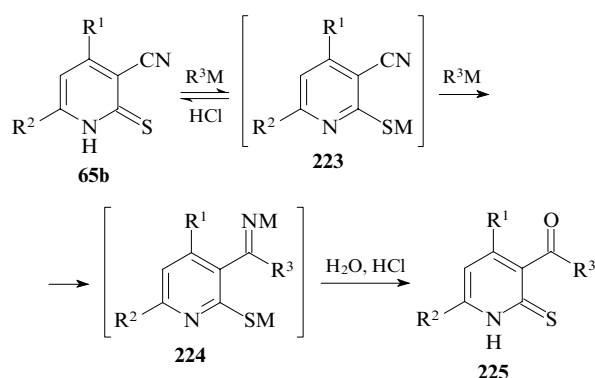


Heterocyclisation of pyridinechalcogenones under the action of 1,2-bis-nucleophiles was carried out. Thus the reaction of spiro-fused 2-(methylthio)tetrahydropyridone **221** with hydrazine hydrate in ethanol gave 3-amino-5-cyano-6-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*b*]pyridine-4-spiro-1'-cyclopentane (**222**) (Refs 52, 88, 120, 121).



4. Other transformations of 3-cyanopyridine-2(1*H*)-chalcogenones

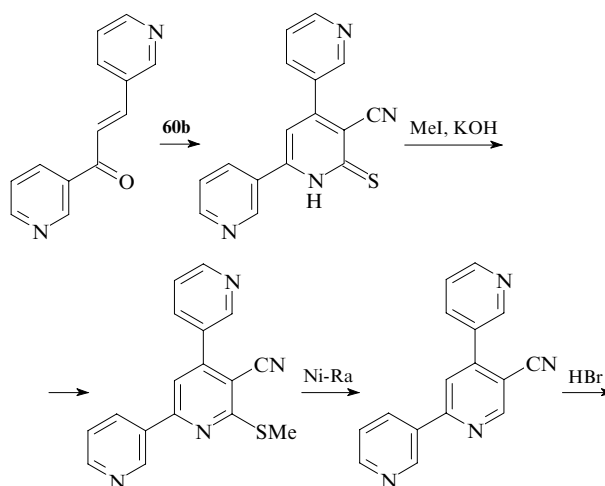
Other chemical transformations of 3-cyanopyridine-2(1*H*)-chalcogenones *e.g.*, hydrolysis of the nitrile group, reaction with organometallic compounds, *etc.*, have been described earlier and are not considered in this review. Suffice it to mention the recently studied reaction of 3-cyanopyridine-2(1*H*)-thiones **65b** with *n*-butyllithium and methylmagnesium iodide in ether, which occurs *via* intermediates **223** and **224** to yield ketones **225**.^{225, 226}

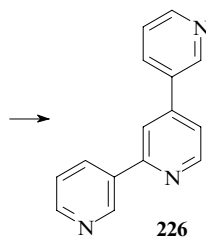


R¹ = H, Me; R² = Me, Prⁿ, Buⁿ, Buⁱ, *n*-C₅H₁₁; R³ = Me, Buⁿ;
M = Li, MgI.

Recently, the attention of investigators has been focused on the reduction of the nitrile group in 3-cyanopyridine-2(1*H*)-thiones and their 2-methylthio derivatives. This reaction can be used for the preparation of aminomethyl- and formyl-substituted pyridines, the promising building blocks for the synthesis of novel fused heterocycles. Catalytic hydrogenation with Raney nickel and reduction with complex metal hydrides [*e.g.*, lithium aluminium hydride, lithium triethoxyaluminium hydride, sodium bis(2-methoxyethoxy)aluminium hydride] were studied. It was found that either the reduction of the nitrile group or the cleavage of the C–S bond took place depending on the reaction conditions and the nature of the catalyst.^{19, 227–230}

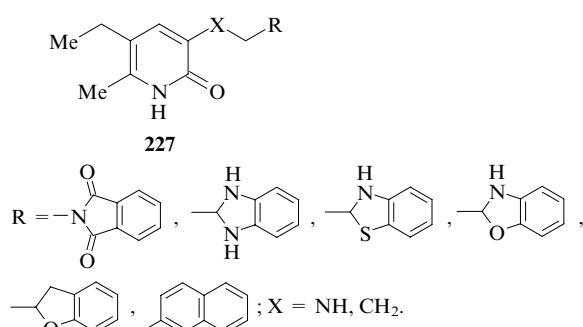
The use of Raney nickel in the synthesis of nicotelline **226**, a minor alkaloid of the tobacco plant, has been described.^{64, 83, 231}





IV. Applications

It is known^{8, 232–238} that 3-cyanopyridine-2(1H)-thiones are used in the commercial production of dyes, pigments, additives to fuels and lubricants, acid-base indicators for titrimetric analysis²³³ and other industrially important substances. Considerably more attention is given to the biological activities of pyridinechalcogenone derivatives. In the first place, this concerns the cardiotonic effect of a vast majority of compounds of this series (Refs 34, 169, 181, 184, 239–260). Some of them were found to possess cardiovascular, coronary and pronounced vasodilatory activities.^{261, 262} Other biological activities of this class of compounds include analgetic and antihypertensive activities,^{117, 170, 247} anti-anaphylactic,^{108, 192, 193} ionotropic,²⁴⁹ antidiabetic,²⁶³ diuretic and sodium-diuretic activities,¹⁵⁰ as well as antioxidant,^{169, 170, 264, 265} antiviral,^{20, 105, 196, 266} antiinflammatory^{109, 167} and antimicrobial activities.^{105–108, 143, 267, 268} Some of these derivatives are potent tranquilisers,^{269–273} antiallergic drugs for treatment of bronchial asthma,²⁶⁹ antihepatitis agents,⁵⁰ etc. Special attention is given to the detection, among pyridones **227**, of inhibitors of reverse transcriptase of human immunodeficiency virus (HIV-1).^{194, 245, 270–277}



Pyridinechalcogenones formed the basis for the development of biodegradable agrochemicals,¹⁷² plant growth regulators, pesticides and herbicides.^{23, 52, 91, 103, 104, 150} Other applications of cyanopyridinechalcogenone derivatives are also known (see Refs 3, 5, 8 and references cited therein).

V. Conclusion

The development of novel chemo-, regio-, stereo- and enantio-selective methods for the synthesis of multifunctional carbo- and heterocycles possessing valuable properties among which pyridine derivatives occupy a special position is one of the major problems of the synthetic organic chemistry of the 21st century. In this context, the development of synthetic procedures and investigations into reactivities of 3-cyanopyridine-2(1H)-chalcogenones as versatile building blocks acquire special importance. Such compounds found wide application in the synthesis of miscellaneous heterocyclic systems containing an annelated pyridine ring.

The analysis of the data on the methods for the synthesis, chemical behaviour and synthetic potentials of 3-cyanopyridine-2(1H)-chalcogenones has made it possible to outline the prospects of this branch of heterocyclic chemistry and to highlight the most promising trends of research in this area. Based on these data, one can expect further successful escalation of studies aimed at the development of novel approaches to the synthesis of fused O,N,S-

heterocycles possessing a broad range of valuable properties on the basis of pyridinechalcogenones.

This review has been written with the financial support of the Russian Foundation for Basic Research (Project No 05-03-32031).

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^a — *Chem. Heterocycl. Compd. (Engl. Transl.)*

^b — *Russ. Chem. Bull., Int. Ed. (Engl. Transl.)*

^c — *Pharm. Chem. J. (Engl. Transl.)*

^d — *Russ. J. Org. Chem. (Engl. Transl.)*

^e — *Dokl. Chem. (Engl. Transl.)*

^f — *Russ. J. Gen. Chem. (Engl. Transl.)*

Features of solid-phase transformations induced by shock compression

S S Batsanov

Contents

I. Introduction	601
II. Shock waves	601
III. Features of phase transitions in shock waves	607
IV. Duration of solid-phase chemical reactions	609
V. Mechanism of ultrafast solid-phase reaction	613
VI. Conclusion	614

Abstract. The results of physicochemical studies of solid-phase transformations under shock compression are analysed. The characteristic time of phase transitions and chemical reactions in shock-compressed solids found experimentally does not exceed one microsecond. Possible reasons for ultrafast atom diffusion are discussed. Hydrodynamic mixing of reactants is believed to be the most feasible mechanism. Prospects for basic and applied research in the field are outlined. The bibliography includes 151 references.

I. Introduction

In synthetic chemistry, the composition and structure of compounds are often varied using high temperature and high pressure techniques. The results obtained are strongly dependent on the level of thermodynamic parameters used. While the range of appropriate high temperatures is limited by the melting or evaporation of a chemical compound, the static pressure is limited by the ultimate strength of the anvil material. Experiments with diamonds made is possible to reach a pressure of up to $\sim 10^6$ atm (~ 100 GPa) paying for an enhanced pressure with progressive diminution of the working volume (to a few micrometres). Such experiments provide new scientific information but not novel materials.

There is also a basically different method of producing high pressures, which is free from this drawback. The technique is called pulse compression of matter using shock waves, or simply shock compression. Physics of pulse pressures rapidly developed during and immediately after the World War II. The shock wave chemistry, as a new avenue of scientific research, emerged in the late 1950s and its development is to a great extent due to achievements in physics and technology of ultrafast methods of investigation. Of particular interest are investigations of the duration and mechanisms of solid-phase transformations induced or assisted by shock waves. This is the subject of the present review, which also concerns the latest advances in shock wave chemistry.

S S Batsanov Centre of High Dynamic Pressures, All-Russian Scientific Research Institute of Physical-Technical and Radiotechnical Measurements, 141570 Mendeleevo, Moscow Region, Russian Federation.
Fax (7-495) 744 81 81, tel. (7-495) 535 92 88, e-mail: batsanov@gol.ru

Received 6 February 2006

Uspekhi Khimii 75 (7) 669–686 (2006); translated by A M Raevskiy

II. Shock waves

1. Introduction to physics of shock waves

A shock wave is a narrow region of compressed matter, which propagates with a supersonic speed. It emerges upon detonation of explosives, collisions between rapidly moving bodies and obstacles, high-power electric discharges and laser ablation of crystals (see references cited in Ref. 1).

If the shock wave is represented as a plane separating the initial and perturbed state of matter, the following equations hold on both sides of the plane in accord with the laws of mass, momentum and energy conservation:

$$\rho_0 D = \rho (D - U), \quad (1)$$

$$P - P_0 = \rho_0 D U, \quad (2)$$

$$\left[(E - E_0) - \frac{U^2}{2} \right] \rho_0 D = P_0 U, \quad (3)$$

where ρ is the density of matter, D is the shock-wave velocity, U is the mass (particle) velocity behind the shock wave front, P is the pressure, E is the internal energy; the subscript 'zero' corresponds to the initial state (the shock wave and particle velocities are also denoted as U_s and U_p , respectively). The state of matter under shock compression is described by the shock adiabat (or Hugoniot adiabat), most often in the P – V or D – U coordinates. If ρ is expressed in g cm^{-3} and the parameters D and U are expressed in km s^{-1} , the pressure P is given in GPa.

It was experimentally established that at pressures below 100 GPa the shock adiabats of many materials obey a linear relation

$$D = c_0 + \lambda U, \quad (4)$$

where c_0 is a parameter similar to the bulk sound velocity and λ is a coefficient, which characterises the slope of the shock adiabat and is of the order of unity

$$\lambda = \frac{D - c_0}{U}. \quad (5)$$

Rodean² proposed a relation between the coefficients c_0 and λ

$$\frac{1}{2} \left(\frac{c_0}{\lambda} \right)^2 = \Delta H_s, \quad (6)$$

where ΔH_s is the heat of sublimation (here, the heat of atomisation) of a solid. It is valid for metals and some crystalline compounds (alkali metal halides and MgO).

Relation (4) can be derived theoretically from the equation of state for internal energy of shock compression. Using the Morse function (known in spectroscopy), the following expressions for the coefficients c_0 and λ were obtained³

$$c_0 = \frac{A}{3B},$$

$$\lambda = \frac{A}{4} - \frac{1}{5},$$

where $A = \alpha r_0$ (α is the thermal expansion coefficient, r_0 is the bond length under normal pressure) and $B = \sqrt{E/2}$ (here E is the bond dissociation energy). Equation (4) with these coefficients quite correctly reproduces the experimental shock adiabats of metals and covalently bonded compounds. In principle, relation (4) can also be derived from other equations of state, e.g., the Birch–Murnaghan and Mie–Grüneisen equations.

Large deviations of the $D = f(U)$ function from linear law are due to physicochemical transformations of compounds under shock compression and, hence, can serve as indicators of such transformations. From Eqn (5) it follows that a change in c_0 will cause antiparallel changes in the λ coefficient, namely, an increase in the sound velocity (at the same parameters D and U) leads to decrease in the slope of the Hugoniot adiabat and *vice versa*. For instance, for three forms of SiO₂ (glass, crystalline quartz and stishovite) the c_0 values are respectively equal to 1.52, 2.20 and 5.07 and $\lambda = 1.74$, 1.60 and 0.18 (see Ref. 4). Analogously, the Hugoniot equations for molybdenum⁵ at room temperature and at 1400 °C, respectively, have the form

$$D = 5.136 + 1.220 U,$$

$$D = 4.78 + 1.42 U.$$

If Eqn (4) fails to correctly describe experimental data, a parabolic equation

$$D = c_0 + \lambda U \pm \mu U^2, \quad (7)$$

with the coefficient $\mu \ll 1$ is used. The generalised shock adiabat equation is as follows⁶

$$D = c_0 + \lambda U + \frac{\mu U^2}{c_0}. \quad (8)$$

For alkali metals, $\lambda = 1.1$ and $\mu = 0.04$; for other metals and inorganic salts, $\lambda = 1.5$ and $\mu = -0.05$ and for organic liquids $\lambda = 2.0$ and $\mu = -0.1$. Methane, solid and liquid CO₂ and water obey the same generalised shock adiabat equation.⁷

$$D = c_0 + 1.9 U - \frac{0.08 U^2}{c_0},$$

where $c_0 = 1.15, 1.8, 1.0$ and 1.95 , respectively.

It should be emphasised that the shock adiabat describes the bulk compression of a body. Initially, the action of dynamic pressure causes elastic compression of a crystal, which is followed by elastoplastic and then bulk compression of the body with an increase in pressure (Fig. 1). Therefore, the shock adiabat begins with a particular non-zero pressure (point 1). At pressures below the pressure corresponding to point 1, the parameters of state are usually obtained by extrapolating experimental data from the bulk compression region to $P = 0$. X-Ray diffraction studies of crystals undergoing shock compression showed that at low shock velocities a single crystal experiences uniaxial compression accompanied by a change in symmetry (e.g., a cubic unit cell is transformed into a tetragonal one) while bulk compression of the body with preservation of initial symmetry occurs at high shock velocities.^{8–12}

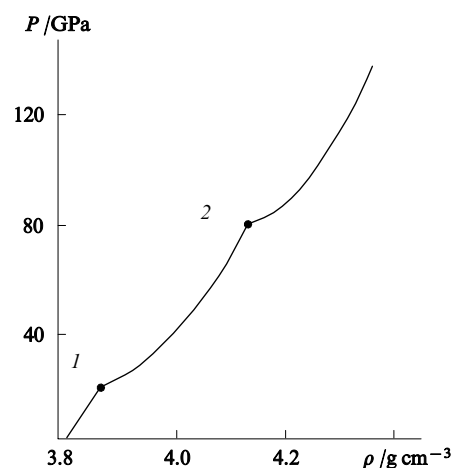


Figure 1. Shock compression diagram of a solid (Al₂O₃ single crystal). Point (1) corresponds to HEL pressure of 20 GPa, and point (2), to a phase transition at 80 GPa. Elastic compression region ($0 < P < 20$ GPa) and bulk compression region ($P > 20$ GPa).

In studies of monolithic bodies it is possible to measure their dynamic elastic limit (Hugoniot elastic limit, HEL). Experimental P_{HEL} values for the polycrystalline state of some elements are listed in Table 1. There are several elements with known P_{HEL} values; therefore, elaboration of methods of *a priori* estimation of these characteristics is required.

Based on the assumption of similarity between the plastic and liquid states of the body, the work of plastic deformation (taken with some coefficient) was equated¹³ to the heat of melting, and an equation relating the HEL pressure to the change in the volume of the body upon ‘mechanical melting’ was derived:

$$P_{\text{HEL}} = k \frac{\Delta H_m}{\Delta V_m}, \quad (9)$$

where ΔH_m is the heat of melting, ΔV_m is the decrease in the volume of the body from the initial volume V_0 to the volume upon mechanical melting, V_m . The calculated P_{HEL} values for a number of elements with presently unknown experimental data are also listed in Table 1.

Table 1. HEL pressures (P_{HEL} /GPa) for chemical elements.^{13, 14}

Experiment		Calculations	
element	P_{HEL}	element	P_{HEL}
Al	0.54	Mo	1.6
Be	0.14–0.55	Nb	2.07
Bi	0.3	Ni	1.0
C	63	Pb ^a	0
Cr	1.6	Sb	0.95
Cu	0.15–0.63	Si	6.5
Ge	5.05	Ta	2.3–2.8
Fe	1.1–1.5	Th	0.14
Mg	0.11	Ti	1.85
		W	3.2–3.9
		B	9.70
		Cd	0.20
		La	0.05
		Pt	2.18
		Re	4.68
		Sc	0.22
		Tl	0.19
		Zn	0.33
		Zr	0.60

^a Annealed sample.

Parameters of Eqn (4) are related to the mechanical characteristics of the body measured under static loading, namely, the isentropic bulk elastic modulus (B_0) and its pressure derivative, by the following equations:¹⁵

$$c_0 = \sqrt{\frac{B_0}{\rho}}, \quad (10)$$

$$\lambda = \frac{B'_0 + 1}{4}.$$

These expressions make it possible to relate the parameter λ to the Grüneisen constant (Γ)

$$\Gamma = \frac{1}{c_V \sigma} \beta V_0 = \frac{1}{c_P} \beta B_0 V_0,$$

where c_V and c_P is the heat capacity at constant volume and pressure, respectively; σ is the isothermal compressibility and β is the bulk thermal expansion coefficient.

The following empirical relationship¹⁶ correctly reproduces the experimental data for metals:

$$\beta = \frac{1}{3} \frac{B'_0 + 1}{B_0 V_0} c_P. \quad (11)$$

From this equation one gets

$$\lambda = \frac{3}{4} \Gamma. \quad (12)$$

A number of equations describing the dependence of λ on Γ are also available. For instance, the coefficient λ is often estimated using the following relation¹⁷

$$\lambda = \frac{1 + \Gamma}{2}. \quad (13)$$

When applied to metals, Eqns (12) and (13) give similar results.

As a rule, Γ is assumed to be inversely proportional to the volume of the body

$$\Gamma V = \Gamma_0 V_0.$$

However, this is not always true. For instance, in the case of NaCl an increase in pressure from 0 to 3 GPa is accompanied by reduction of the volume and a decrease in the Grüneisen constant of the material from 1.52 to 1.40 (see Ref. 18), whereas heating of molybdenum to 1400 °C leaves the Γ value unchanged (1.52).⁵

All experimentally determined coefficients in the Hugoniot equations for elements and inorganic compounds available at the moment (data taken from monograph⁴ or from more recent studies cited in this review), as well as those calculated using expressions (10) are listed in Tables 2–4. All these data refer to low-pressure phases. In most cases the experimental and calcu-

Table 2. Coefficients in the Hugoniot equations of chemical elements.⁴

Element	c_0	λ	Element	c_0	λ	Element	c_0	λ	Element	c_0	λ
Li	4.760 4.659	1.065 1.15	Ge	3.151 3.77	1.79 1.375	Sb	1.98 2.429	1.63 1.525	Tc	— 4.97	—
Na	2.624 2.585	1.188 1.225	Sn	2.437 2.727	1.688 1.55	Bi	1.861 1.795	1.520 1.675	Re	4.068 4.18	1.375 1.60
K	1.991 1.932	1.17 1.25	Pb	1.981 1.967	1.603 1.60	V	5.050 5.13	1.227 1.325	Fe	4.63 4.647	1.33 1.775
Rb	1.232 1.304	1.184 1.225	Ti	4.937 4.827	1.04 1.35	Nb	4.472 4.46	1.114 1.475	Co	4.743 4.747	1.227 1.15
Cs	0.363 0.972	1.583 1.20	Zr	3.812 3.70	0.977 1.20	Ta	3.431 3.42	1.159 1.10	Ni	4.501 4.530	1.627 1.55
Cu	3.899 3.986	1.520 1.55	Hf	2.954 2.87	1.121 1.25	O	2.327 1.20	1.215 1.35	Ru	— 5.055	— 1.90
Ag	3.178 3.177	1.773 1.675	B	— 9.06	— 1.075	S	2.334 2.13	1.588 1.75	Rh	4.775 4.639	1.331 1.375
Au	3.063 2.979	1.563 1.75	Al	5.333 5.278	1.356 1.45	Se	— 1.87	— 0.925	Pd	3.955 3.911	1.701 1.85
Be	7.993 8.030	1.132 1.10	Ga	2.501 3.144	1.560 1.00	Te	3.242 1.83	0.888 1.575	Os	— 4.170	— 1.375
Mg	4.540 4.489	1.238 1.30	In	2.560 2.401	1.477 1.65	Cr	5.153 5.00	1.557 1.55	Ir	3.930 4.015	1.536 1.45
Ca	3.438 3.397	0.968 1.05	Tl	1.809 1.721	1.597 1.575	Mo	5.100 5.11	1.266 1.30	Pt	3.605 3.614	1.560 1.575
Sr	2.10 2.128	0.94 0.975	Sc	4.496 4.48	0.955 0.95	W	4.015 4.09	1.252 1.20	He	0.712 0.761	1.36 1.35
Ba	1.108 1.603	1.369 0.90	Y	3.381 3.00	0.725 0.85	H	— 1.37	— 2.075	Ne	— 0.895	— 2.55
Zn	3.031 2.80	1.608 1.775	La	2.064 1.915	1.012 1.225	F	— 2.18	— 1.35	Ar	1.249 1.02	1.588 1.375
Cd	2.434 2.22	1.759 1.90	N	1.572 1.246	1.365 1.225	Cl	— 2.53	— 1.55	Kr	0.70 0.84	1.72 1.30
Hg	1.75 1.58	1.72 1.85	P	— 3.584	— 1.575	Br	1.51 1.88	1.24 1.55	Xe	1.16 0.815	1.40 1.40
C	12.16 11.39	1.00 1.20	As	— 3.195	— 1.325	I	1.50 1.71	1.46 1.55	Th	2.18 2.26	1.24 1.40
Si	7.99 6.48 (see ^a)	1.42 1.275 (see ^a)				Mn	— 4.185	— 1.70	U	2.51 2.43	1.51 1.75

Note. Here and in Tables 3 and 4 the values of the parameter c_0 are given in km s^{−1}; figures in the numerator denote experimental data and figures in denominator denote theoretical data. ^a Data taken from Ref. 19.

Table 3. Coefficients in the Hugoniot equations of low-pressure phases of metal and NH₄ halides.⁴

Cation	Fluorides		Chlorides		Bromides		Iodides	
	c_0	λ	c_0	λ	c_0	λ	c_0	λ
Li	5.15	1.35	3.93	1.41	2.92	1.33	2.87	0.89
	5.26	1.55	3.96	1.50	2.67	1.65	2.17	1.75
Na	4.25	1.36	3.385	1.38	2.62	1.32	2.09	1.576
	4.15	1.52	3.415	1.55	2.555	1.55	2.12	1.575
K	2.324	1.65	2.15	1.54	1.93	1.44	1.787	1.372
	3.55	1.55	3.02	1.60	2.40	1.60	1.97	1.60
Rb	2.067	1.419	1.565	1.615	1.585	1.47	1.337	1.518
	2.72	1.62	2.44	1.60	2.05	1.60	1.78	1.575
Cs	1.63	1.68	2.182	1.481	2.06	1.36	1.85	1.33
	2.31	—	2.133	1.60	1.88	1.60	1.64	1.65
Cu	—	—	3.08	0.21	—	—	2.50	0.43
	—	—	3.08	1.27	2.74	1.25	2.50	1.25
Ag	—	—	—	—	—	—	—	—
	2.93	—	2.81	1.85	2.505	1.95	2.02	1.09
Tl	—	—	1.85	1.54	—	—	1.35	1.56
	1.49	1.30	1.83	1.575	1.69	1.60	1.55	1.62
NH ₄	—	—	3.59	1.404	—	—	—	—
	—	—	3.92	1.575	2.89	1.425	2.43	1.3

Table 4. Experimentally determined coefficients in the Hugoniot equations of low-pressure oxide, chalcogenide, nitride and carbide phases.

Phase	c_0	λ	Phase	c_0	λ
BeO	8.44	1.22	TiO ₂	2.926	1.865
MgO	6.60	1.37	ZrO ₂	4.38	1.37
CaO	3.80	1.59	SiO ₂ (see ^f)	2.20	1.596
MnO (see ^a)	5.32	1.18	SiO ₂ (see ^g)	5.07	0.183
FeO	3.72	1.59	SiO ₂ (see ^h)	1.52	1.74
NiO (see ^b)	5.35	1.21	GeO ₂ (see ⁱ)	5.23	1.96
ZnS	3.13	1.30	GeO ₂ (see ^j)	0.63	1.84
ZnSe	4.00	1.15	MnO ₂	3.632	1.52
SnS	2.370	1.156	UO ₂	3.88	1.11
SnTe	2.474	1.468	TiB ₂ (see ^k)	8.622	0.795
FeS	2.886	1.603	MgF ₂	3.50	1.56
TiC	5.17	1.42	CaF ₂	4.76	1.30
HfC	5.11	1.53	Mg(OH) ₂	4.75	1.27
SiC	8.00	0.98	FeOOH	4.47	1.60
NbC	5.38	1.46	FeS ₂	5.15	1.52
TaC	3.32	1.49	Fe ₂ O ₃	6.24	1.39
WC	5.63	1.16	Fe ₃ O ₄	4.26	1.37
BN (see ^c)	7.48	1.47	Fe ₃ C	4.60	1.87
AlN (see ^d)	3.27	1.81	Al ₂ O ₃	7.93	1.50
TiAl (see ^e)	4.36	2.92	Si ₃ N ₄ (see ^l)	4.585	1.489

^a Data taken from Ref. 20. ^b Data taken from Ref. 21. ^c Data taken from Ref. 22. ^d For NaCl-type structure.²³ ^e Data taken from Ref. 24. ^f Quartz. ^g Stishovite. ^h Glass. ⁱ Rutile-type structure. ^j Quartz-type structure. ^k Data taken from Ref. 25. ^l Data taken from Ref. 26.

lated values are similar. Differences between them are due to the phase transformations at elevated pressures (as a result, the characteristics determined under shock compression correspond to certain phases that differ from the phases for which the B_0 and B'_0 were measured; this is the case for, e.g., tellurium).

Table 5 presents the coefficients in the Hugoniot equations of low-molecular-mass compounds and polymers obtained from Refs 4, 27–30 or calculated by the least squares method from experimental D and U values reported in the same studies.

Table 5. Coefficients in the Hugoniot equations of the low-pressure phases of low-molecular-mass compounds and polymers.

Compound	c^a	λ	Compound	c^a	λ
N ₂	1.59	1.36	(C ₂ H ₅) ₂ O	1.67	1.455
NH ₃	2.00	1.51	CHBr ₃	1.265	1.533
H ₂ O	1.50	2.00	C ₂ H ₅ Br	1.58	1.36
CO	1.54	1.40	C ₂ H ₂ Cl ₂	1.11	1.75
CO ₂	2.16	1.465	CH ₂ Br ₂	1.0	1.6
CS ₂	1.64	1.46	CH ₂ I ₂	0.96	1.54
CCl ₄	1.47	1.57	formic acid	1.982	1.406
CH ₄ (115 K)	2.841	1.168	acetic acid	2.299	1.267
C ₆ H ₁₄	1.738	1.446	butyric acid	2.128	1.384
C ₇ H ₁₆	1.808	1.450	aniline	2.506	1.275
C ₁₀ H ₂₂	1.970	1.458	anthracene	3.21	1.445
C ₁₃ H ₂₈	2.013	1.460	phenanthrene	3.097	1.417
C ₁₄ H ₃₀	2.095	1.463	pyrene	3.031	1.457
C ₁₆ H ₃₄	2.127	1.464	polystyrene	2.48	1.63
C ₆ H ₆	1.88	1.58	polyethylene ($\rho = 0.92$)	2.83	1.408
C ₆ H ₅ CH ₃	1.72	1.66	polypropylene	3.00	1.42
C ₆ H ₅ NO ₂	2.01	1.59	polyurethane	2.24	1.71
C ₆ H ₃ (NO ₂) ₃	2.318	2.025	paraffin	2.960	1.531
C ₆ H ₂ CH ₃ (NO ₂) ₃	2.390	2.050	plexiglass ($\rho = 1.18$)	3.08	1.308
CH ₃ NO ₃	2.07	1.34	teflon ($\rho = 2.18$)	2.18	1.580
CH ₃ OH	1.73	1.50	nylon	2.500	1.747
C ₂ H ₅ OH	1.785	1.575	rubber	1.84	1.44
C ₄ H ₉ H	1.868	1.497	foam plastic		
C ₅ H ₁₁ H	1.988	1.487	$\rho = 0.30$	0.15	1.290
C ₆ H ₁₃ H	2.324	1.378	$\rho = 0.65$	1.07	1.340
C ₃ H ₅ (OH) ₃	3.07	1.34	$\rho = 0.70$	1.19	1.350
CO(CH ₃) ₂	1.91	1.38	acetonitrile	2.754	1.088

^a Coefficient c (km s⁻¹) can be significantly different from c_0 .

Since the bulk and elastic compression of a body differ by

$$\Delta = D - c_0,$$

the coefficient λ depends on the compressibility of the material. For instance, based on the λ values listed in Table 2, metals can be divided into two groups. One group comprises the main-group elements (except for Cr and Group VIII metals) characterised by $\bar{\lambda} = 1.12 \pm 13\%$; while the other group comprises transition metals with $\bar{\lambda} = 1.61 \pm 7\%$. The difference is due to lower compressibility of the d-metals compared to the s,p-elements. Caesium ($\lambda = 1.58$) presents a particular case, which is probably due to physicochemical transformations of this metal (oxidation or phase transitions) in the course of sample preparation or during the shock compression experiments.

The aforesaid concerns monolithic bodies. However chemists most often work with powders. Here, the porosity of the materials should be taken into account. Propagation of a shock wave through a porous material is accompanied by the 'collapse' of pores and compaction of the powder to form a monolithic body, friction of particles during compaction, their grinding due to unloading (expansion) of the hard material to a softer one or to a pore, deformation of crystalline grains and plastic flow, which leads to heat release and possible contact melting of particles. Highly porous materials are heated to so high temperatures that the effect of heating can exceed the effect of the high pressure (anomalous compression) (Fig. 2).³¹ Shock compression of porous materials with very high porosities made it possible to obtain dense high-temperature plasma.^{32–34}

A number of models are available, in which porous materials under shock compression are treated as loose monolithic bodies (a review of such models can be found in Ref. 35). The Hugoniot adiabats of powders are also calculated under assumption of heterogeneous medium ('mixture of monolithic body and air'). The following equation was derived⁶ assuming a seven-fold decrease in the pore volume upon compression

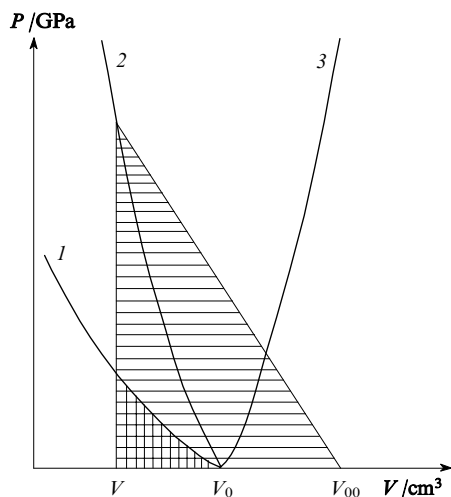


Figure 2. Shock compression diagrams of bodies of different porosity. Monolithic body ($V_0 \rightarrow V$) (1), porous body ($V_{00} \rightarrow V$) (2), anomalous compressibility of highly porous material (starting point is shifted towards V_0) (3); regions filled with horizontal lines and squares correspond to the energies of compression of porous and monolithic bodies, respectively; V is the final volume of compressed body, V_0 is the volume of monolithic body and V_{00} is the powder volume.

$$U_*^2 = U^2 + \frac{6}{7}(m-1)PV_0. \quad (14)$$

Here U_* is the particle velocity in the powder, U is the particle velocity in the monolithic body, and $m = V_{00}/V_0$, where V_{00} is the powder volume and V_0 is the monolithic body volume.

From the U_* value found from Eqn (14) at constant pressure and powder density one can determine the corresponding shock-wave velocity D_* . In a particular range of pressures the calculated U_* and D_* values can be described by an equation similar to Eqn (4)

$$D_* = a + bU_*.$$

The results of calculations using this equation are in agreement with the experimental data for powders with moderate porosities. But as the sample porosity increases, the parameters a in the experimental Hugoniot equations decrease down to zero. Unlike c_0 , the parameter a cannot be treated as the bulk sound velocity in the porous material; its value lies in the range between the sound velocity inside the grain and the speed of slow motion of the grains involved in 'relay'-type sound transmission in the sample. This approach corresponds to the Touvenin model,³⁶ which considers powders as systems of plates that transmit perturbation in a porous medium.

It was experimentally shown that the behaviour of a powder under shock compression differs from that of a monolithic body. For instance, experiments involving throw of aluminium and copper impactors in porous aluminium ($\rho = 63\%$ of the density of monolithic body) showed that the same pressure corresponds to different shock-wave velocities (difference is 300 m s^{-1}) while different pressures are measured at the same shock-wave velocities in the powder, depending on the impactor material.³⁷ This effect is impossible under shock compression of monolithic bodies.

The Hugoniot parameters

$$D_{1,2} = c_{1,2} + \lambda_{1,2} U_{1,2} \quad (15)$$

of a binary mixture (alloy) composed of the solids 1 and 2 can be calculated using the additivity scheme

$$U_{1,2}^2 = xU_1^2 + (1-x)U_2^2, \quad (16)$$

where x is the mass fraction of a component. Relation (16) has the sense of the law of energy conservation, because the energy of a

mass unit of the mixture equals the sum of the energies of the components that experienced shock compression at the same pressure.

If the Hugoniot adiabats of components are unknown, one can use their mechanical characteristics and sum the B/ρ ratios of the components 1 and 2 with allowance for their mass fractions (because these parameters have the dimension of energy) and then determine the coefficients $c_{1,2}$ as follows

$$c_{1,2} = \sqrt{\frac{B_1}{\rho_1}x + \frac{B_2}{\rho_2}(1-x)},$$

where $\lambda_{1,2}$ is the weight-average value of λ_1 and λ_2 owing to a small difference between these parameters.

The dynamic pressure produced by shock waves differs from static pressure by very short duration of the periods of pressure rise ($\sim 10^{-12} \text{ s}$) and stationary action ($\sim 10^{-6} \text{ s}$). Tensile stress (negative pressures) produced in the solid in the unloading wave allows the shock wave to reach the surface of the sample, which is accompanied by spalling phenomena. These features can cause basically new effects under the action of shock waves on substances compared to those observed at high static pressures.

Whereas determination of dynamic pressures presents no severe difficulties, measuring the shock temperatures is a rather complicated task. In this case the most objective thermocouple method is slow, while optical pyrometry data (this technique is characterised by very short time delay) are interpreted under assumptions (blackbody model, uniform emission of radiation from the surface) that require experimental check-up. A recently proposed, new promising technique for measuring the shock temperatures involves the use of NMR spectroscopy. To date, it was only employed in a study of molybdenum.³⁸ Experimental shock Hugoniots of heated substances are necessary for solving a number of physicochemical problems. However, their number is limited. Such adiabats can be obtained by measuring the bulk elastic moduli at different temperatures.

There is a few crystals with known shock compression characteristics at different temperatures. These are NaCl and LiF,¹⁸ Mo⁵ and SiO₂.³⁹ Heating of the first two materials from 25 to 400 °C causes a decrease in c_0 from 3.3 to 2.9 km s⁻¹ (NaCl) and from 5.0 to 4.5 km s⁻¹ (LiF); the parameter λ decreases from 1.7 to 1.5 (NaCl) and from 1.5 to 1.3 (LiF). The same parameters of molybdenum vary in different fashion on heating from room temperature to 1400 °C; namely, c_0 changes from 5.14 to 4.78 km s⁻¹ while λ changes from 1.22 to 1.42. In glassy SiO₂, the bulk sound velocity (~ 0.75 of the longitudinal sound velocity) increases from 4.46 to 4.84 km s⁻¹ in the temperature range 20–1050 °C. In molten SiO₂, it increases from 4.90 to 4.93 km s⁻¹ in the temperature interval from 1530 to 2010 °C.

The bulk elastic modulus of ZrO₂ and its pressure derivative (265 GPa and 4.0, respectively) remain unchanged in the temperature range from 25 to 1400 °C,⁴⁰ but since the density of the body decreases on heating in this case, it follows from Eqns (10) that the coefficient c_0 increases while the parameter λ retains its value. The results of B_0 measurements for a number of metals at -273 (B_1) and 27 °C (B_2) showed⁴¹ a decrease in this parameter on heating.

Element	Al	Cu	Fe	Pb	α -Pu
B_1/B_2	1.075	1.036	1.030	1.104	1.303

A large change in the elastic modulus of α -Pu is due to changes in the 5f-electron shell of plutonium atom.

No general trend in the influence of temperature on the parameters of Eqn (4) has been revealed so far. This effect should be studied in each particular case.

2. Recovery of shock compression products

Ryabinin⁴² pioneered in the recovery and investigation of the products of shock compression of chemical compounds. Despite the lack of interesting chemical results, his study opened a new research avenue in the physics of shock waves, which was called

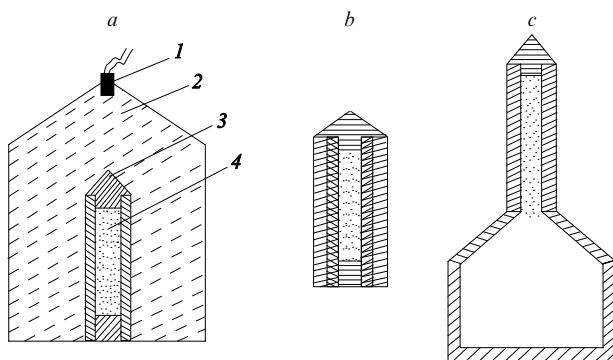


Figure 3. Schemes of experimental setups with cylindrical recovery ampoule (a), cylindrical recovery ampoule with layered shell (b) and recovery ampoule with large cavity (c). Detonator (1), explosive (2), ampoule (3) and sample to be compressed (4).

'recovery experiments'. Later on, cylindrical ampoules employed by Ryabinin were significantly simplified and modified. Here we will consider the main types of such ampoules.

Figure 3a presents a scheme of typical experimental setup with a steel cylindrical ampoule. The modification of the ampoules consists in the use of layered shells made of different materials (Fig. 3b). The shells provide a stepwise loading of the substance by shock waves owing to difference between the shock-wave velocities in different materials. Yet another modification consists in the use of an attached large container (Fig. 3c) for expansion (scattering) and subsequent quenching of shock compression products in the course of unloading. Prior to explosion, the cylindrical ampoules can be heated⁴³ or cooled (by, e.g., liquid nitrogen) in order to adjust the thermodynamic conditions. To the same end, water or other substances with high heat capacity can be added to the sample to be compressed (they absorb heat and thus provide corresponding cooling).

In the case of uniformly distributed charge of the explosive, cylindrical ampoules provide an axially symmetrical compression of the substance with minimum deformation of the sample. However, if the explosive is concentrated within some sectors of the cross section (Fig. 4), a strong deformation of the ampoules can be achieved. If the empty regions in the charge (see positions 1 in Fig. 4) are filled with materials of different mechanical hardness, it is possible to control the degree of the ampoule deformation.

Owing to very high pressure in the axial (Mach) region, cylindrical ampoules are, as a rule, used for the synthesis and

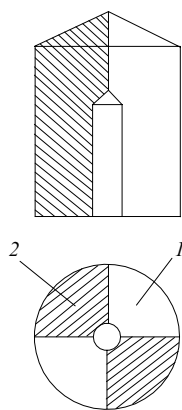


Figure 4. Sections of cylindrical ampoule with sector arrangement of explosive. (1) Air (or other inert material), (2) explosive.

modification of chemical compounds. If the thermodynamic parameters in this region are to be reduced, cylindrical ampoules with a metallic rod at the centre are employed. This allows repeated reflection of the shock wave from the rod and walls, thus causing the pressure to increase with minimum heating of the substance.

An important modification was the invention of dynamic-static compression ampoules⁴⁴ where the compound is surrounded by the working substance (e.g., KBr) which undergoes a reversible phase transition. Under loading, KBr undergoes a structural transition of the NaCl $\rightarrow$ CsCl type accompanied by a 15% reduction of the volume, while in the unloading stage potassium bromide should return to its initial state. However, the hard recovery ampoule, which is made of strain-hardening steel and therefore becomes even harder during shock compression, makes the expansion of the working substance impossible. As a result, a residual (static) pressure is produced inside it (Fig. 5). The internal static pressure equal to the phase transition pressure (2 GPa) is rather high; this precludes annealing of thermally unstable high-pressure phases, in particular, a Würtzite-type boron nitride (w-BN) polymorph.⁴⁵

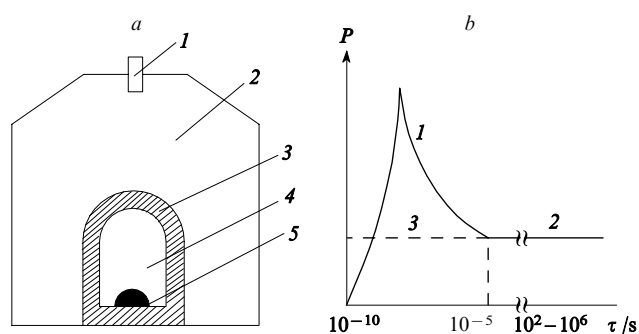


Figure 5. Experimental setup for dynamic-static compression (a) and corresponding pressure-time diagram (b).

(a) Detonator (1), explosive (2), ampoule (3), working substance (e.g., KBr) (4) and sample to be compressed, e.g., graphite-like boron nitride (g-BN) (5).

(b) Temporal evolution of dynamic pressure (1), static pressure (2) and phase transition pressure (2 GPa for KBr) (3).

Another group of recovery systems includes plane ampoules in which pressure is produced using a mud cap (Fig. 6a) or by throw of impactor plate (Fig. 6b). By varying the composition of the explosive, the material and the thickness of the impactor plate it is possible to change the magnitude and duration of the dynamic pressure. Additionally, such systems provide a better possibility

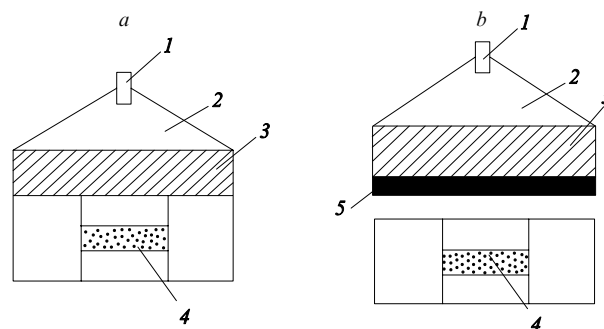


Figure 6. Schemes of plane recovery ampoules employed under shock compression using a mud cap (a) and throw of an impactor (b). Detonator (1), plane wave generator (2), explosive (3), sample to be compressed (4) and impactor plate (5).

for heating of the substance under study without contact between the ampoule and explosive before explosion. Uniaxial loading in plane ampoules is convenient for pressure measurements and calculations, but the design of the experimental setup is labour-consuming. Plane ampoules are most often used for explosive compaction or pre-activation of brittle powders, because in this case the thermodynamic parameters in the bulk of the sample are the same and can easily be controlled. Forced high-strain-rate deformation of samples also appeared to be efficient for compaction. To this end, the diameter of the pellet made of the substance under study should be smaller than the diameter of the ampoule. Planar impact is followed by plastic flow of the sample across the inner section of the ampoule, which sometimes results in transparent samples of rather strong materials.

Stepwise loading of samples in plane ampoules is attained using layered shells or impactors. Here, the temperature of the substance compressed is much lower (isentropic compression) than in the case of single-shot loading with the same explosive. In order to increase the pressure in the plane recovery ampoules, schemes with counter-propagating shock waves are used (Fig. 7). Other types of plane recovery ampoules were described in a review⁴⁶ and in a monograph.⁴

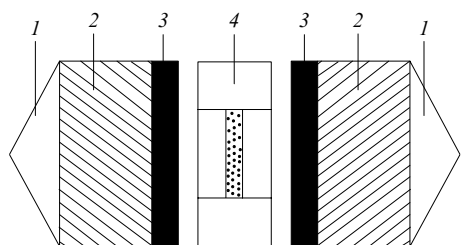


Figure 7. Scheme of a device for shock compression experiments using counter-propagating shock waves. Plane wave generator (1), explosive (2), impactor (3) and sample to be compressed (4).

The most industrially important procedure for recovery of explosion products involves placing a mixture of the substance under study and the explosive in a mechanically hard chamber for preservation of the expanding detonation products. For better annealing of detonation products, the charge is surrounded by an ice shell. The advantage of this technique consists in the absence of recovery ampoules, which makes the process much cheaper. Additionally, expansion of products within a large cavity causes annealing of high-pressure phases. The detonation parameters of, e.g., TNT ($P = 18.4$ GPa, $T = 2900$ °C) are sufficient to ensure transformation of graphite to diamond. As a result, the yield of diamond upon detonation of a graphite–explosive mixture or a pure explosive giving carbon as a solid detonation product can be as high as tens per cent. This is an order of magnitude higher than the yield provided by the ampoule technique (although the detonation diamond particles are much smaller than the particles obtained using the ampoule method). In Russian Federation, detonation diamonds are produced on a large-scale basis.

Probabilistically (assuming a homogeneous detonation cloud), the formation of detonation diamonds in the form of clusters comprising about $\sim 10^4$ atoms is impossible. Indeed, detonation of TNT or TNT–RDX alloys gives H_2 , CO, CO_2 , H_2O , NO, NO_2 , carbon clusters C_n ($n = 1-6$), etc. as products. Even if we restrict ourselves to these products, the probability of formation of a diatomic carbon cluster in the detonation cloud equals 1/7, the addition of the third and fourth carbon atom reduces the probability to 1/49 and 1/343, respectively, etc. Therefore, the probability of formation of a cluster comprising ten carbon atoms approaches zero. Nevertheless, the number of

atoms in the actually formed clusters is three orders of magnitude larger!

We believe that this can be explained by heterogeneous (layered) structure of the detonation cloud. The layers mainly include carbon atoms or hydrogen or water molecules, etc. The formation of layers can be understood if we assume that, upon detonation, all fragments of the explosive molecule have the same kinetic energy of $mv^2/2$ (m and v are the mass and velocity of a molecular fragment). Then, the velocities of the detonation products are inversely proportional to $\sqrt{m}$ and the detonation cloud will contain layers of atoms or molecules of different masses. Formation of diamond clusters will occur in the layer that comprises mainly carbon atoms. Similar masses of different molecules in the same layer impose a limitation on the growth of cluster and it is contaminated with impurities, which is observed in the experiments.

Methods of preservation of the shock compression and detonation products are used for chemical purposes, namely, for performing phase transformations and synthesis of novel compounds. Shock-induced syntheses and compaction, pre-sintering and catalytic activation of brittle materials have been documented in a review.⁴⁷

III. Features of phase transitions in shock waves

Iron shock compressibility studies⁴⁸ revealed a break in the Hugoniot curve at 13 GPa, corresponding to the α -Fe $\rightarrow$ ϵ -Fe transition. Analysis of ϵ -Fe fragments found upon disruption of target unambiguously indicated a phase transition with a duration of $\tau \leq 10^{-6}$ s. Optical studies^{49,50} showed that transitions under shock compression occur 10^7 – 10^{14} times faster than in static experiments.

What is the reason for high rate of the phase transitions under dynamic compression?

Variation of the bond lengths in crystals upon polymorphic transformations lie within the range of amplitudes of thermal atomic vibrations ($\sim 10\%$ of the bond length). Therefore, the duration of the phase transition can be estimated from shock-induced thermal atomic jumps. The action of shock waves causes fragmentation of crystalline grains, produces vacancies and dislocations in them and also causes heating of the body to very high temperatures, which favours intensification of atomic vibrations. The frequency of thermal vibrations is given by

$$w = A \sqrt{\frac{kT}{m}}, \quad (17)$$

where A is a constant, k is the Boltzmann constant and m is the atomic mass. At room temperature, for hydrogen atom one has $w = 6 \times 10^{13} \text{ s}^{-1}$ and $\tau \approx 2 \times 10^{-14} \text{ s}$; for $m = 100$ the time changes by an order of magnitude; with allowance for high pressure and activation energies⁵¹ one gets $\tau \approx 10^{-12} \text{ s}$, which is in agreement with experimental data.

Intensive studies of polymorphic transformations of simple bodies (elements) and compounds under shock compression began in the mid-1950s. Experiments showed that the dynamic phase transition pressures are similar, often being somewhat higher than the static transition pressures. This is due to the hydrostatic character of shock compression (see above) and to the fact that the dynamic loading temperature is higher than the temperature at which static experiments are carried out (usually, room temperature).

Analysis of the available experimental data made it possible to solve a number of fundamental problems concerning the kinetics and mechanisms of shock-induced phase transitions. We will consider these problems from the structural point of view, based on the experimental data only.

First of all, mention should be made of the anisotropy of phase transitions in the crystals of alkali metal halides. Namely, if the crystallographic axis (111) is normal to the shock wave front, the NaCl $\rightarrow$ CsCl type transitions occur at lower pressures, which

corresponds to compression of the unit cell along its spatial diagonal.⁵² This mechanism was studied in more detail using KCl samples; the phase transition points at 2.5, 2.2 and 2.1 GPa along the $\langle 100 \rangle$, $\langle 110 \rangle$ and $\langle 111 \rangle$ directions, respectively, were observed.⁵³ The anisotropic phase transition was explained in terms of atomic displacements along the spatial diagonal of the unit cell. However, coherent atomic displacements cannot cause transformation of the graphite lattice into the diamond lattice. Phase transitions require destruction (amorphisation) of the starting crystalline graphite. This conclusion is substantiated by the maximum yield of diamond in the detonation-induced transformation of the most defect carbonaceous material, namely, carbon black.

Analysis of these experimental findings gave an impetus to studies on geometric modelling of phase transitions that served as a basis for a separate avenue of scientific research.⁵⁴

In the graphite–hexagonal diamond (lonsdaleite) and g-BN–w-BN systems both the initial and final modifications have the same symmetry and the phase transition is driven by the puckering of planar hexagonal graphite sheets accompanied by the formation of sp^3 -bonds between the close-lying atoms belonging to neighbouring sheets. A metastable g-BN phase was detected⁵⁵ with an interplanar separation of 3.28 Å, which is smaller than in the single crystal (3.33 Å), and 002 X-ray reflections are broadened owing to structural deformation in this direction. Annealing of the wurtzite-type BN polymorph causes the formation of the g-BN phase by the same mechanism, but in the reverse order.⁵⁶

Shock compression of CdF_2 , CaF_2 and $CuBr$ results in reduction of the unit cell parameters by 0.002, 0.003 and 0.047 Å, respectively (lattice parameters were measured with an accuracy of ± 0.0005 Å) with retention of the unit cell symmetry and valences of the metal atoms.⁴ Isomorphic reduction of unit cell parameters after shock compression was small, but the dielectric constants (ϵ) responsible for the character of chemical bonding changed substantially, namely, they increased from 7.1 to 7.9 for fluorite and from 10.0 to 17.8 for $CuBr$. This is quite clear, since even a small shortening of the distance compared to the equilibrium value causes a dramatic strengthening of electron interaction and an increase in the atomic polarisabilities. Heating of isomorphically compressed crystals is accompanied by exothermic effect and the crystal structures and properties return to the initial state.

Isomorphic transitions also occur under the action of high static pressures. For instance, the unit cell parameters of samarium chalcogenides are dramatically reduced owing to an increase in the valence of the metal [$Sm(II) \rightarrow Sm(III)$]. In dynamic experiments isomorphic reduction of structural parameters is due to quenching of the shocked samples that occurs with retention of the oxidation state of the atoms.

Specific phase transitions were detected under shock compression of Nb_2O_5 and Ta_2O_5 crystals. Shock compression causes minor changes in the composition and results in the formation of TiO_2 -type structures.⁵⁷ Therefore, this transition is followed by the formation of a structure in which 20% of sites in the metal lattice are vacant (*i.e.*, compounds of the $M_{0.8}O_2$ type are formed). Shock compression of Ln_2S_3 ($Ln = Tb, Dy, Ho, Er, Y$) causes a $Ho_2S_3 \rightarrow Th_3P_4$ -type structural transition; here, each ninth site in the metal sublattice is replaced by a vacancy.⁵⁸ A similar transformation was observed under shock compression of CeF_4 , ThF_4 and UF_4 . These fluorides experienced a $ZrF_4 \rightarrow LaF_3$ structural transition accompanied by the formation of 25% vacant sites in the cation sublattice (*i.e.*, $MF_4 \rightarrow M_{0.75}F_3$ transition).⁵⁹ Such transformations were not detected under static compression, because denser structures with ordered system of defects are retained only upon rapid quenching of corresponding phases during the shock-wave unloading.

An interesting phase transition occurred in TiO under shock. The initial phase belongs to the monoclinic system ($a = 5.85$, $b = 9.34$, $c = 4.14$ Å, $\beta = 107^\circ 32'$). After shock compression the

diffraction pattern exhibited no weak lines while the intense lines corresponded to cubic lattice with $a = 4.176$ Å. In this case the phase transition accompanied by an increase in symmetry is also driven by generation of numerous defects that are characteristic of this crystal.⁶⁰

As shown above, the shock wave technique makes it possible to produce negative pressures that can be realised in the rarefaction wave in the form of tensile stress in the samples under study. Phase transformations at negative pressures can result in the formation of loose structures that cannot appear at $P \geq 0$. Such a structure was first found in our study of turbostratic BN under shock compression. We found a very small amount of a new polymorph (E-phase)⁶¹ whose density was lower than that of w-BN. The last-mentioned phase is formed only after annealing of defects and corresponding increase in the degree of crystallinity of the initial graphite-type boron nitride polymorph (w-BN is formed under shock compression of g-BN if the density of the starting phase is at least ≥ 2.2 g cm^{−3}). The Hugoniot adiabats of the BN samples with different densities show a similar trend.⁴ The structural parameters of E-BN are very similar to those of a certain fullerene phase:^{62, 63}

Parameter	$a/\text{\AA}$	$b/\text{\AA}$	$c/\text{\AA}$	$\rho/\text{g cm}^{-3}$
E-BN	11.14	8.06	7.40	2.50
C ₆₀	11.16	8.17	7.58	2.50

It is important that the E-phase is formed under shock compression only in the axial region of cylindrical ampoules if there is a cavity that appeared under the action of tensile stress in the compressed material after irregular collisions of shock waves. More recently, this phase was obtained by researchers from other groups under the action of various physical factors on g-BN.^{64–69}

Now we will consider yet another unusual type of phase transitions, which is atypical of physics of high static pressures. Usually, heating is accompanied by polymorphic transformations with the formation of looser structures, but there exist a number of crystalline compounds (*e.g.*, PbO , MnS , Ln_2S_3 , Ln_2O_3 , TiO_2 , ZrO_2 and LnF_3) that undergo phase transitions accompanied by densification upon heating. Under shock compression these compounds are transformed into phases with lower density (compared to the initial phase) and looser atomic structure (Table 6).

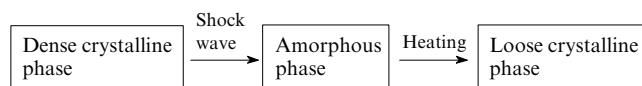
Table 6. Characteristics of anomalous phase transitions.⁷⁰

Composition	Initial phase		After shock compression	
	structural type	$\rho/\text{g cm}^{-3}$	structural type	$\rho/\text{g cm}^{-3}$
Tm_2S_3	Ho_2S_3	6.27	new type	6.06
Nd_2O_3	A-form	7.42	C-form	6.29
SmF_3	LaF_3	6.93	YF_3	6.64
HoF_3	LaF_3	7.83	YF_3	7.64
GeSSe	α -phase	4.0	γ -phase	3.6
GeSTe	α -phase	5.1	γ -phase	4.7
GeSeTe	α -phase	5.6	γ -phase	5.2
ZrO_2	tetragonal	6.03	monoclinic	5.83
PbO	orthorhombic	9.72	tetragonal	9.43

Anomalous phase transitions accompanied by loosening upon dynamic compression were explained by the action of negative pressures, however detailed studies revealed a more complex phenomenon. Under the action of a shock wave the lattice of the solid is disordered, dislocations are produced, and at higher concentration of defects the crystalline compound transforms to amorphous substance with minimum density (for the given composition). Heating of such a material causes its crystallisation in a phase with minimum density. Upon further heating the material crystallises in a denser phase. This mechanism was experimentally proved taking $GeSeTe$ ⁷¹ and Nd_2O_3 ⁷² as exam-

ples. Here, amorphous phases transformed into crystalline modifications with minimum density upon heating. The temperatures of successive transitions can differ insignificantly; besides, it is difficult to reach the desired range of thermodynamic parameters under shock compression. Therefore, these transitions have not long been detected.

Thus, an anomalous phase transition can be described by the following scheme:



Correctness of this scheme is substantiated by occurrence of anomalous transitions under static shear compression and upon intense irradiation.⁴

The structural approach to the description of the features and mechanisms of phase transitions under shock compression (see above) is not unique. For instance, the kinetic and thermodynamic aspects of this problem were also considered.⁷³

IV. Duration of solid-phase chemical reactions

1. Measurements of the duration of solid-phase reactions

The fact that the shock compression time is sufficient for a phase transition to occur was experimentally established in 1956.⁴⁸ As to solid-phase reactions, this was a moot question for long, because either synthesis or decomposition of chemical compounds in the recovery ampoules can occur both under shock and after unloading due to residual heat.

A solid-phase reaction proceeds in several steps. These are fragmentation of grains and cleavage of chemical bonds in the initial components, mixing of different reagents to bring them into contact at the atomic level and, finally, growth of new-phase crystals to a size that ensures their existence. Since diffusion in solids is slow, being even slower at high pressures (its rate is at least six orders of magnitude slower than the rate required for the synthesis on the microsecond time scale), solid-phase reactions seemed to be hardly probable. At the same time, gas–solid and liquid–solid chemical interactions that take a few microseconds have long been known (see, *e.g.*, Refs 74 and 75).

Actual duration of solid-phase reactions under shock compression was determined by measuring the time of the onset of heat release in exothermic reactions, by search for high-pressure phases among the synthesis products, by elucidating mechanical after-effects of shock-induced transformations in the recovery ampoules and, finally, by measuring the shock-wave velocities and pressure in the reacting mixtures.

a. Temperature measurements

Thermocouple measurements of the temperature of the reaction



were carried out in our research group since 1968 for a period of two decades. The duration of the experiments gradually shortened from 10^{-1} to $\leq 10^{-4}$ s due to the use of thinner thermocouples and improvement of experimental procedure (see references cited in Ref. 76). Measurements were carried out in the recovery ampoules rigidly joined to massive metallic slab in order to ensure immobilisation of the ampoules during the explosion. In order to obtain objective information, the dynamic compression was carried out under the same conditions for the reacting mixture Sn + S, individual components (Sn, S) and reaction product (SnS). Experiments showed that the residual temperatures of these individual compounds measured 0.1 s after explosion varied in the order $110 \rightarrow 120 \rightarrow 130$ °C, whereas that of the reacting mixture reached a value of 1110 °C, which corresponds to a 50% chemical conversion.

The results of X-ray diffraction study of the samples of the recovered products taken from different regions of the ampoule

showed that the synthesis occurs mainly in the axial region of the cylinder (in the so-called Mach stem) and the extent of conversion and the product composition (SnS or SnS₂) depend on the dispersion of the initial powder, which indicates a solid-phase character of the reaction.

The results of thermocouple measurements were checked calorimetrically. After an accurately measured time interval (from several tens of seconds to 1–2 min) after explosion, the recovery ampoule containing the reacting mixture and the product was taken out of the explosion chamber and placed in a water calorimeter. After cessation of heat release in the calorimeter, the temperature of the ampoule was calculated. Then, the ampoule was taken out of the calorimeter, heated in a furnace to a certain higher temperature and again placed in the explosion chamber. This was done in order to cool the ampoule under the same conditions as after the explosion. The cooling curve was measured using a thermocouple. Such cooling curves allow an exact extrapolation of the calorimetrically measured temperatures to zero time instant. The results obtained by the two methods differed by a few per cent. In the cylindrical ampoules with the diameter of the orifice in the bottom plug equal to the diameter of the Mach stem, the substance in the axial region was blown away, which made it possible to determine calorimetrically the contribution of the Mach region to the overall enthalpy of the sample.

Further shortening of the duration of the temperature measurements in the reacting systems was attained by using an optical pyrometer. The results of the studies of Al + Fe₂O₃,⁷⁷ Ni + Al,^{78,79} Sn + S,⁸⁰ and Sn + Te mixtures⁸¹ showed that the synthesis is completed after nearly 10^{-7} s. It is significant that for the Sn + S mixture the dependence of the temperature changes on the pressure applied passes through a maximum (Fig. 8). This indicates that the reaction can occur in a limited range of pressures. Raising the pressure favours SnS formation, which is accompanied by compaction, but simultaneously the thermal effect (and, hence, the thermodynamic driving force) of the reaction decreases.⁷⁶

Real-time studies of the temperature dependences of the shock-induced interaction of magnesium, aluminium and titanium with sulfur were reported.^{82–84} The reaction durations were about 50 ns and the extent of conversion varied from 0.2 to 0.5. An optical study of the Al–S system revealed a dependence of the rate of the shock-induced reaction on the dispersity of the reacting particles, which proves the solid-phase character of the process. Under explosive loading using a TNT–RDX alloy the Mg–S system shows that the first temperature rise region is followed by a region of gradual increase in temperature due to the development of the reaction after unloading. This can serve as a model for the situation in the recovery ampoules.

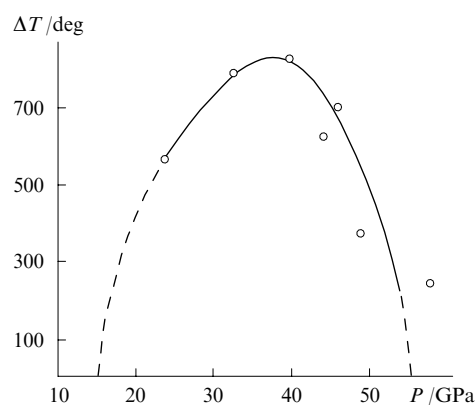


Figure 8. Shock temperature plotted vs. pressure in Sn + S reacting mixture.

b. Kinematic measurements

Kinematic measurements (*i.e.*, measurements of parameters under shock compression) provide objective information on possible chemical transformations in a mixture of solids. Deviation of the shock compression curve of Sn + S mixture⁸⁵ toward a larger volume and/or pressure at $P \geq 15$ GPa was the first direct proof of the fact that the duration of a solid-phase reaction is of the order of a few microseconds. More recently, chemical reactions in shock waves were detected in the compressibility studies of Sn + Te (at $P > 45$ GPa),⁸¹ Ti + C (at $P > 15$ GPa)⁸⁶ and Ti + Ni (at 3.2 GPa) mixtures.⁸⁷ According to unpublished data obtained by G A Adadurov and S V Pershin (N N Semenov Institute of Chemical Physics, Russian Academy of Sciences), the shock compressibility curves of Fe + S and Cu + Al mixtures exhibit kinks at 28 and 32 GPa, respectively, upon increase in volume (Fig. 9).

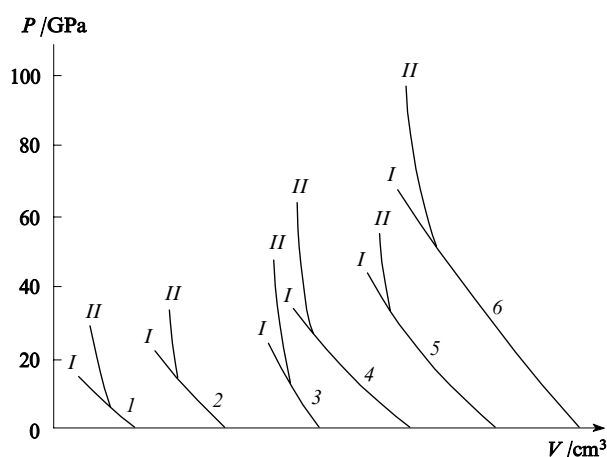


Figure 9. Kinks in the shock compressibility curves of various smixtures in the region of chemical interaction. Ni + Ti (~7 GPa) (1), Sn + S (~15 GPa) (2), Ti + C (~15 GPa) (3), Fe + S (~28 GPa) (4), Cu + Al (~32 GPa) (5) and Sn + Te (~55 GPa) (6); in all cases I refers to the mixture and II refers to the product.

Generally, the chemical interaction between the components of a mixture can be accompanied by either a decrease or an increase in volume. For the compositions M^zX^{8-z} ($X = \text{Cl, Br, I; S, Se, Te; P, As, Sb}$), the synthesis of compounds of Group 1B, 2B and 3B metals leads to an increase in the volume, whereas the synthesis of compounds of Group 1A, 2A and 3A metals leads to a decrease in the volume (this is partially compensated by an increase in the volume due to thermal expansion). The magnitude of the changes in the volume can be estimated with ease. Indeed, the exothermic effect lies in the range $100\text{--}200\text{ kJ mol}^{-1}$, the heat capacity is of the order of $40\text{--}50\text{ J (mol K)}^{-1}$ and the temperature of the substance increases to $2000\text{--}4000\text{ }^\circ\text{C}$. The thermal expansion coefficients of solids are about 2×10^{-5} ; therefore, these temperature changes cause the volume to increase by $4\%\text{--}8\%$. Physical measurements showed that the degree of conversion in shock waves is at most 0.5; therefore, the actual increase in volume due to thermal expansion is $2\%\text{--}4\%$. It is these numerical values that should be used when comparing the volumetric changes occurring as a result of a chemical reaction.

As typical examples, we will consider changes in the molar volumes of the low-pressure phases in the reactions



where $M = \text{Zn, Ca}$.

Calculations were performed using the expression

$$V = V_0 \left(1 - \frac{U}{D} \right), \quad (18)$$

derived by combining Eqn (1) and Eqn (2). Here V and V_0 are the initial and final volumes of the body, D and U are the shock and particle velocities (see Section II). For ZnS, the U and D values can be determined from the experimental Hugoniot adiabat⁸⁸ and for CaS this can be done using the Hugoniot adiabat reconstructed from Eqns (10) and the results of supersonic measurements of B_0 (64 GPa) and B'_0 (4.2). For Zn + S and Ca + S mixtures, the particle velocities can be calculated using the additivity scheme from the Hugoniot adiabats of the elements (see Table 2) and Eqn (16). Having determined the $U_{1,2}$ values for a number of the pressure values and knowing the density of the mixtures, one can calculate D_1 using expression (15) and then the V values from Eqn (18). The $P = f(V)$ dependences were established using the following characteristics:

for Zn + S

$$D = 2.085 + 1.804 U, \rho = 3.95\text{ g cm}^{-3};$$

for ZnS

$$D = 3.13 + 1.30 U, \rho = 4.085\text{ g cm}^{-3};$$

for Ca + S

$$D = 2.93 + 1.13 U, \rho = 1.73\text{ g cm}^{-3};$$

and for CaS

$$D = 4.95 + 1.30 U, \rho = 2.61\text{ g cm}^{-3}.$$

Since the synthesis of zinc and calcium sulfides is accompanied by heat release (Q), one should take into account the additional 'thermal pressure' ΔP_Q . According to the Mie–Grüneisen model, at $\Gamma V = \text{const}$ it can be calculated using an approximate relation

$$\Delta P_Q = \frac{2\Gamma Q}{V(\Gamma + 2) - \Gamma V_0}. \quad (19)$$

The Q values for ZnS and CaS are 191.8 and 473.2 kJ mol^{-1} , respectively (see Ref. 89). In fact, the conversions in shock waves are at most 50%; therefore, the parameters of Eqn (19) are as follows: $0.5 Q$, $\Gamma = 0.68$ (ZnS)⁸⁸ and $\Gamma = 1.41$ (CaS).⁹⁰

Finally, we must allow for the change in the thermal effect due to the different compressibility of the mixture and the product. The difference in the shock compression work

$$E_c = \frac{P(V_0 - V)}{2}$$

between the mixture and the product in the $M + S \rightarrow MS$ system causes a decrease in Q by

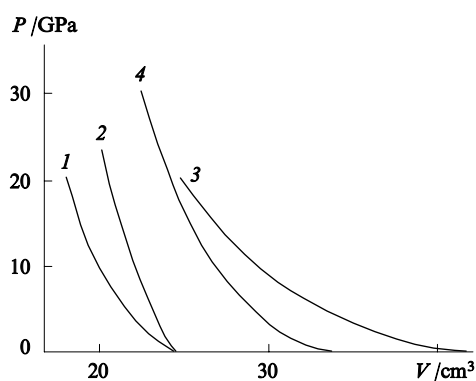
$$\Delta E_c = E_c(M + S) - E_c(MS).$$

Table 7 presents the results of the $V = f(P)$ calculations using the relations listed above and the P^* values for the heated compounds obtained by summation of the P and ΔP_Q values. Analysis of the data in Table 7 and the plots in Fig. 10 shows that the P – V Hugoniot curve deviates towards larger volumes upon the formation of ZnS and towards smaller volumes for the synthesis of CaS. Raising the pressure causes the curves for CaS and Ca + S to approach each other.

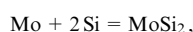
This result is important for the understanding of the processes occurring, *e.g.*, under shock compression of a $\text{Mo} + 2\text{Si}$ mixture. A kink in the P – V plot towards smaller volumes in the pressure range $6.5\text{--}7\text{ GPa}$ was interpreted⁹¹ as a result of the melting of silicon and corresponding increase in the compressibility of the mixture. It was assumed⁹¹ that capillary flow of molten silicon limits the deformation of the molybdenum particles and mixing between the reactants. However, in another study by these authors a partial interaction in the same system, detected in the recovery experiments was interpreted as a reaction of solid molybdenum with molten silicon.⁹² According to Vreeland,⁹³ the reactions of titanium, niobium and molybdenum with silicon proceed by

Table 7. Changes in molar volumes during shock-induced syntheses $M + S \rightarrow MS$.

P /GPa	V (see ^a)	E_c (see ^b)	V (see ^a)	E_c (see ^b)	Q (see ^b)	ΔP_Q /GPa	P^* /GPa
Mixture Zn + S			Compound ZnS				
0	24.68	0	23.86	0	95.9	0	0
3	21.98	4.05	22.35	2.25	94.1	2.93	5.93
6	20.62	12.2	21.23	7.9	91.6	3.06	9.06
9	19.71	22.35	20.35	15.8	89.35	3.17	12.17
12	19.03	33.9	19.62	25.45	87.45	3.27	15.27
15	18.50	46.35	19.01	36.4	85.95	3.37	18.37
Mixture Ca + S			Compound CaS				
0	41.70	0	26.74	0	236.6	0	0
5	33.32	20.95	24.99	4.37	220	13.0	18.0
10	29.31	61.95	23.70	15.2	189.8	12.4	22.4
15	26.77	112.0	22.69	30.4	155.0	11.0	26.0
20	24.95	167.5	21.87	48.7	117.8	9.0	29.0
25	23.56	226.7	21.18	69.5	79.4	6.5	31.5

^a In $\text{cm}^3 \text{mol}^{-1}$; ^b in kJ mol^{-1} .**Figure 10.** Shock compressibility curves for various mixtures. Zn + S (1), ZnS (2), Ca + S (3) and CaS (4).

heterogeneous (liquid–solid) mechanism. The kink in the $P-V$ curve⁹¹ can be due to the reaction



which is accompanied by a decrease in the volume by 27.7% (see Ref. 94). The heat of the reaction (132 kJ mol^{-1}) has no effect on the volume ratio, because the volume of the product increases only by a few per cent.

Probably, similar processes also occur under shock compression of Al + SiO_2 mixture. A kink in the Hugoniot adiabat of this mixture with a decrease in the volume was interpreted⁹⁵ as a quartz $\rightarrow$ stishovite transition. The chemical interaction resulting in Al_2O_3 is also accompanied by compaction and release of much higher energy (619 kJ mol^{-1} for stoichiometric composition), which makes this reaction preferred. Additionally, the kink in the shock adiabat of the mixture was detected at 20 GPa, whereas the phase transition in pure quartz occurs at 38 GPa. Voskoboinikov⁹⁶ analysed the shock adiabats of the mixture and compound and showed that in this case the chemical reaction is more probable than a phase transition.

To decide between the phase transition and shock-induced chemical transformation accompanied by compaction, it is sufficient to measure the temperature, because the heat of a chemical reaction is usually an order of magnitude higher than that of polymorphic transformation. For instance, kinks in the Hugoniot adiabats of CS_2 and C_6H_6 at $P > 6 \text{ GPa}$ with a decrease in

volume⁹⁷ can be treated as phase transitions. However, the results of optical measurements⁹⁸ revealed a stepwise increase in the temperature of the medium by more than 250°C at these pressures, which indicates a chemical reaction (in this case, decomposition). If the decrease in the volume upon a shock-induced chemical transformation is small, it can be compensated by thermal expansion and the shock adiabat will exhibit no features. For instance, the volumes of organofluorine compounds are changed insignificantly,⁹⁹ whereas the changes in the temperature are large, namely, a stepwise increase by 500°C at $P > 22 \text{ GPa}$ owing to decomposition.¹⁰⁰ Similarly, a shock compression study¹⁰¹ of teflon at $P > 34 \text{ GPa}$ showed an abrupt increase in the speed of sound behind the shock-wave front and almost smooth shock adiabat curve. A chemical reaction in the Nb + Si mixture substantiated by the recovery experiments was detected from a jumpwise increase in the speed of sound.¹⁰²

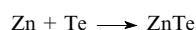
Yet another method of detection of physicochemical transformations under dynamic loading is the study of shock wave damping. From general physical considerations it follows that¹⁰³

$$\frac{\partial D}{\partial \tau} = \frac{c}{c + U - D},$$

where c is the speed of sound behind the shock-wave front. A phase transformation accompanied by densification is characterised by an increase in D and a decrease in U ; therefore, the damping rate will increase.

Measurements in shock compressed metal–oxide mixtures revealed dramatic changes in the shape of the $P = f(\tau)$ curves after particular pressures were reached.¹⁰⁴ For instance, a fivefold increase in the shock wave damping in the Mg + SiO_2 mixture (sample thickness 2 mm) in the pressure range 24.0–28.8 GPa, a twofold increase for the Mg + TiO_2 mixture at 29.6–31.2 GPa, a threefold increase for the Mg + Fe_2O_3 mixture at 18.8–23.6 GPa and a fourfold increase for the Al + Fe_2O_3 mixture at 17.1–22.8 GPa were observed compared to monotonic changes in the damping rates beyond these pressure ranges. In all cases the volumes of products were smaller than those of the starting mixtures. Correspondingly, the deviations of the compressibility curves for these reactions should be opposite in sign compared to the deviations of the compressibility curves for the shock-induced reactions characterised by an increase in volume.

A shock-induced solid-phase reaction



was studied using cold and pre-heated mixtures.¹⁰⁵ The shock velocity in the mixture pre-heated to 242°C showed a jumpwise increase by 0.7 km s^{-1} . Since an exothermic reaction begins at this temperature, the shock velocity jump can be explained by energy transfer from the chemical reaction to the shock wave in the zone of high dynamic pressure. An increase in the shock velocity induced by exothermic reaction was also revealed in a study of the reaction in the Zn + S mixture.¹⁰⁶

In 1993, researchers from the USA first reported pressure measurements in the course of chemical transformations using piezoelectric transducers; in particular, a reaction with a micro-second duration was detected in the Ti–Si system. A review of corresponding studies is available.¹⁰⁷

c. Estimation of the reaction duration from mechanical changes in recovery ampoules

The temperature and kinematic measurements are labour-consuming and therefore cannot be used for quick analysis of the duration of chemical transformations under shock compression. Taking into account the fact that shock-induced synthesis occurs mainly in the axial region of cylindrical ampoules (Mach stem whose size is determined by the energy supplied), the reaction can be detected from the change in the Mach stem diameter and from the action of the Mach stem on the bottom of the ampoule (spall plate) behind the shock wave front.¹⁰⁸

Shock compression experiments carried out under the same conditions revealed a larger diameter and deeper spall for the Sn + S mixture compared to SnS, the mass of the spall plate being 0.06 and 0.003 g, respectively. Since the velocity of the motion of the spall element is given by

$$v = 2U,$$

for this system one gets $v = 4.3 \text{ km s}^{-1}$. From here the kinetic energy of the spall plate, E is about 60 kJ mol^{-1} for the mixture and nearly 3.2 kJ mol^{-1} for the compound. The difference, $\sim 57 \text{ kJ mol}^{-1}$, is the increase in energy equal to the contribution of the heat of the chemical reaction to the energy of the Mach wave. This difference corresponds to an extent of conversion of 30%, which is similar to the reaction yield determined from the temperature and kinematic measurements.

Similar spalling features in the Sn + Te system were observed using more energetic explosives ($D_0 = 7.3 \text{ km s}^{-1}$) and, correspondingly, at a higher pressure of the onset of the chemical reaction detected in kinematic measurements.

Studies of spalling phenomena in the recovery ampoules during shock compression of Ti + C and Zn + S mixtures using explosives with a detonation velocity of 6.2 km s^{-1} in the former and 7.2 km s^{-1} in the latter case showed the formation of compounds TiC and ZnS in ~ 7 and $\sim 90\%$ yields, respectively.¹⁰⁹ A regular decrease in the Mach stem diameter with an increase in the stiffness difference (ρc^2) between the shell and the content of the cylindrical ampoule was also established in that study. The stiffnesses of compounds TiC and ZnS are higher than those of the corresponding mixtures; therefore, a decrease in the difference in ρc^2 between the shell and the substance under study causes extension of the Mach region in the shock compressed material.

Endothermic transformations lead to narrowing of the Mach stem. A dark Mach stem appeared in the axial region of the cylindrical ampoule at a distance of about two diameters from the upper end upon shock compression of CuCl. The downward motion of the Mach stem was accompanied by its monotonous extension in a conical fashion. Once a certain intensity was reached, the substance in the Mach zone melted and the Mach stem narrowed; further motion toward the bottom of the ampoule was again accompanied by extension of the Mach stem until the next melting of the powder.

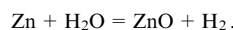
2. Solid-phase reactions

The formation of high-pressure phases as a result of a chemical reaction indicates that the reaction proceeds in the high-pressure zone. To date, a large body of experimental data on the decomposition and synthesis reactions has been accumulated. In the former case the interacting atoms are inside molecules or coordination polyhedra of crystals, *i.e.*, they can be treated as being in contact with one another, the decomposition occurs instantaneously and time is only taken for the separation and nucleation of a new phase. The latter case requires dispersion and mixing of particles, cleavage of chemical bonds and diffusion of reactant atoms followed by the formation of products and nucleation. Clearly, the decomposition processes are faster than syntheses.

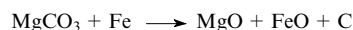
Indeed, disproportionation of Al_2SiO_5 into Al_2O_3 and SiO_2 under the action of high-energy shock waves results in the formation of a high-pressure SiO_2 phase with stishovite-type structure.^{110, 111} Similar phases are formed under shock compression of ZnBaGeO_4 ,¹¹² Mg_2SiO_4 ¹¹³ and ZrSiO_4 .¹¹⁴ A high-pressure boron nitride phase (c-BN) was produced by shock-induced disproportionation of $\text{BH}_3 \cdot \text{NH}_3$.¹¹⁵ Explosive decomposition of organic compounds mixed with explosives, resulting in the formation of diamond as detonation product was reported.^{116, 117} Disproportionation of PbO upon shock compression by high-energy shock waves in a cylindrical ampoule occurs behind the front of the incident shock wave. Propagation of the reflected wave through a mixture is accompanied by separation of the mixture components and accumulation of lead in the Mach region.¹¹⁸ Therefore, the chemical reaction occurs in the region

between the incident and reflected waves and has a duration of $10^{-7} - 10^{-6} \text{ s}$.

At high pressure, water possesses the properties of acid. Because of this, metals preceding hydrogen in the electrochemical series should dissolve in this modification of water. Taking into account this fact, we shock compressed a mixture of zinc powder and ice in cylindrical recovery ampoules cooled with liquid nitrogen before explosion using high-power explosives ($D_0 \geq 6.2 \text{ km s}^{-1}$). Analysis of the recovered product revealed the formation of zinc oxide and dihydrogen following the reaction



The reaction products cannot result from pyrolysis of water, because the temperature of the ampoule after explosion was only slightly higher than room temperature. Similar reactions proceed with other metals (B, Al, Ga, Ge, Ti, Zr, Nb, Cr, Mo, W, Mn) that dissolve in acids, *i.e.*, the chemical transformation does occur in the high-pressure zone.¹¹⁹ A similar experiment¹²⁰ using a cylindrical ampoule with a large reservoir for expansion and quenching of reaction products (see Fig. 3c) resulted in cubic zirconia (high-pressure phase). The reaction



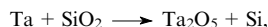
was used for the synthesis of hexagonal diamond (lonsdeilite).¹²¹

Consider now yet another aspect, which also indicates a shock-wave character of chemical transformations. Thermodynamics operates with positive pressures. As mentioned above, shock compression technique allows production of negative pressures and formation of loose structures.

A shock compression study¹²² of Nd_2O_3 revealed the formation of a polymorph called E-phase. According to spectral analysis data, the E-phase also contained SiO_2 ($\sim 30\%$). Experiments proved that spall microparticles from the inner surface (mainly from the bottom and to a lesser extent from the walls) of the recovery ampoule served as the source of SiO_2 . The density of the E-phase (1.6 g cm^{-3}) is much lower than those of the starting neodymium oxide (7.42 g cm^{-3}) and quartz (2.65 g cm^{-3}). A very small amount of single crystals of this phase was obtained. The crystals had a monoclinic lattice ($a = 7.5$, $b = 8.7$, $c = 10.3 \text{ \AA}$; $\beta = 104^\circ$) and low refractive index ($n_g = 1.57$, $n_m = 1.56$, $n_p = 1.54$), whereas the refractive index of the starting neodymium oxide is 2.10. The E-phase of neodymium oxide is insoluble in acids or alkalis and exhibits a high thermal stability with a reversible change of colour from white to violet. Attempts to obtain this phase under shock compression of $\text{Nd}_2\text{O}_3 + \text{Si}$, $\text{Nd}_2\text{O}_3 + \text{SiO}$ and $\text{Nd}_2\text{O}_3 + \text{SiO}_2$ mixtures using various explosives failed. Namely, reactions at any reagent ratios resulted in conventional neodymium silicates of different compositions characterised by high densities and refractive indices. Apparently, the reactivity of the spall elements is strongly different from the bulk sample reactivity due to an increase in the concentration of ruptured chemical bonds in such species upon spalling from the monolithic body.

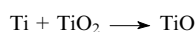
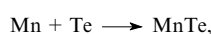
Similar results were obtained in a shock compression study of $\text{Zr} + 2\text{S}$ mixture, which revealed the formation of ZrS_2 with 'shrunk' unit cell parameters.¹²³ In a detailed study the product was identified as a solid solution $\text{Zr}_{1-x}\text{Fe}_x\text{S}_2$. Here, the source of iron was also the recovery ampoule (no solid solution is formed when using ampoules with quartz embeddings) and the product yield was dependent on the smoothness of the inner surface of the ampoule. The last-mentioned feature means that iron microparticles are spalled from scratches on the inner walls. It is important that no solid solution is formed under shock compression of a mixture of ZrS_2 with iron powder, or by thermal method because the product obtained by shock-induced synthesis decomposes to ZrS_2 and FeS on heating.

When using spall microparticles of elements with equal electronegativities (heat of reaction is zero) as reactants, the thermodynamic situation can change. An example is provided by the reaction



which proceeds under shock compression of SiO_2 in tantalum ampoule,¹²⁴ being impossible under normal conditions.

The supply of iron spall microparticles from the walls of a cylindrical ampoule to the material compressed is governed by the density of the material (the higher the density the lower the supply) and by the physicochemical processes occurring under shock compression. In particular, an increase in the yield of the dense phase from 45% to 85% during the phase transformation of BN is accompanied by fivefold more intense contamination of the sample with iron from the cylindrical ampoule. Shock compression of PbO , PbF_2 and ZnS accompanied by phase transformations in the compounds causes a twofold increase in the contamination of samples with iron compared to the shock compression of the high-pressure phases that do not undergo any transformations. The contamination of products of the shock-induced syntheses



with iron is two times (MnTe , TiO) or even two orders of magnitude (SnS) higher compared to inert compounds of the same compositions under the same conditions. Correspondingly, shock-induced decomposition of CdCO_3 to CdO is accompanied by not only a reduction of temperature and densification but also a decrease in the extent of contamination with iron by an order of magnitude.

An additional argument substantiating the conclusion that solids can undergo chemical transformations under shock is provided by the fact that reactions occur mainly in the axial region of the cylindrical ampoule (Mach region).^{91,94} This seemed obvious for long, because the pressure and temperature are maximum in the Mach stem, decrease in the adjacent layer (here, the reaction is only partially completed) and reach minimum values at the walls of the ampoule where no reaction occurs at all. However, it remains unclear why heat released in the shock compressed mixture (extent of chemical conversion is $40 \pm 10\%$ according to experimental data) does not initiate the process in other regions of the sample that contact the hot zone?

The reason for such a behaviour is the high pressure in the Mach zone, which leads to reduction of the temperature of the reacting mixture (see a dome-shaped plot of temperature changes under shock compression of $\text{Sn} + \text{S}$ mixture in Fig. 8).¹²⁵ What processes do occur in the product after unloading if the high pressure underestimates the heat (it can reach zero upon further heating; this is called 'cold synthesis')? Since the compression–expansion cycle is reversible, unloading should be followed by heat release, but why the heat released does not initiate a chemical reaction in the unloaded sample in the region near the axis of the ampoule?

The answer to this question deserves special studies, however to a first approximation one can assume that in the course of unloading at negative pressures the substance arrives at an additional minimum on the potential surface. Probably, this minimum corresponds to an ordered defect or dislocation lattice, because the densities of all substances synthesised by explosion technique were different from the reference values. For instance, heating of shock-synthesised CrTe is accompanied by densification of the material and corresponding exothermic effect at 410°C . However, we failed not only to complete a transition of the compound to the normal state but even to reach the density of the initial mixture after storage of the sample at 700°C for 2 h.¹²⁶ Therefore, shock-induced synthesis results in compounds that possess new properties. Partial completion of exothermic reactions in recovery ampoules under shock compression can be treated as yet another criterion for occurrence (or absence) of the chemical interaction of solids in the high dynamic pressure zone.

V. Mechanism of ultrafast solid-phase reaction

Experimental facts indicating that solid-phase syntheses can proceed under shock (see above) require a non-trivial explanation. Indeed, conventional diffusion in solids is much slower than that providing the microsecond durations of chemical reactions. Ultrafast atom diffusion in shock compressed materials was explained by several factors. These are a very high concentration of defects, plastic deformation,^{127,128} heterogeneous heating of components with different stiffness,¹²⁹ reduction of activation energy due to crystal lattice breakdown upon phase transitions^{130,131} or melting of one or all reactants.¹²⁷ Although all these factors favour a decrease in the activation energy and acceleration of diffusion, they are insufficient to provide an explanation for the mechanism of ultrafast mixing of components in the reacting mixture and separation of reaction products, a threshold-type character of the reaction pressure and other experimental data.

We have hypothesised that ultrafast forced diffusion of mixture components is due to the particle velocity difference between the components under shock compression.⁸⁵ This was experimentally proved in a number of studies^{132,133} (see also Refs 134 and 135). Indeed, if solid reagents 1 and 2 possess the same mechanical properties, namely, the same shock adiabats and, hence, the particle velocities ($U_1 = U_2$), the motion of the material behind the shock wave front resembles the motion of a chessboard with the same pattern of black and white squares. If differently coloured squares move at different velocities, the velocity difference represents the velocity of forced diffusion ($U_d = U_1 - U_2$), which causes deformation and interdiffusion of the squares. It is important that U_d increases as the pressure increases; this contradicts conventional concepts of retardation of diffusion upon densification. Based on this model, it is possible to immediately determine the mixing time; therefore, the reaction duration can be found as follows

$$\tau \approx \frac{d}{U_d},$$

where d is the grain size. For instance, at $U_d = 1 \text{ km s}^{-1}$ and $d = 0.1 \text{ mm}$ one gets $\tau \approx 10^{-7} \text{ s}$.

Strictly speaking, the rate of forced diffusion in a heterogeneous mixture is not equal to $\Delta U_{1,2}$. Here, a fraction of $\Delta U_{1,2}$ should be used with allowance for unloading of the stiff component into the softer body. For most compounds at moderate pressures this fraction is about 0.5 and therefore the characteristic diffusion time (mixing time) should be determined using the relation^{80,136}

$$\tau = \frac{2d}{\Delta U_{1,2}}.$$

Knowing the Hugoniot adiabats for Sn , S and Te , one can find with ease that for the $\text{Sn} + \text{S}$ mixture (particle size $100 \mu\text{m}$) the time $\tau = 0.3 \mu\text{s}$ corresponds to a pressure of 10 GPa and for the $\text{Sn} + \text{Te}$ mixture (the same particle size) the time $\tau = 0.8 \mu\text{s}$ corresponds to a pressure of 50 GPa. This is consistent with experimental data with allowance for the scatter in the particle size and errors in pressure measurements in the reacting mixture.

How does interdiffusion occur? The most probable model for this process is as follows. Propagation of a shock wave through a heterogeneous mixture of powders is accompanied by fragmentation of grains into blocks of size up to $50\text{--}100 \text{ \AA}$ (according to X-ray diffraction data⁴) due to unloading of the stiff material into milder grains. These blocks ('spalled squares') are mixed at a forced diffusion rate. In this case the chemical reaction immediately occurs on the surfaces of the contacting blocks, thus involving from 20% to 40% of the total number of atoms. It is this degree of conversion that is detected by various physical methods (see above). Probably, reactions on the particle surfaces are also favoured by contact melting of grains during shock compression.

The mechanical properties, *e.g.*, U of the reaction product differ from those of the starting components. Due to the particle velocity difference between the reactants and product the particle surfaces are 'cleaned' from the reacting layer, which ensures continuous chemical interaction.

Different stages of solid-phase reactions, namely, grinding before reaction, interdiffusion and, finally, chemical interaction were considered in studies on the microstructure of products of shock compression of powder mixtures $M + 2\text{Si}$ ($M = \text{Al, Ti, V, Nb, Ta, Cr, Mo, W, Fe}$).^{94, 137–140} Since the pressure and temperature in cylindrical ampoules rapidly decrease from the axial region to periphery, a transition from the mixture of components to compounds synthesised can be observed using the same sample by analysing its cross-section. With the known law of pressure changes across the section of the cylindrical ampoule one can determine the threshold reaction pressure.⁹⁴

Yet another feature should be noted. The degree of conversion is 100% in the axial region of the cylindrical ampoule, decreases as the shock wave intensity decreases towards the periphery of the cylinder and is zero (no reaction) on the walls of the ampoule, although the decrease in pressure should cause the heat of the reaction to increase. This can be explained as follows: the characteristic time of unloading of a shock compressed body in the laboratory experiments with charges 40–60 mm in diameter is $\sim 10^{-6}$ s; the decrease in the dynamic pressure from 100 to 1 GPa means that the duration of the action of the high pressure in each step $\Delta P = 1$ GPa is shortened to $\sim 10^{-8}$ s, which is insufficient for interdiffusion of large reactant particles. Thus, shock-initiated solid-phase chemical reactions proceed with different yields at the same pressure depending on the pressure 'prehistory'. In other words, the results depend on whether the optimum pressure was produced by detonation of a corresponding explosive (here, the duration is $\sim 10^{-6}$ s) or was attained during the drop from a higher level and therefore acts in each step for a much shorter time.

An important feature of shock-initiated reactions is a threshold character of the behaviour of their thermodynamic parameters. Several criteria for the explanation for this phenomenon were proposed. Krüger *et al.*¹⁴¹ assume that the threshold of the reaction $\text{Ni} + \text{Si}$ is determined by the critical energy necessary for initiation of the reaction. Iyer *et al.*¹⁴² determined the threshold wave velocity for the reaction $\text{Ni} + \text{Al}$; Meyers¹⁴³ assumes that the threshold of the onset of the reaction $\text{Nb} + \text{Si}$ is due to melting of silicon; and Thadhani *et al.*¹⁰⁷ concluded that the threshold of the solid-phase interaction is the ultimate strength of the crystalline particles, *i.e.*, the shock-initiated reaction is a mechanochemical process. According to our model, the pressure corresponding to the onset of the reaction is determined by the time taken by the forced diffusion front (due to the mass velocity difference between components) to travel a distance equal to the particle size.

The thermodynamic and kinetic aspects of shock-initiated solid-phase reactions were considered and the results of numerical modelling of the mechanisms of these reactions were presented.¹⁹

Theoretical treatment of the possibility of solid-phase detonation as a result of exothermic shock-initiated reaction was reported.^{144, 145} Constant shock-wave velocities in the reacting mixtures of zinc and sulfur powders and aluminium and fluoropolymer were observed.^{106, 146} Investigations of this phenomenon are of fundamental importance.

VI. Conclusion

There are three promising avenues of research on the chemical transformations under the action of shock waves.

One of them involves improvement of the shock-wave loading techniques, which permits separate variation of thermodynamic parameters of the interacting bodies. For instance, if one reactant is placed in a target and the other reactant is the impactor material, it is possible to increase the chemical potential difference between the reactants that have similar or equal electronegativities (*i.e.*, a

low or zero heat of formation) and therefore do not react under normal conditions. An example is provided by $\text{B} + \text{Sb}$ mixture for which no shock-induced interaction of the components was reported so far.

The second avenue of research in the field of shock-induced synthesis, which has no analogues in traditional chemistry, involves the use of spall microparticles as reactants. In this connection the cumulative effect is of considerable interest. It allows one to generate dense microparticle flows from planar or conical hollownesses in various metals and to control the thermodynamic parameters of reactants by varying the angle of the hollowness, the type of the explosive and the distance to the target.

The third promising field of chemical applications of the shock-wave technique is the synthesis at negative pressures, which results in the formation of loose structures. Macroscopic loose structures can be obtained by shock compression of a mixture of the desired material and explosive in a recovery ampoule. Compression of the ampoule and compaction of the powder are followed by internal detonation and formation of pumice.¹⁴⁷ It is possible to control both the pore concentration and pore topography, which seems to be promising for application in catalysis with allowance for improvement of catalytic activity under shock (see references cited in Ref. 47).

Dynamic-static compression of nanocrystalline powders can also find certain applications. Transition from macroscopic particles to nanoparticles is accompanied by an increase in the elastic modulus by tens of per cent.^{148–151} This is due to the surface energy of micropowders. In the bulk crystal the proportion of the surface energy is negligible, but in an array of size 100 Å and a bond length of 2 Å the number of surface atoms is 6×50^2 or 12% of the total number of atoms. The potential energy of the material increase by the same value and, since $E \sim BV$, the elastic modulus will also increase by 12% at the same volume, which is consistent with experimental data. Will attempts to compact diamond nanopowders to monolithic state at the same size be successful, the novel material should be harder than conventional diamond single crystals or polycrystals.

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^e — *High Temp. (Engl. Transl.)*

^f — *Dokl. Phys. (Engl. Transl.)*

^g — *Combust. Explos. Shock Waves (Engl. Transl.)*

^h — *Thech. Phys. (Engl. Transl.)*

ⁱ — *Russ. J. Inorg. Chem. (Engl. Transl.)*

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^l — *High Energy Chem. (Engl. Transl.)*

Phase equilibria in the W–C system and tungsten carbides

A S Kurlov, A I Gusev

Contents

I. Introduction	617
II. Phase equilibria and the crystal structures of phases in the W–C system	618
III. Phase equilibria in the W–Co–C system	625
IV. Electronic structures of tungsten carbides	626
V. Methods of synthesis of tungsten carbides and WC–Co alloys with different grain sizes	628
VI. Conclusion	634

Abstract. The results of experimental and theoretical investigations of phase equilibria in the W–C system and of the crystal and electronic structures of tungsten carbides are generalised. The phase diagram of the W–C system supplemented by new compounds is considered. The sequence of phase transformations associated with ordering of lower hexagonal carbide β -W₂C is analysed. The region of existence of cubic carbide γ -WC_{1–x} is discussed in detail. The generalised information on the phase equilibria in the ternary system W–Co–C, which forms the basis for the synthesis of hard alloys WC–Co, is given. Methods of synthesis of tungsten carbides and hard alloys based on them are considered. Modern methods for the synthesis of nanostructured hard alloys are discussed in detail as well as their structures and properties. The bibliography includes 131 references.

I. Introduction

Carbides of Group IV–VI transition d-metals belong to non-stoichiometric interstitial compounds.^{1–4} Transition metals of Groups IVA and VA (Ti, Zr, Hf, V, Nb, Ta) form cubic carbides MC_y with the B1-type structure (NaCl), while the metals of Groups VA and VIA (V, Nb, Ta, Cr, Mo, W) form in addition lower hexagonal carbides M₂C_y with the L'3-type structure (W₂C).[†]

A characteristic feature of the structures of these compounds is the presence of the face-centred cubic (fcc) or hexagonal [simple or closely-packed (hcp)] metal lattice, in which the carbon atoms are located in the centre of octahedral or trigonal interstitials of the metal lattice. The metal structure changes with the formation of carbides. In carbides, the metal lattice symmetry differs from that of transition metal lattices. Group IV metals (Ti, Zr, Hf), which have the hcp structure, form carbides with the fcc metal sublattices. Metals with the body centred cubic (bcc) structure (V, Nb, Ta, Cr, Mo, W) form carbides with the cubic or hexagonal metal sublattices. The changeover of the crystal structure of

metals upon formation of carbides suggests strong metal–carbon interactions and negligible interactions between carbon atoms.⁵

In carbides, the carbon atoms, that are located in the interstitial voids of the metal sublattice form a non-metal sublattice. Unoccupied interstitials are called structural vacancies and designated as □. Together with carbon atoms, they form a substitutional solution in the non-metal sublattice. The presence of structural vacancies is a characteristic feature of carbides that belong to the group of non-stoichiometric compounds. The concentration of vacancies and their distribution type have a strong effect on the properties of such carbides. The results of experimental and theoretical studies on how the distribution of atoms and vacancies affects the structure and properties of strongly non-stoichiometric compounds are generalised in monographs.^{1–4,6}

Carbides of Group IV–VI transition d-metals have the highest melting points and are the hardest among all the compounds known.^{3,4,7–12} Therefore, these carbides are used in manufacturing structural and tool materials capable of operating at elevated temperatures, in aggressive media and under heavy loads; they make it possible to develop protective and hard coatings, *etc.* Tungsten carbide WC is not the hardest or the most refractory compound, *viz.*, its melting point (~ 3060 K) is low as compared with non-stoichiometric carbides TiC_y, ZrC_y, HfC_y, VC_y, NbC_y and TaC_y and its hardness (18–22 GPa at 300 K) is also low as compared with these carbides.^{3,4} However, the hardness of WC is sufficiently stable and decreases relatively slightly with the increase in temperature from 300 to 1200–1300 K. Moreover, as compared with carbides of other transition metals, tungsten carbide has a higher modulus of elasticity and a lower coefficient of thermal expansion. It is the combination of the aforementioned properties and their temperature stability that determines the use of WC in the production of wear-resistant hard alloys, which form the basis of all tool materials.

Tungsten carbide was first synthesised in 1893.¹³ The synthesis of refractory carbides including WC from oxides, in which calcium carbide is used as the reactant, was described.¹⁴ The industrial production of hard alloys based on WC started 20–25 years after its discovery and goes on at present.¹⁵

A S Kurlov, A I Gusev Institute of Solid State Chemistry, Urals Branch of the Russian Academy of Sciences, ul. Pervomaiskaya 91, 620219 Ekaterinburg, Russian Federation. Fax (7-3433) 74 44 95, tel. (7-3433) 62 35 23, e-mail: kurlov@ihim.uran.ru (A S Kurlov), tel. (7-3433) 74 73 06, e-mail: gusev@ihim.uran.ru (A I Gusev)

Received 19 September 2005

Uspekhi Khimii 75 (7) 687–708 (2006); translated by T Ya Safonova

[†] Hereinafter, the lattice types of inorganic compounds are shown according to the following book: W B Pearson *The Crystal Chemistry and Physics of Metals and Alloys* (New York, London: Wiley, 1972); in the parentheses, the typical example of a given type is shown.

The practical interest in tungsten carbide determines the active fundamental investigations of its crystal and electronic structure and also of the physicochemical properties of both WC as such and related compounds and systems that contain it. In the past 20 years, the most active studies were associated with the synthesis and application of nanocrystalline tungsten carbide.

II. Phase equilibria and the crystal structures of phases in the W–C system

In addition to tungsten and carbon, the W–C system includes two phases, namely, W_2C and WC, each having several structural modifications, which are stable in certain temperature and concentration ranges (Fig. 1).

Two successive editions of a handbook on a phase diagrams of binary alloys^{16,17} show the generalised phase diagram of the W–C system, which is mainly based on earlier diagrams of this system^{18–21} and takes into account in part the results of another publication.²² A later handbook²³ represents a phase diagram from a paper by Rudy and Hoffman,²¹ while a Russian handbook²⁴ reproduces a phase diagram of the W–C system given in the handbook cited.¹⁶ Relatively few authors dealt with phase equilibria in the W–C system; however, they used different designations for the discovered phases, which led to the confusion in the description of this system. Even in the handbooks,^{16,17} the table that describes the W–C system confuses the designations for the disordered hexagonal and orthorhombic W_2C phases. To

avoid confusion, in this review, the designations for the W–C system are taken from Ref. 17 (corrected for the revealed mistake). As the illustration, in certain cases we also show the designations used in other sources.

Four modifications are described for lower tungsten carbide W_2C . Three of them are low-temperature β'' - W_2C , intermediate β' - W_2C and high-temperature β - W_2C , which were also designated^{12,18,21} as α -, β - and γ - W_2C , respectively. However, the structures of these modifications were proposed based on the limited experimental data. The structure of yet another modification designated as ε - W_2C (Ref. 25) was revealed sufficiently reliably in neutron diffraction studies.^{25–29}

In all W_2C modifications, tungsten atoms form a hcp metal sublattice, in which one-half of octahedral interstitials are occupied by carbon atoms. These atoms are randomly distributed over the interstitials at high temperatures and are ordered at low temperatures. The possibility of the formation of several structural modifications of W_2C is associated with different types of distribution of carbon atoms. Higher carbide WC with the hexagonal structure is designated as δ -WC [α -WC (Ref. 22) or simply WC (Refs 12 and 21)]. Furthermore, the compositions between lower and higher tungsten carbides include the cubic phase γ - WC_{1-x} [designated also as β -WC (Ref. 22) or α - WC_{1-x} (Refs 12 and 21) or simply WC_{1-x}]. For the first time, tungsten carbide with the cubic structure and the unit cell parameter of 0.416 nm was synthesised³⁰ by its deposition from $W(CO)_6$ vapour and described as a cubic modification of W_2C . Later, a cubic carbide with a unit cell parameter of 0.425 nm was synthesised³¹ in a spark discharge between the electrodes made of hexagonal WC, which were placed into a petroleum bath, and characterised also as lower carbide W_2C . Other authors³² who also detected the cubic modification of tungsten carbide identified it as yet another high-temperature modification of W_2C . However, at present, cubic carbide γ - WC_{1-x} is considered as a structural modification of higher tungsten carbide.

Now, we discuss characteristic features of the crystal structure of phases in the W–C system.

Metallic tungsten has the bcc structure [space group $Im\bar{3}m$ (O_h^9)] of its own structural type A2 (type W). Such a structure is also typical of alkali metals, vanadium, niobium, tantalum, chromium and α -Fe. The crystal structure base contains two atoms in positions 2(a) with coordinates (0 0 0) and (1/2 1/2 1/2).

According to studies by Rudy *et al.*^{18–21} and in line with the phase diagram of the W–C system (see Fig. 1), the most high-temperature phase β - W_2C has a hexagonal [space group $P6_3/mmc$ (D_{6h}^4)] structure of the $L'3$ -type (Fig. 2). The existence of lower

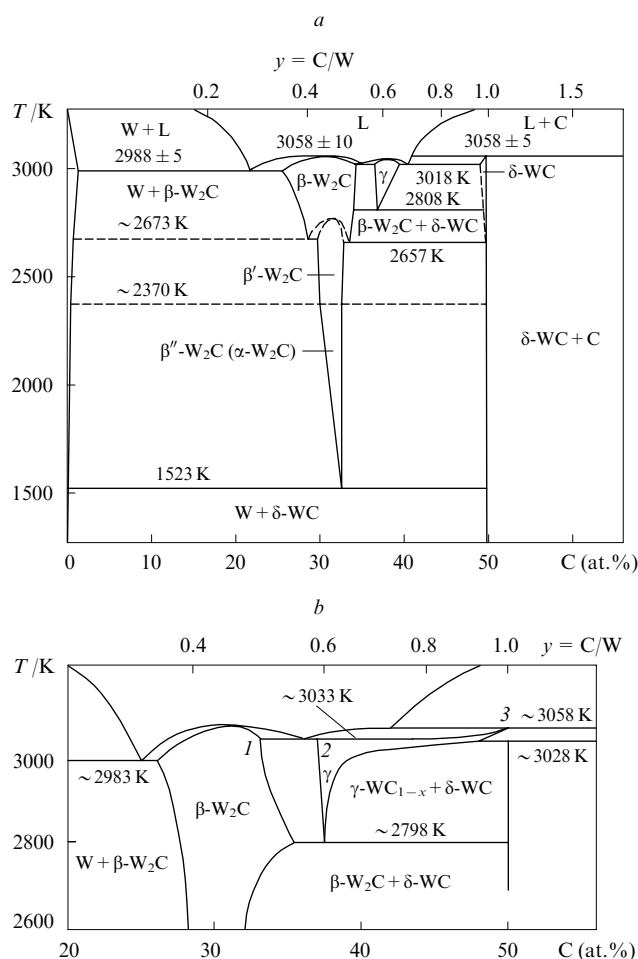


Figure 1. Generalised phase diagram of the W–C system (a) (see Refs 16, 17) and a fragment of this diagram in the high temperature region (b) (see Ref. 22).

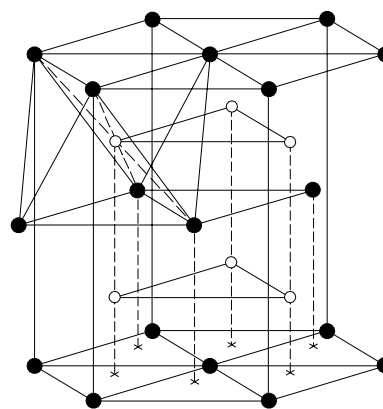


Figure 2. Hexagonal structure of the $L'3$ -type of lower disordered carbide β - W_2C .^{1,2}

Tungsten atoms (solid circles) form a hcp sublattice the octahedral interstitials (open circles) of which are randomly occupied by carbon atoms with a probability of 1/2.

tungsten carbide W_2C with the $L'3$ -type structure was directly proved in a neutron diffraction study,²⁵ in which the disordered W_2C phase was observed together with the ordered phase of this carbide. For high-temperature totally disordered W_2C , the $L'3$ -type structure is quite reasonable by analogy with other lower carbides and nitrides. Particularly, the $L'3$ -type hexagonal structure is typical of most non-stoichiometric lower carbides and nitrides M_2X_y ($M = V, Nb, Ta$; $X = C, N$) with the exception of V_2N . In the unit cell of β - W_2C , two tungsten atoms occupy the positions $2(c)$ with coordinates $(1/3 \ 2/3 \ 1/4)$ and $(2/3 \ 1/3 \ 3/4)$ and one carbon atom is randomly distributed between positions $2(a)$ with coordinates $(0 \ 0 \ 0)$ and $(0 \ 0 \ 1/2)$. In other words, the hexagonal β - W_2C phase is disordered, and its carbon atoms randomly occupy one-half of all octahedral interstitials in the tungsten sublattice; hence, the probability of the occupation of any octahedral interstitial is equal to $1/2$. In the β - W_2C structure, along the c axis, the A and B layers formed by metal atoms alternate with the X layers formed by the non-metal lattice sites in the ... AXBXAXBX ... sequence. The hexagonal β - W_2C phase has a homogeneity region from $WC_{0.34}$ to $WC_{0.52}$ and is stable in the temperature range from 2670–2720 K to the melting temperature at 3000–3050 K. The unit cell parameters of the β - W_2C phase with the composition $WC_{0.52}$ were recorded⁹ to be $a = 0.2992$, $c = 0.4722$ nm and are somewhat larger, viz., $a = 0.3002$ and $c = 0.475$ – 0.476 nm according to data from Ref. 19.[‡]

In the X-ray diffraction experiments, the modifications of lower tungsten carbide, namely, β - W_2C , β' - W_2C , β'' - W_2C and ε - W_2C , are virtually indistinguishable, because they have the same hexagonal metal sublattice and the scattering power of tungsten atoms is many times higher as compared with carbon atoms. Indeed, according to calculations, the changes in the carbon atom distribution in the W_2C lattice are reflected in the X-ray diffraction spectrum only in the range of small angles (Fig. 3). The intensities of $(110)_{\text{orthorhomb}}$, $(111)_{\text{orthorhomb}}$ reflections typical of orthorhombic carbide β' - W_2C , $(001)_{C6}$ reflections of carbide β'' - W_2C with the $C6$ -type structure and also $(101)_\varepsilon$ reflections typical of ε - W_2C do not exceed 0.5% of the intensity of the strongest reflection $(101)_{L'3}$ [or $(101)_{C6}$, $(121)_{\text{orthorhomb}}$, $(210)_\varepsilon$ of the corresponding structure]. In other words, in a real X-ray diffraction study, these reflections are well at the background level and far below the experimental error of intensity measurements.

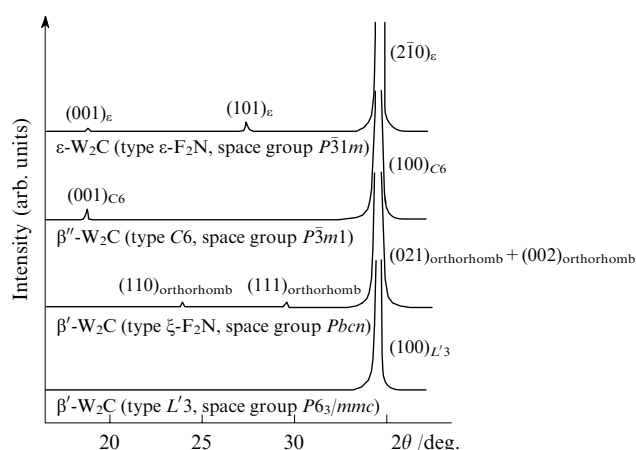


Figure 3. X-Ray diffraction patterns (Cu $K\alpha_{1,2}$ radiation) of different modifications of lower carbide W_2C in the small angle 2θ range for the $WC_{0.50}$ composition, calculated without regard for atomic displacements.^{18, 21}

The modification β' - W_2C of lower tungsten carbide has the rhombic symmetry, although its metal sublattice retains a hexagonal closely packed structure similar to the structure of high-temperature carbide β - W_2C . The structure of orthorhombic β' - W_2C is not yet known with certainty, but can be assigned to the PbO_2 type with the space group $Pbcn$ (D_{2h}^{14}). For this structure, the atomic positions can be specified only in general, namely, the carbon atoms occupy positions $4(c)$ with coordinates $(0 \ y \ 1/4)$ and the tungsten atoms are in positions $8(d)$ with coordinates $(x \ y \ z)$. Based on the comparison of experimental and theoretical positions of the reflections in the X-ray diffraction pattern, it was concluded¹⁸ that lower carbide β' - W_2C (β - W_2C) has an orthorhombic structure similar to the ζ - Fe_2N -type structure of ordered carbide Mo_2C and pertains to the same space group $Pbcn$.³³ However, as was noted above, the hexagonal disordered, trigonal and orthorhombic modifications of W_2C with the same unit cell parameters of the disordered phase are indistinguishable as regards the positions of their X-ray reflections at $2\theta > 30^\circ$. In the range of small angles $2\theta < 30^\circ$, in which the X-ray diffraction spectra are slightly different (see Fig. 3), no reflections were observed¹⁸ and no attempts were undertaken to estimate their possible intensities. Thus, the literature contains no experimental structural data which would substantiate the detection of the orthorhombic lower tungsten carbide β' - W_2C . Moreover, the authors of the study¹⁸ incorrectly determined the coordinates of tungsten atoms in the suggested structure of β' - W_2C carbide [the positions $8(d)$ occupied by tungsten atoms were claimed to have the coordinates $(3/8 \sim 3/8 \sim 1/2)$].

The unit cell of orthorhombic carbide β' - W_2C has the parameters $a = 0.4728$, $b = 0.6009$ and $c = 0.5193$ nm.¹⁸ Our analysis of the distribution of atoms in this unit cell, which is a derivative of the hexagonal cell with the $L'3$ -type structure has shown that tungsten atoms occupy $8(d)$ positions with coordinates $(1/4 \sim 1/8 \sim 1/12)$ and carbon atoms are in $4(c)$ positions with coordinates $(0 \sim 3/8 \ 1/4)$. As compared with the high-temperature hexagonal phase β - W_2C (Fig. 4a), the β' - W_2C phase with

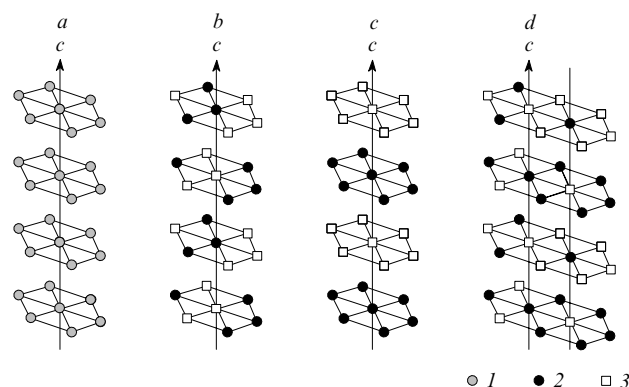


Figure 4. Distribution of carbon atoms in lower carbides β - W_2C (a), β' - W_2C (b), β'' - W_2C (c) and ε - W_2C (d), which are ideal as regards both their compositions and structures.

Planes formed by the non-metal sublattice sites are located normally to the c axis of the basic disordered structure of the $L'3$ -type; tungsten atoms are not shown.²

(a) the $L'3$ -type of β - W_2C carbide with the random distribution of carbon atoms and vacancies; (b) β' - W_2C carbide of the Mo_2C (ζ - Fe_2N) type with the ordered distribution of carbon atoms and vacancies in each plane of the non-metal sublattice; (c) β'' - W_2C (α - W_2C) carbide of the $C6$ type with the ordered distribution of carbon atoms and vacancies in the alternating vacant and carbon-atom-occupied planes of the non-metal sublattice; (d) ε - W_2C carbide of the ε - Fe_2N type with alternating planes of the non-metal sublattice, in which each vacancy is surrounded by six carbon atoms or each carbon atom is surrounded by six vacancies; (1) positions of non-metal interstitial atoms, which are randomly occupied by carbon atoms with a probability of $1/2$; (2) carbon atoms; (3) vacancies.

[‡] Unit cell parameters of all phases discussed in this review were obtained for quenched samples at room temperature.

the ζ -Fe₂N-type structure (Fig. 4b) is ordered with respect to the non-metal sublattice. It is assumed that orthorhombic carbide β' -W₂C has the homogeneity region from WC_{0.34} to WC_{0.49} and exists in an intermediate temperature interval from ~2370 K to 2670–2750 K (see Fig. 1). The later studies failed to detect the orthorhombic (space group *Pben*) phase of β' -W₂C.

The low-temperature phase β'' -W₂C (α -W₂C) is ordered, but the temperature range of its existence and its crystal structure are not yet reliably determined. An electron-diffraction study³⁴ dealt with lower tungsten carbide, which was synthesised by carburisation of a thin metal tungsten film in the carbon monoxide atmosphere at ~1400 K for 5 min. The diffraction pattern of this carbide revealed 74 reflections, which pointed to the ordering of carbon atoms. Presumably, the β'' -W₂C phase has the C6 (*anti*-CdI₂)-type structure with the space group No. 164– $P\bar{3}m1$ (D_{3d}^3); other possible ways of ordering were ignored. In the rhombohedral (trigonal) structure of the C6 type, the layers of carbon atoms regularly alternate with the layers of structural vacancies, being oriented normally to the *c* axis. The layers formed solely by carbon atoms are located between the pairs of layers AB formed by tungsten atoms, and the layers of vacant interstitials, *i.e.*, structural vacancies, are located between the pairs of metal layers BA (Fig. 4c). Note that according to data,³⁴ tungsten atoms occupy virtually ideal positions in the lattice (*z* = 0.25), although the spaces along the *c* axis between the metal layers separated by the layers of vacancies should be slightly shorter than the spaces between the metal layers separated by a carbon-atom layer.

Thus, the ideal structure of β'' -W₂C (α -W₂C) contains two tungsten atoms in positions 2(*d*) with coordinates (1/3 2/3 1/4) and (2/3 1/3 3/4), a carbon atom in position 1(*a*) with coordinates (0 0 0) and a vacant site in position 1(*b*) with coordinates (0 0 1/2). A comparison of the considered structure with that of the high-temperature disordered phase β -W₂C (see Fig. 4c) clearly shows that, as a result of ordering, the positions 2(*a*) one-half of which are randomly occupied by carbon atoms are split into positions 1(*a*) and 1(*b*), where the former are occupied by carbon atoms and the latter remain vacant. At ~2300 K, the homogeneity region of β'' -W₂C (α -W₂C) phase extends from WC_{0.34} to WC_{0.48}; a decrease in temperature is accompanied by narrowing of this region and, finally, its disappearance at 1523 K and a composition of WC_{0.48} (see Fig. 1). The compositions WC_{0.41} and WC_{0.50} of the β'' -W₂C phase have the unit cell parameters *a* = 0.2985, *c* = 0.4717 and *a* = 0.3001, *c* = 0.4728 nm, respectively.¹⁹ If the temperature drops below 1523 K, lower carbide β'' -W₂C decomposes to give W and higher carbide δ -WC (WC). Note that later publications provided no information on the rhombohedral (trigonal) [$P\bar{3}m1$ (D_{3d}^3)] modification β'' -W₂C of lower tungsten carbide with the C6-type structure. It cannot be ruled out that the phases β' -W₂C and β'' -W₂C described in the literature are in fact the same phase differing in the structures and the degrees of ordering of carbon atoms and vacancies.

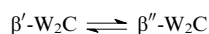
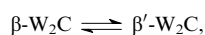
Insofar as the X-ray diffraction technique fails to accurately determine the structure of W₂C modifications, neutron diffraction analysis was applied^{25–29} in the studies of lower tungsten carbide. W₂C was synthesised by sintering of a pressed powder mixture of tungsten and carbon black (W : C = 2 : 1) at high temperature in vacuum for 3 h; then, the samples were quenched from temperatures of 2670, 2570, 2470 and 2370 K by quick immersion into a bath filled with liquid tin.²⁵ According to X-ray diffraction data, at 293 K all the samples synthesised had a hexagonal metal sublattice with the parameters *a* = 0.2992 and *c* = 0.4721 nm. The diffraction spectra of W₂C, which were obtained with the use of a monochromatic neutron beam (λ = 0.1131 nm), revealed, along with structural reflections, weak superstructural reflections which indicated the ordering of carbon atoms and vacancies to form a trigonal ϵ -W₂C phase which pertains to the ϵ -Fe₂N structural type. The unit cell parameters of the ϵ -W₂C phase were found²⁵ to be *a* = *a*_{L/3} $\sqrt{3}$ = 0.5184 and *c* = *c*_{L/3} = 0.4721 nm.

Tungsten carbide samples with the composition ~WC_{0.43–0.45} synthesised by sintering of pressed mixtures of tungsten and carbon black powders at 1920 K for 30–50 h followed by their 10-min cooling to room temperature, were studied.²⁶ Neutron diffraction analysis has shown that carbon atoms are ordered according to the ϵ -Fe₂N structural type (*i.e.*, the same type as that reported in Ref. 25). It was found that the ϵ -W₂C phase has a trigonal structure and pertains to the No. 162– $P\bar{3}1m$ (D_{3d}^1) space group; the unit cell parameters are as follows: *a* = 0.5185 and *c* = 0.4723 nm. In the ideal trigonal structure of this carbide, all tungsten atoms occupy 6(*k*) positions with coordinates (1/3 0 1/4) and carbon atoms occupy 1(*a*) positions with coordinates *c* (0 0 0) and 2(*d*) positions with coordinates (1/3 2/3 1/2), while positions 1(*b*) (0 0 1/2) and 2(*c*) (1/3 2/3 0) remain vacant. Figure 4d illustrates the distribution of carbon atoms and vacancies in the non-metal sublattice of ideal trigonal (space group $P\bar{3}1m$) ϵ -W₂C carbide. However, the best agreement between the experimental and theoretical neutron diffraction patterns was achieved when the population of the positions in the non-metal sublattice by carbon atoms was varied, and a small number of these atoms occupied positions 2(*c*).

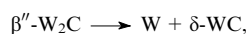
Neutron diffraction analysis (λ = 0.1225 nm) was also used²⁷ for studying the structure of WC_{0.45} carbide, which was synthesised by the arc fusion of pellets pressed from a mixture of tungsten and carbon powders followed by their quenching to room temperature at a rate of 150 deg s^{–1}. According to the data shown, the studied carbide had the same trigonal (space group $P\bar{3}1m$) crystal structure as in earlier studies;^{25,26} the unit cell parameters are *a* = 0.5181, *c* = 0.4722 nm. The best agreement with the experimentally found intensities of reflections (as in Ref. 26) was achieved with allowance made for the different population of non-metal-sublattice sites with carbon atoms; with regard to their population, the sample composition was WC_{0.42}. The trigonal structure (space group $P\bar{3}1m$) of the lower carbide ϵ -W₂C with unit cell parameters *a* = 0.5190, *c* = 0.4724 nm was also revealed;^{28,29} a small number of carbon atoms occupied positions 1(*b*) and 2(*c*), which remain completely vacant in an ideal structure of the ϵ -Fe₂N type.

Thus, neutron diffraction studies^{25–29} of lower tungsten carbide samples, which were quenched from the arc fusion temperature²⁷ and the temperatures of 2670–2370 K (see Ref. 25) and 1920 K,²⁶ revealed only a trigonal (space group No. 162– $P\bar{3}1m$) ordered phase with the ϵ -Fe₂N-type structure. In all the cases, the ordering degree did not reach its maximum. The orthorhombic (space group *Pben*) β' -W₂C phase with the Mo₂C-type structure and the rhombohedral (trigonal, space group No. 164– $P\bar{3}m1$) β'' -W₂C phase with the C6-type structure were not found by the neutron diffraction analysis.

The temperatures of consecutive phase transformations



and eutectoid decomposition



namely, ~2750, ~2410 and 1530 K, respectively, were determined¹⁸ using specially designed instruments.³⁵ The high-temperature differential thermal analysis (DTA) involved³⁵ a highly sensitive optical (photodiodes and micropyrometer) system for measuring the temperature and the temperature difference between the working and reference samples ΔT . This system allowed one to perform measurements up to 3900 K. With the use of such instruments, the temperatures of phase transformations in hafnium, zirconium and titanium and also in lower carbides of tantalum, molybdenum, and tungsten, *i.e.*, Ta₂C, Mo₂C and W₂C, were determined.³⁵ Figure 5a shows a DTA curve, which confirms the presence of consecutive transformations of lower tungsten carbide.¹⁸ The authors only noted that all the effects observed at temperature decrease were exothermic. The

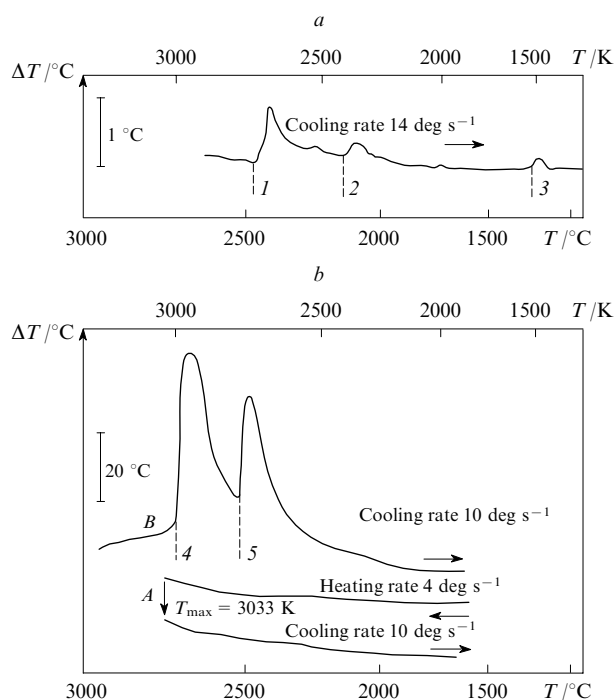


Figure 5. DTA curves of $\text{WC}_{0.48-0.49}$ (32.7 at.% of carbon) (a) and a carbide containing 51.0 at.% of carbon (b).^{18, 21}

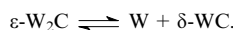
The measurements were carried out on a specially designed set-up (see Ref. 35) which allowed measuring the absolute difference of temperatures ΔT between the standard sample and the sample under study, which depends on the initial experimental conditions; hence, the heat effect can have the opposite sign as compared with the measurements carried out on a standard DTA set-up (the arrows indicate the direction of temperature change);

(1–5) see text.

small magnitude of thermal effects could be caused by the incomplete transformation due to the too rapid cooling. With allowance made for the results of neutron diffraction studies,^{25–29} it is more likely that the effects at ~ 2750 and 1530 K (positions 1 and 3), which are observed in the DTA curve, correspond to the transformation



and the eutectoid decomposition



The $\gamma\text{-WC}_{1-x}$ phase has a cubic [space group $Fm\bar{3}m$ (O_h^5)] structure of the B1 type (NaCl) (Fig. 6), which is typical of all non-stoichiometric carbides and nitrides MX_y of Group IV and V transition metals. The researchers who discovered^{30–32} this phase considered it an additional high-temperature phase of lower carbide W_2C . However, based on the theoretical possibility that carbon atoms can occupy all octahedral interstitials in the fcc sublattice of tungsten, it seems more reasonable to consider this phase as a structural modification of higher tungsten carbide. Cubic tungsten carbide was also obtained³² as a result of the electrospark treatment of tungsten foil, *i.e.*, by generating electric discharge between the foil and a graphite electrode. The existence of cubic WC was confirmed.²² A phase of $\gamma\text{-WC}_{1-x}$ ($\beta\text{-WC}$) with the B1-type cubic structure was revealed³⁶ in the products of the plasmochemical synthesis of tungsten carbide; the synthesis was carried out in the argon arc plasma from the tungsten and carbon powders or a tungsten powder and methane. The synthesis with methane gave a product containing from 74% to 96% cubic WC_{1-x} with particles measuring 2–16 nm. No data on the

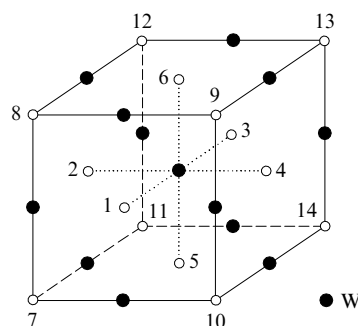


Figure 6. The B1-type (NaCl) structure of cubic carbide $\gamma\text{-WC}_{1-x}$.^{1, 2} Non-metal sublattice sites are numbered. The first coordination sphere of a tungsten atom in the unit cell centre is formed by sites 1–6 of the non-metal sublattice located in the centres of cell faces; the third coordination sphere is formed by sites 7–14 of the same sublattice, which are located in the cube corners. The second coordination sphere of the central tungsten atom is formed by twelve metal atoms located in the middle of edges.

chemical composition of the obtained cubic phase $\gamma\text{-WC}_{1-x}$ were presented.³⁶

Superconducting transition temperature (T_c) for cubic carbides MoC, WC and solid solutions NbC–MoC, NbC–WC, NbC–TaC, TaC–MoC, TaC–WC, MoC–WC with the B1 structure were determined.^{37, 38} Cubic tungsten carbide was synthesised by rapid quenching from the molten state. According to data from Ref. 37, the T_c value is sufficiently high, namely, 10 K for stoichiometric cubic carbide $\text{WC}_{1.0}$ and 9 K for cubic $\text{WC}_{0.85}$. Yet another sample, which, in addition to the cubic phase, contained lower hexagonal tungsten carbide and a large amount of free carbon, was shown to have $T_c = 8.1$ K. Assuming that, in the first approximation, the unit cell parameter of cubic WC_{1-x} and its temperature of the superconducting transition depend linearly on the carbon content, then $T_c = 8.1$ K corresponds to cubic carbide $\text{WC}_{0.71-0.72}$ with the unit cell parameter $a_{B1} = 0.424$ nm. Note that the temperatures of the transition into the superconducting state of hexagonal carbides $\beta\text{-W}_2\text{C}$ and $\delta\text{-WC}$ are 3.6 and 0.3 K, respectively,³⁷ *i.e.*, substantially lower than those of the cubic phase $\gamma\text{-WC}_{1-x}$.

It was noted³⁹ that the electrospark treatment of the molten samples of tungsten carbide and certain WC-based hard alloys produces cubic carbide $\gamma\text{-WC}_{1-x}$. A cumulative explosion of tungsten, graphite and ammonium nitrate powders allowed the synthesis of samples that contained up to 50 vol.%–70 vol.% $\gamma\text{-WC}_{1-x}$;⁴⁰ the explosion conditions were equivalent to those of steady-state sintering at the temperature of 2770–3270 K. Note that in these studies^{39, 40} cubic carbide $\gamma\text{-WC}_{1-x}$ was designated as $\beta\text{-WC}_{1-x}$.

According to the phase diagram of the W–C system (see Fig. 1), the single-phase cubic carbide $\gamma\text{-WC}_{1-x}$ exists in the composition range of $\text{WC}_{0.58}\text{--WC}_{0.65}$ at temperatures above 2790–2810 K. Moreover, $\gamma\text{-WC}_{1-x}$ was found in the two-phase regions ($\beta\text{-W}_2\text{C} + \gamma\text{-WC}_{1-x}$) and ($\gamma\text{-WC}_{1-x} + \delta\text{-WC}$). The position of the lower boundary of the homogeneity region of cubic carbide $\gamma\text{-WC}_{1-x}$ is independent of the temperature and corresponds to the $\text{WC}_{0.59}$ composition;²² the upper boundary shifts to higher carbon contents with the increase in the temperature and can reach the stoichiometric composition $\text{WC}_{1.00}$ (see Fig. 1b). In particular, at 3000–3040 K, cubic carbide $\gamma\text{-WC}_{1-x}$ has a homogeneity region much wider than reported,^{19–21} namely, $\text{WC}_{0.59}\text{--WC}_{0.92}$; at $\sim 2800\text{--}2810$ K, its eutectoid decomposition to $\beta\text{-W}_2\text{C}$ and $\delta\text{-WC}$ (WC) takes place.

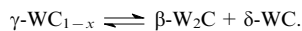
Figure 5b shows DTA curves for cubic tungsten carbide containing 51.0 at. % carbon. As is seen, its heating along curves A up to ~ 3033 K without any exposure at the maximum temperature failed to melt the sample; its subsequent cooling from 3033 to 1940 K revealed no heat effects. However, curve B measured

after the sample was cooled upon its brief exposure at ~ 3270 K, *i.e.*, from its melt, demonstrates peaks corresponding to strong exothermic heat effects at ~ 2990 and ~ 2790 – 2810 K (positions 4, 5). From the viewpoint of the authors,²¹ these effects were caused by the following reversible transformations:

the eutectics formation



and the eutectoid decomposition



According to the conditions under which curves *A* and *B* were recorded, cubic carbide $\gamma\text{-WC}_{1-x}$ is formed relatively easily from the melt, but the direct solid-phase transformation



is either hindered (for it to happen, the temperature should change slowly near the transformation temperature T_{trans}) or the temperature range of its existence near the stoichiometric composition WC is very narrow.

The phase equilibria in the W–C system were studied²² in the temperature interval from 2770 to 3100 K (see Fig. 1*b*) with the use of the X-ray diffraction method, chemical and metallographic analyses and also of the DTA method. To determine the phase composition, the samples heated to 2870 K (or higher) were quenched by cooling to 1800 K in 20 s and lower to 1300 K in 40 s. Samples with the composition between W_2C and WC were quenched from $T \geq 2800$ K by their quick immersion into liquid tin with the temperature of 600–650 K. High-temperature DTA was carried out with the use of specially designed (see a patent of Goton⁴¹) instruments. The temperature interval used in study²² was narrower than that used by Rudy;^{18–21} this is why those phase transitions of lower carbide W_2C , which are associated with its ordering, could not be detected at temperatures below 2750 K.

By and large, the results of independent studies^{18–22} on the determination of the temperature and concentration positions of phase boundaries in the W–C system are almost identical. For example, differences between the found phase-transformation temperatures do not exceed 10 K, *i.e.*, they lie within the experimental error range. However, the region of existence of high-temperature cubic monocarbide $\gamma\text{-WC}_{1-x}$ in the phase diagram was studied in more detail.²² Particularly, a thorough metallographic and X-ray study was carried out for samples quenched from the temperatures above and below 2798 K (the DTA method has shown that a reversible phase transformation takes place at 2798 K in samples containing from 35 at.% to 50 at.% of carbon). Figure 7 illustrates the changes in the microstructures of samples containing 40 at.% of carbon and quenched from 2778 and 2808 K. A sample quenched from 2778 K contained two hexagonal phases W_2C and WC (Fig. 7*a*). A sample quenched from 2808 K also contained two phases $\beta\text{-W}_2\text{C}$ and $\delta\text{-WC}$ but had a different pearlite-like microstructure (Fig. 7*b*), which appeared as a result of the eutectoid decomposition of cubic carbide $\gamma\text{-WC}_{1-x}$ formed at $T > 2798$ K. Cubic carbide $\gamma\text{-WC}_{1-x}$ can be directly visualised in the microstructure of samples quenched from higher temperatures (2988–3023 K) in the solid state, and also in the microstructures of samples quenched from the melt from 3043–3063 K (Fig. 8). It was shown²² that at 3030–3055 K $\gamma\text{-WC}_{1-x}$ has a wide homogeneity region, namely, from $\text{WC}_{0.59}$ to $\text{WC}_{0.98-1.00}$ (see Fig. 1*b*).

High temperature of the transition into the superconducting state, namely, 10 K,^{37,38} confirms that the composition that corresponds to the upper boundary of the homogeneity region of $\gamma\text{-WC}_{1-x}$ is stoichiometric, *i.e.*, $\text{WC}_{1.0}$. It is known^{3,4,42} that, among the cubic carbides of Group IV–VI transition metals, stoichiometric carbides $\text{NbC}_{1.0}$ and $\text{TaC}_{1.0}$ have the highest T_c (10–12 K); however, T_c quickly drops to ~ 4 K upon their deviation from stoichiometry to $\text{NbC}_{0.9}$ or $\text{TaC}_{0.9}$ and $T_c \leq 1$ K for $\text{NbC}_{0.8}$ and $\text{TaC}_{0.8}$. According to Willens and Buether,³⁷ a

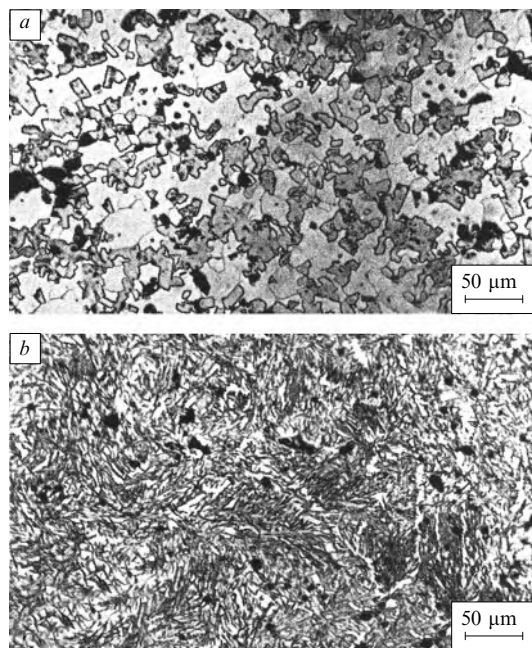


Figure 7. Microstructures of carbide samples with 60 at.% of W and 40 at.% of C quenched from 2778 (*a*) and 2808 K (*b*).²² (*a*) The sample contains hexagonal phases of $\beta\text{-W}_2\text{C}$ (light grains) and $\delta\text{-WC}$ (dark grains); (*b*) the sample contains additional phases $\beta\text{-W}_2\text{C}$ and $\delta\text{-WC}$, but has a pearlite-type microstructure which has appeared at the eutectoid decomposition of cubic $\gamma\text{-WC}_{1-x}$ formed at $T > 2798$ K (see text).

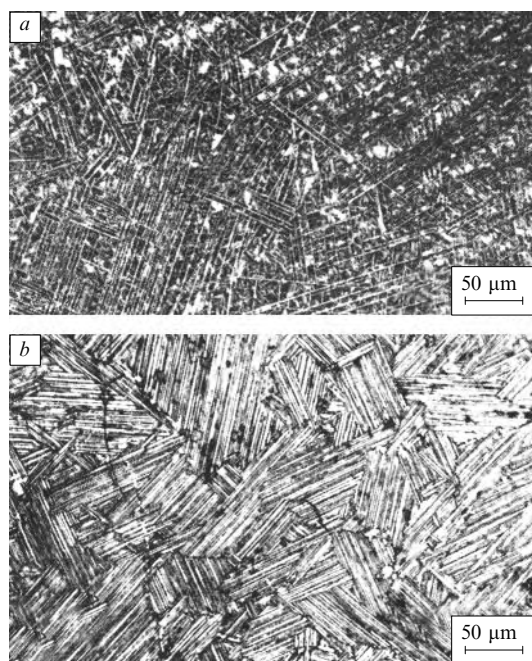


Figure 8. Microstructures of samples with cubic carbide $\gamma\text{-WC}_{1-x}$ obtained by quenching from the melt.²² (*a*) A sample with 45 at.% of C quenched from 3043 K contains inclusions of hexagonal monocarbide $\delta\text{-WC}$ in the matrix of cubic $\gamma\text{-WC}_{1-x}$; (*b*) eutectic ($\beta\text{-W}_2\text{C} + \gamma\text{-WC}_{1-x}$) microstructure of a sample with 36 at.% of carbon quenched from 3053 K. The sample surface is etched with a 10% NaOH + 30% $\text{K}_3\text{Fe}(\text{CN})_6$ mixture.

decrease in the carbon content in cubic tungsten carbide causes a relatively smaller decrease in T_c .

The unit cell parameter of $\gamma\text{-WC}_{1-x}$ carbide is $a_{B1} \approx 0.427$ nm;³² that for cubic carbide $\text{WC}_{0.82}$ is $a = 0.4215$ nm.²² Cubic tungsten carbide with an unknown composition was found to have the unit cell parameter of 0.4229 nm,³⁶ while almost stoichiometric cubic carbide was shown³⁹ to have $a = 0.4248$ nm. The unit cell parameters of cubic carbides $\text{WC}_{1.0}$, $\text{WC}_{0.85}$ and $\text{WC}_{0.72}$ were shown³⁷ to be 0.4266, 0.4252 and 0.4240 nm, respectively. For cubic carbide $\text{WC}_{0.61}$, $a = 0.4220$ nm was found;^{19,21} the extrapolation of this value to defect-free cubic carbide gave $a = 0.4265$ nm.⁴³ The unit cell parameter of cubic carbide $\gamma\text{-WC}_{1-x}$ of the unknown composition was found to vary from 0.4222 to 0.4263 nm;⁴⁰ such a small unit cell parameter of cubic carbide $\gamma\text{-WC}_{1-x}$ could be caused by oxygen impurity, because the sample was obtained in a cumulative explosion in ammonium nitrate which contains oxygen. The best agreement was observed for the unit cell parameter values found for cubic carbide $\gamma\text{-WC}_{1-x} \equiv \gamma\text{-WC}_y$ ($y \equiv 1-x$)^{19,21,37–39,43} (Fig. 9). These data are adequately described by a quadratic function

$$a_{B1} = 0.4015 + 0.0481y - 0.0236y^2 \text{ (nm)}$$

and unambiguously point to the increase in the unit cell parameter of the $\gamma\text{-WC}_{1-x}$ phase with the increase in the carbon content.⁴⁴

Higher tungsten carbide $\delta\text{-WC}$ (WC) has a negligibly small homogeneity region (or does not have it at all). Its hexagonal [space group $P\bar{6}m2$ (D_{3h}^1)] lattice pertains to its own structural type B_h (the WC type) with the unit cell parameters $a = 0.2906$ and $c = 0.2837$ nm.^{7,9,10,19} In this structure, tungsten atoms occupy positions 1(a) with coordinates (0 0 0) and carbon atoms are located in positions 1(d) with coordinates (1/3 2/3 1/2).⁴⁵ Tungsten and carbon atoms in $\delta\text{-WC}$ (WC) form simple hexagonal sublattices, in which carbon atoms are located in the centres of trigonal prismatic interstitials of the tungsten sublattice (Fig. 10). The results of simulations of the crystal and electronic structures of hexagonal WC, which were performed⁴⁶ by the pseudopotential local-orbital method confirmed the stability of this compound; the estimated unit cell parameters $a = 0.288$ and $c = 0.281$ nm well agree with experimental results.

A positron lifetime study found an experimental confirmation for the stoichiometry of hexagonal monocarbide $\delta\text{-WC}$.^{47,48} Samples of powder and sintered WC and also samples of a hard WC–Co alloy were studied. The positron lifetime spectra of WC revealed the short-lived ($\tau_{\text{free}} = 124 \pm 10$ ps) and more long-lived ($\tau_{\square\text{W}} = 175 \pm 20$ ps) components. The former corresponds to the annihilation of positrons from the free state, the latter corresponds to the capture and annihilation of positrons in the metal vacancies the concentration of which is very low. No components

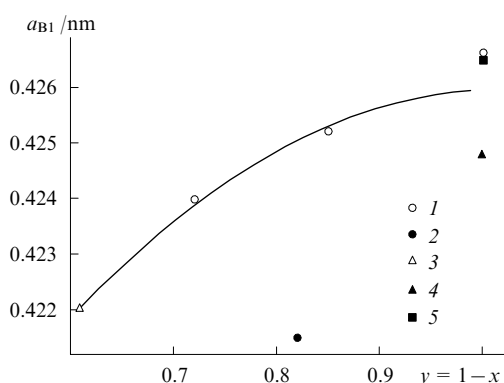


Figure 9. Changes in the unit cell parameter a_{B1} of cubic carbide $\gamma\text{-WC}_{1-x} \equiv \gamma\text{-WC}_y$ ($y \equiv 1-x$) with the B1-type structure in its homogeneity region.⁴⁴ (1–5) The data are taken from Refs 37, 38; 22; 19, 21; 39; 43, respectively.

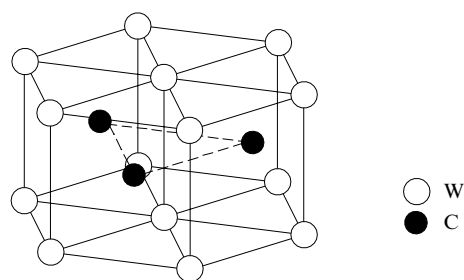


Figure 10. Hexagonal structure of higher carbide $\delta\text{-WC}$ (WC).

that would correspond to the positron annihilation in the carbon-sublattice vacancies were found. Upon the irradiation of $\delta\text{-WC}$ with electrons with the energy of 1 MeV, the positron lifetime spectrum contained only one component, namely, with a lifetime of ~ 136 ps. It was shown⁴⁷ that this component corresponds to the capture and annihilation of positrons in the carbon vacancies, which have appeared upon the irradiation. Indeed, the kinetic energy, which is imparted by the 1-MeV electrons to carbon and tungsten atoms in the collisions, is higher than the displacement threshold of the carbon atom from its position but lower than the displacement threshold of the tungsten atom; hence, the vacancies were induced only in the carbon sublattice of the carbide. Due to the higher imparted energy, the irradiation of $\delta\text{-WC}$ with electrons with the energy of 2.5 MeV resulted in the displacement of both carbon and tungsten atoms and the appearance of vacancies in both sublattices.⁴⁸ A comparison of the experimental results^{47,48} with those obtained in the calculations of the positron lifetime by the method of linear muffin-tin orbitals in the atomic sphere approximation (LMTO-ASA)⁴⁹ in a model carbide WC with the cubic B1-type lattice demonstrated good agreement of calculations with experimental data for $\tau_{\square\text{W}}$ in a metal vacancy and a noticeable deviation in the positron lifetime $\tau_{\square\text{C}}$ in a carbon vacancy. On the whole, the results^{47,48} confirmed that, under normal conditions, higher hexagonal carbide $\delta\text{-WC}$ is stoichiometric and has no carbon vacancies in its carbon sublattice.

Thus, among tungsten carbides, only higher hexagonal carbide $\delta\text{-WC}$ (WC) has virtually no homogeneity region, whereas lower carbides W_2C and cubic $\gamma\text{-WC}_{1-x}$ have relatively wide homogeneity regions. Table 1 gives information on the crystal structures of the phases in the W–C system. It should be borne in mind that the conclusions made in those studies in which the structures of non-stoichiometric tungsten carbides were determined only based on the X-ray diffraction data are merely the assumptions. Particularly, this concerns W_2C , the non-metal sublattice of which was assumed ordered with respect to both atoms and vacancies. The structures of non-stoichiometric tungsten carbide compounds found by the neutron diffraction analysis are more confident and reliable.

The main difference between the phase diagrams of the W–C system proposed by Rudy *et al.*,^{19–21} on the one hand, and Sara,²² on the other hand, concerns the position and width of the homogeneity region of cubic carbide $\gamma\text{-WC}_{1-x}$. The authors of the former studies^{19–21} were short of experimental results sufficient to determine the position of this carbide in the phase diagram and had to use the analogy with the Mo–C system studied earlier.^{50,51} Thus, having detected the $\beta\text{-MoC}_{1-x}$ (Mo_3C_2 or $\text{MoC}_{0.67}$) phase with a narrow homogeneity region, they assumed that the WC_{1-x} phase in the W–C system has the same stoichiometric composition W_3C_2 ($\text{WC}_{0.67}$) and the equally narrow homogeneity region.[§]

[§] It is not by accident that the paper by Rudy *et al.*,¹⁹ in which the version of the phase diagram of the W–C system presented in Fig. 1a was published, was entitled ‘W–C System: supplemental information on the Mo–C system’.

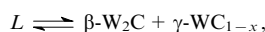
Table 1. Crystal structure of phases that can exist (according to different authors) in the W–C system at $T > 1300$ K.

Phase		Existence region (at.% of C)	Unit cell parameters /nm			Space group	Pearson symbol	Lattice type and symmetry
designations as in Fig. 1 (data from Ref. 17)	designations in other studies		<i>a</i>	<i>b</i>	<i>c</i>			
W	W	0–1.0	0.3165			$Im\bar{3}m$ (O_h^9)	<i>cI2</i>	A2 (W type), bcc
β -W ₂ C	γ -W ₂ C (see ^a)	~ 25.5–34.0	0.3002		0.475–0.476 (see ^b)	$P6_3/mmc$ (D_{6h}^4)	<i>hP3</i>	$L'3$ (W ₂ C type), hexagonal
β' -W ₂ C	β -W ₂ C (see ^a)	~ 29.5–33.0	0.4728	0.6009	0.5193 (see ^c)	$Pbcn$ (D_{2h}^{14})	—	PbO ₂ or Mo ₂ C (ζ -Fe ₂ N) type, orthorhombic
β'' -W ₂ C	α -W ₂ C (see ^a)	~ 29.5–32.5	0.2985 (see ^d)		0.4717 (see ^d)	$P\bar{3}m1$ (D_{3d}^3)	<i>hP3</i>	C6 (<i>anti</i> -CdI ₂ type), rhombohedral
	ϵ -W ₂ C (see ^f)	~ 29.5–33.0 (at $T \approx 2500$ K)	0.3001 (see ^e)		0.4728 (see ^e)	$P\bar{3}m1$ (D_{3d}^1)	—	ϵ -Fe ₂ N type, trigonal
γ -WC _{1-x}	α -WC _{1-x} (see ^g)	~ 37.0–39.5 (see ^g)	0.4265 (see ^h)			$Fm\bar{3}m$ (O_h^5)	<i>cF8</i>	B1 (NaCl type), cubic
	β -WC (see ⁱ)	~ 37.1–50.0 (see ^j)	0.4252 (see ^k)					
δ -WC	WC (see ^g)	~ 50	0.2906		0.2837 (see ^b)	$P\bar{6}m2$ (D_{3h}^1)	<i>hP2</i>	B _h (WC type), hexagonal
	α -WC (see ^j)							
C	C	100	0.142		0.339	$P6_3/mmc$ (D_{6h}^4)	<i>hP4</i>	A9 (C, graphite), hexagonal

Note. In the study,¹⁷ the phase diagram of the W–C system takes into account the structural data,^{18–22, 34} some of which were not confirmed later; trigonal (space group $P\bar{3}1m$) ϵ -WC phase the existence of which was reliably confirmed^{25–29} is not shown in the phase diagram of the W–C system (see Ref. 17). Here and in Table 2, the γ -WC_{1-x} phase is identical to the γ -WC_y ($y \equiv 1-x$) phase.

^a Refs 18, 21; ^b Ref. 19; ^c Ref. 18; ^d Ref. 19 for WC_{0.41}; ^e Ref. 19 for WC_{0.50}; ^f Ref. 25; ^g Ref. 21; ^h Ref. 43 for WC_{1.0}; Refs 22, 36; ⁱ Ref. 22; ^k Ref. 31 for WC_{0.85}.

At the same time, it follows from the study by Sara²² that the homogeneity region of cubic γ -WC_{1-x} is much wider than that given in Refs. 19–21 and reaches the WC_{1.0} composition, which agrees with the results of later studies (see Refs 32, 36–39). However, for a cubic carbide of the stoichiometric composition WC_{1.0}, the phase diagram (see Fig. 1 b)²² contains no temperature region of its existence, while the region of the existence of the γ -WC_{1-x} has such boundaries at $(1-x) \rightarrow 1$ that the temperature decrease merely from 3058 to 3028 K causes the following consecutive transformations in the WC_{1.0} composition: first, a peritectic transformation and then a peritectoid one. This is highly improbable. Moreover, the line of phase equilibrium 1–2–3 (see Fig. 1 b) is shown incorrectly in the cited study, namely, from a horizontal that corresponds to the non-variant eutectic process

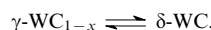


this line gradually transforms into a monovariant curve, which is physically impossible and incorrect from the viewpoint of thermodynamics. The phase equilibrium shown could be possible if point 2 was a singular point, *i.e.*, a kink point. However, this in turn, would have led to the narrowing of the temperature interval of the existence of a two-phase region $L + \gamma\text{-WC}_{1-x}$ and to the shift of its lower boundary to higher temperatures, which contradicts the DTA results.²² If a cubic carbide with the stoichiometric composition WC_{1.0} had at least a narrow temperature range of stability and the two consecutive phase transitions were somewhat shifted in the composition with respect to one another, then the noted inaccuracies and contradictions could be eliminated and the total body of experimental results could be taken into account.

Figure 11 shows the phase diagram of the W–C system, which was constructed⁴⁴ with allowance made for the presence of the temperature interval of existence of cubic carbide WC_{1.0} and also for experimental results^{18–22, 32, 36–39} and the results of new structural and magnetic-susceptibility studies of tungsten carbides synthesised in our studies. It is evident that, in the temperature range of 3058–2993 K, in the vicinity of the WC_{1.0} composition, a decrease in temperature results first in the peritectic formation of cubic tungsten carbide from the melt



and then in the transformation of cubic monocarbide into the hexagonal modification



The temperature of the eutectoid decomposition

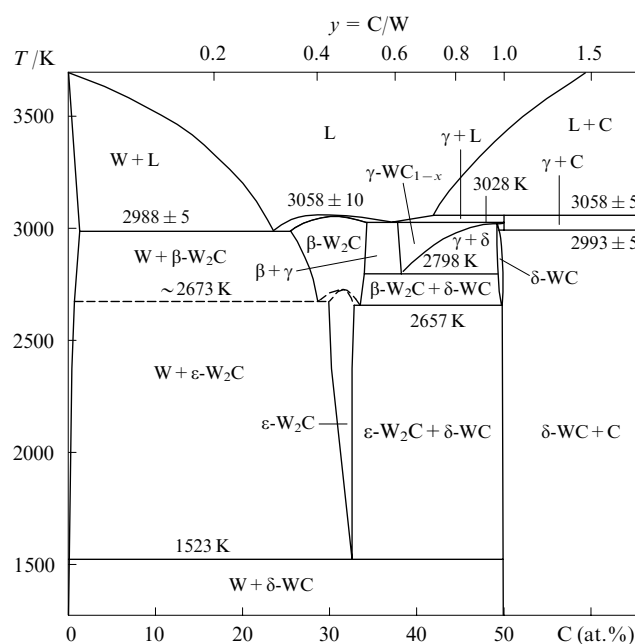
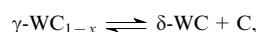


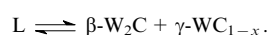
Figure 11. Phase diagram of the W–C ($\gamma\text{-WC}_{1-x} \equiv \gamma\text{-WC}_y$) system⁴⁴ with corrected positions of phase boundaries in the region of lower tungsten carbide W₂C. Corrections were introduced according to the neutron diffraction results^{25–29} (see text).

Table 2. Special points in the phase diagram of the W–C system (Fig. 11) at a temperature above 1300 K (according to Ref. 44 with corrections made in the region of the existence of lower tungsten carbide W₂C).

Reaction	Composition of phases involved in the reaction (at.% of C)			<i>T</i> /K	Reaction type
$L \rightleftharpoons W$	0	0	—	3755 ± 5	melting
$L \rightleftharpoons \beta\text{-W}_2\text{C}$	~30.6	~30.6	—	3058 ± 10	congruent melting
$L + C \rightleftharpoons \gamma\text{-WC}_{1-x}$	~42.0	100.0	50.0	3058 ± 5	peritectics
$L \rightleftharpoons W + \beta\text{-W}_2\text{C}$	~23.5	~1.2	~25.5	2988 ± 5	eutectics
$L \rightleftharpoons \beta\text{-W}_2\text{C} + \gamma\text{-WC}_{1-x}$	~37.0	~34.3	~37.8	3028 ± 5	"
$\gamma\text{-WC}_{1-x} \rightleftharpoons \delta\text{-WC}$	~49.3	~49.3	—	3008 ± 5	polymorphic transformation
$\gamma\text{-WC}_{1-x} \rightleftharpoons \delta\text{-WC} + C$	50.0	~49.8	100.0	2993 ± 5	eutectoid decomposition
$\gamma\text{-WC}_{1-x} \rightleftharpoons \beta\text{-W}_2\text{C} + \delta\text{-WC}$	~38.2	~34.0	~49.5	2798 ± 5	the same
$\beta\text{-W}_2\text{C} \rightleftharpoons W + \varepsilon\text{-W}_2\text{C}$	~28.6	~0.7	~29.7	2673 ± 10	"
$\beta\text{-W}_2\text{C} \rightleftharpoons \varepsilon\text{-W}_2\text{C}$	~31.6	~31.6	—	2728 ± 10	disorder – order transformation
$\beta\text{-W}_2\text{C} \rightleftharpoons \varepsilon\text{-W}_2\text{C} + \delta\text{-WC}$	~33.5	~32.8	~49.8	2657 ± 10	eutectoid decomposition
$\varepsilon\text{-W}_2\text{C} \rightleftharpoons W + \delta\text{-WC}$	~32.6	0	50.0	1523 ± 5	the same



equal to 2993 K (see Fig. 11) was found from the results of DTA²¹ for a sample with 51 at.% carbon. This value was assigned to the temperature of the eutectic²¹



However, even according to the phase diagram version proposed,²¹ such a carbide composition falls beyond a region where this phase equilibrium is permitted. Therefore, this temperature cannot be the temperature of the eutectic. Although the temperature interval of the equilibrium existence of $\gamma\text{-WC}_{1-x}$ (see Fig. 11) is small, the cubic carbide of the stoichiometric composition WC_{1.0} can at least be quenched from the melt, which agrees with the experimental results.^{37, 38}

The phase diagram W–C published in study⁴⁴ contains the following corrections in the positions of phase boundaries in the lower tungsten carbide W₂C region, which were introduced with allowance made for the neutron diffraction results:^{25–29} the $\varepsilon\text{-W}_2\text{C}$ phase is shown in place of phases $\beta'\text{-W}_2\text{C}$ and $\beta''\text{-W}_2\text{C}$, the existence of which is not confirmed experimentally. These corrections are reflected in Fig. 11. The special points in the phase diagram of this system at temperatures above 1300 K are described in Table 2.

III. Phase equilibria in the W–Co–C system

The wide application of high-strength hard alloys formed in the pseudobinary system WC–Co brought about the investigations of the phase equilibria in the ternary system W–Co–C.

Information on the phases in the W–Co–C system which was obtained before 1952 is generalised in a review,⁵² where new diffraction, metallographic and DTA studies of this system were carried out. In addition, the liquidus surface projection, the total isothermal cross-section at 1673 K and the pseudobinary *c* vs. *T* diagrams along the cross-sections C–Co₄₃W₅₇ and WC–Co were constructed, in which the stable and metastable phase equilibria were specified. In the pseudobinary cross-section WC_y–Co (16 mass % of Co), the effect of the carbon content on the phase equilibria and structure of alloys was studied.⁵³ The results of the metallographic and diffraction studies of the M₆C-type cubic η -carbides, which are formed in the W–Co–C system, were discussed.⁵⁴ Particularly, η -carbide Co₂W₄C with a cubic cell parameter, which varied from 1.107 to 1.125 nm depending on the carbon content, was revealed; two total isothermal cross-sections of the W–Co–C system were constructed at temperatures 1273 and 1673 K. The stability of η -carbides of the M₆C type in the W–Co–C system was also considered by other authors⁵⁵ who showed additional isothermal cross-sections in this system at 1373

and 1573 K. The experimental studies of phase equilibria in the W–Co–C system at 1423 K were supplemented by thermodynamic calculations.⁵⁶

According to the results of numerous studies, the system W–Co–C forms several ternary compounds, viz., cubic [space group $Fd\bar{3}m$ (O_h^h)] η -carbides Co₂W₄C (see Ref. 54) and Co₄W₂C (see Ref. 57) of the M₆C type and also two hexagonal [space group $P6_3/mmc$ (D_{6h}^4)] CoW₃C carbides with the Co₃W₉C₄ (see Ref. 58) and Co₆W₂₀C₇ structures.⁵⁹ Note that the Co₃W₉C₄ structure has two types of metal sublattice interstitials, in which carbon atoms are located as follows: in the unit cell, two carbon atoms of eight are located in the centre of trigonal prisms formed by six tungsten atoms, while the remaining six carbon atoms are in the centres of octahedra formed of five tungsten and one cobalt atoms. A comprehensive study of these carbides showed that all of them can exhibit a noticeable carbon deficiency, i.e., they are non-stoichiometric; hence, their compositions should be written with allowance made for the possible non-stoichiometry, namely, Co₂W₄C_{*y*}, Co₄W₂C_{*y*} and CoW₃C_{*y*}. Carbides Co₂W₄C_{*y*} and Co₄W₂C_{*y*} are often united into a single phase Co₃W₉C₄_{*y*}. It is evident that here we have a pseudobinary solid solution between Co₂W₄C_{*y*} and Co₄W₂C_{*y*}. For the case of deficient carbon content, this variable-composition phase corresponds to the ~Co₆W₆C_{*y*} carbide in the phase diagram.

The results of the aforementioned studies are taken into account in a comprehensive survey,⁶⁰ which is devoted to the thermodynamic properties and phase equilibria in the W–Co–C system; moreover, the author of this survey carried out calculations to refine the phase equilibria by means of the CALPHAD method (see Ref. 61) using the approximations and models described elsewhere.⁶² Figure 12 shows a series of isothermal cross-sections of the ternary system W–Co–C at 2073, 1773, 1698, 1673, 1548 and 1443 K, which were constructed based on these calculations and are shown in a handbook.⁶³ All isothermal cross-sections contain carbide of the ~Co₆W₆C composition and a solid solution Co₃W₉C_{*y*} [in the survey cited (Ref. 60), they appear as M₁₂C and M₆C, respectively]. In the isothermal cross-section at 1273 K, the solid solution Co₃W₉C_{*y*} is absent but a η -carbide Co₂W₄C appears.⁶⁰ As is seen, the ternary compounds are formed where the carbon content in an alloy is lower than the tungsten content. Note that the isothermal cross-section of the W–Co–C system at 1273 K ignores the existence of the hexagonal intermetallic phase Co₃W, which stabilises at $T \leq 1350$ K and decomposes *via* the peritectoid reaction at ~1360 K.

Figure 13 shows a section of the ternary system W–Co–C cut along the WC–Co plane. This section contains two- and three-phase regions. In this system, the liquid phase appears at 1560–1593 K. According to the survey cited (Ref. 60), the maximum solubility of WC in solid cobalt does not exceed

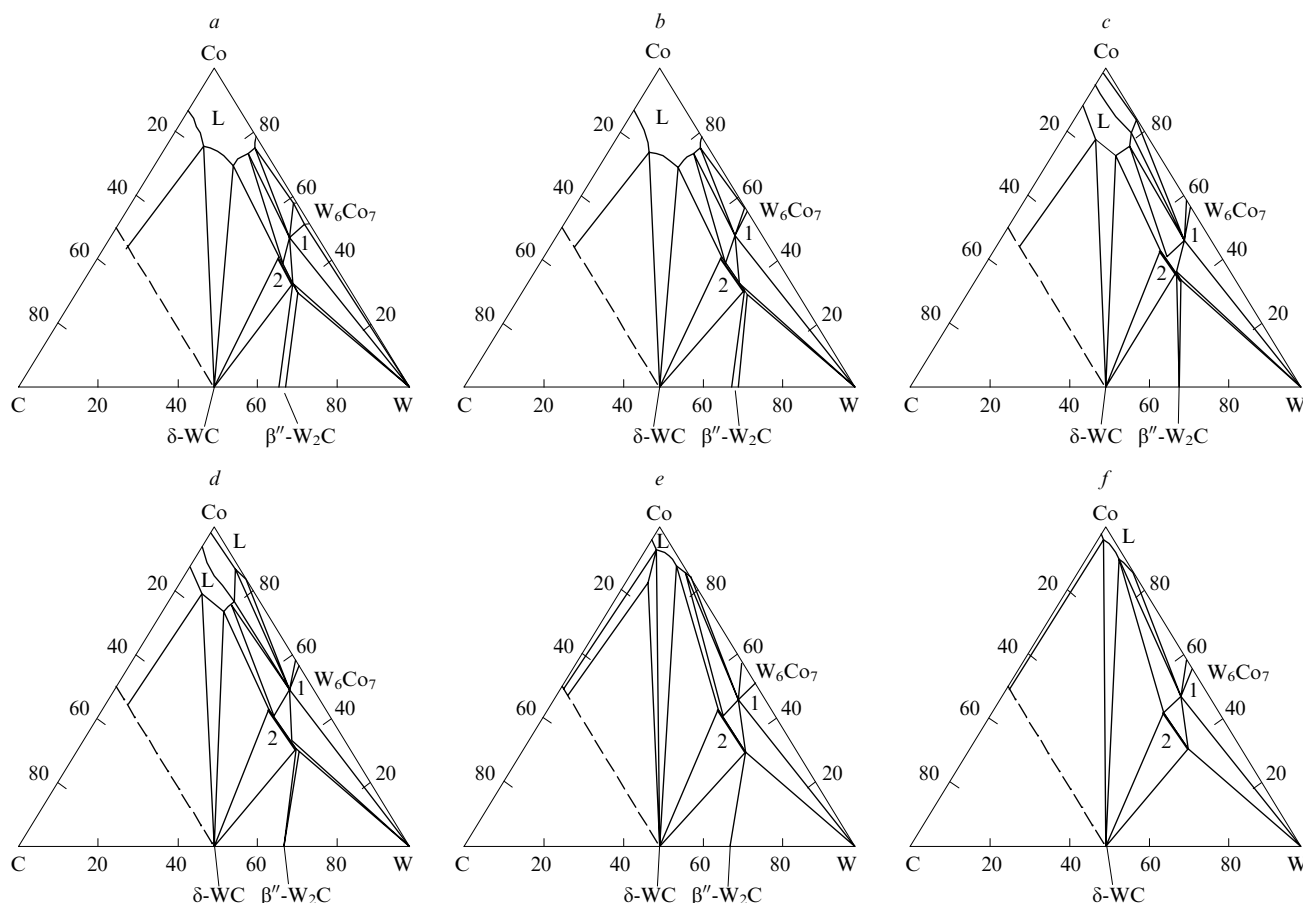


Figure 12. Isothermal cross-sections of the ternary W–Co–C system at 2073 (a), 1773 (b), 1698 (c), 1673 (d), 1548 (e) and 1443 K (f).⁶³ The concentrations are shown in at. %, the triple point position corresponds to the results of thermodynamic calculations;⁶⁰ (1) $\text{Co}_6\text{W}_6\text{C}_7$, (2) $\text{Co}_3\text{W}_3\text{C}_3$.

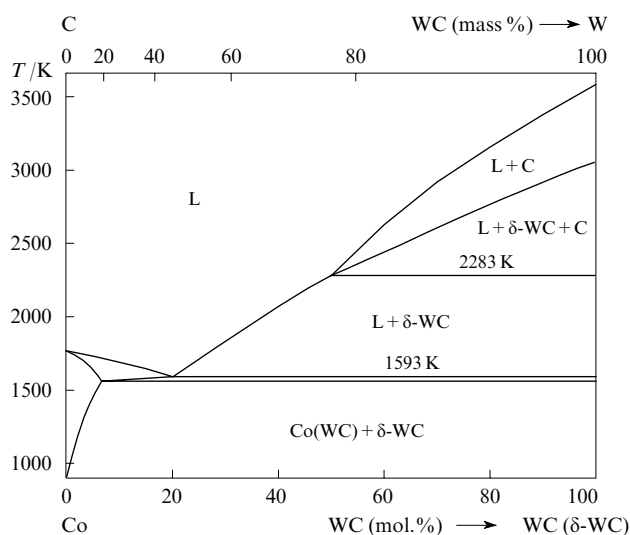


Figure 13. Section of the ternary W–Co–C system cut along the WC–Co plane.⁶⁰

6.7 mol.% (or 19.3 mass %); as the temperature decreases to 1270 K, the solubility does not exceed 3 mol.% (~9 mass %). According to the earlier data (see Ref. 7, vol. 1, p. 262), the maximum solubility of WC in cobalt reaches 22 mass %. A solid solution of WC in cobalt Co(WC) is formed as a result of the diffusion dissolution and appears when the sintering temperature of the WC–Co system reaches 1420–1570 K. A part of cobalt

which does not belong to the solid solution composition passes into the liquid phase that wets the carbide grains.

IV. Electronic structures of tungsten carbides

The band structures of hexagonal and cubic carbides W_2C and WC were calculated.^{46, 64–68} The electronic structure of hexagonal carbide WC was calculated⁶⁴ by a non-self-consistent method of augmented plane waves (APW). A more correct investigation of the band structure in the bulk and on the surface of hexagonal carbide WC was performed by a self-consistent linear method of augmented plane waves (LAPW).⁶⁵

Figure 14a shows the calculated curve of the density of electronic states for hexagonal WC. The Fermi level is located near the curve minimum, and the density of electronic states on this level is relatively low, viz., approximately 0.34 eV^{-1} ($\sim 4.6 \text{ Ry}^{-1}$) per unit cell. The Fermi surface of hexagonal WC has small hole and electron ‘pockets’ in the vicinity of K and L sites of the Brillouin zone.⁶⁵

The electronic structure of hexagonal WC was calculated⁴⁶ by the pseudopotential local-orbital method. Figure 14b shows the resulting curves of the density of electronic states [it is the density of spin states $N_{\text{sp}}(E)$ that was calculated; to make the comparison easier, the figure shows the density of electronic states $N(E) = 2N_{\text{sp}}(E)$ in place of the density of spin states]. It is evident that the calculated^{46, 65} density-of-states curves of hexagonal WC are in adequate agreement with one another, viz., the Fermi level is located in a distinct density-of-states minimum and the quantity $N(E_F)$ is $\sim 0.3 \text{ eV}^{-1}$ per unit cell. Presumably,^{46, 65} it is the small density of electronic states on the Fermi level that determines the high stability of this carbide. The low temperature of the WC

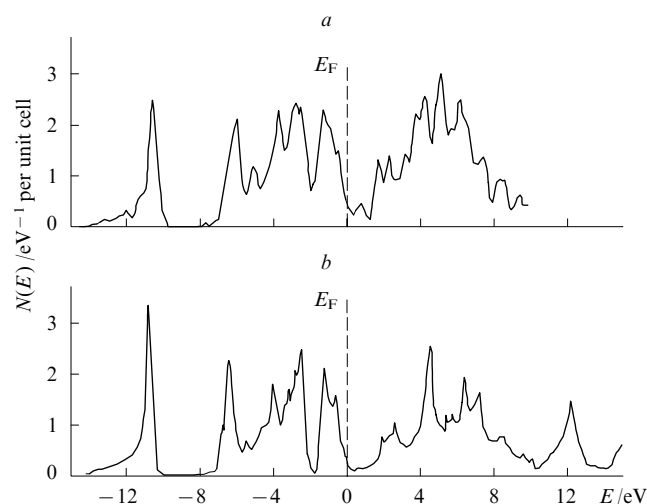


Figure 14. Curves of the total density of electronic states $N(E)$ for hexagonal (space group $P\bar{6}m2$) tungsten monocarbide. (a) LAPW calculations;⁶⁵ (b) calculations by the pseudopotential local-orbital method.⁴⁶

transition into the superconducting state [~ 1.3 K (see Ref. 69)] was also associated⁴⁶ with the low $N(E_F)$.

The linear method of muffin-tin orbitals in the atomic sphere approximation (LMTO-ASA) used for calculation⁶⁶ of the densities of states not only for higher hexagonal tungsten carbide, but also for cubic ($B1$ -type structure) monocarbide WC [as was shown above (see Section II), to date, non-stoichiometric cubic carbide WC_y with $y \leq 0.82$ is experimentally detected, although the upper boundary of the homogeneity region of cubic tungsten carbide approaches $WC_{1.0}$]. Figure 15 shows the calculated curves of the density of states $N(E)$.

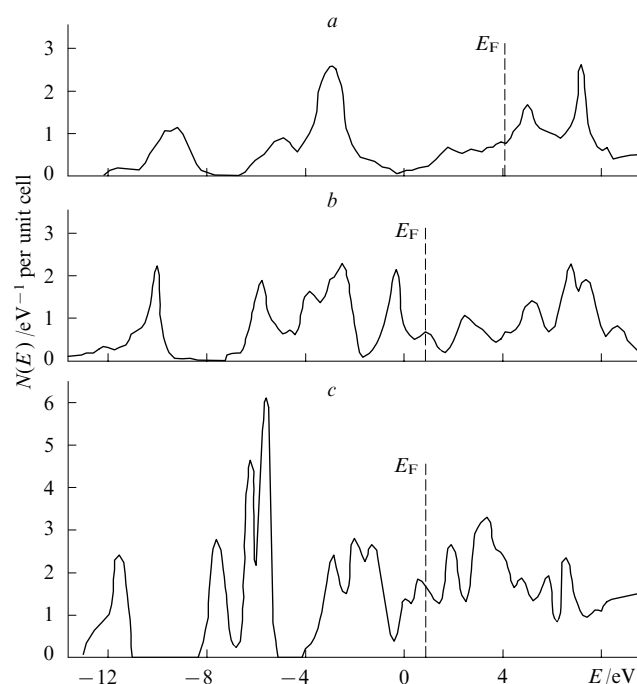


Figure 15. Curves of density of electronic states $N(E)$ of tungsten carbides in the LMTO-ASA approximation.⁶⁶ (a) Hexagonal monocarbide WC (space group $P\bar{6}m2$), (b) cubic monocarbide WC (space group $Fm\bar{3}m$, $B1$ -type structure), (c) lower hexagonal carbide W_2C (space group $P6_3/mmc$).

The curves of the density of electronic states $N(E)$ for hexagonal WC, which are shown in Figs 14 and 15a, differ, first of all, in the Fermi level position. According to calculations,⁶⁶ the Fermi level of this carbide is located in a band formed largely by the 5d states of tungsten, and $N(E_F) = 0.78$ eV⁻¹ per unit cell (10.6 Ry⁻¹), i.e., almost twice greater than it follows from other calculations.^{46,65} Note that in their later publication,⁶⁷ the authors of a study⁶⁶ showed a different density-of-states curve of hexagonal WC, which is closer to those calculated in the studies^{46,65} and has the Fermi level in a different position near the $N(E)$ minimum and also a lower $N(E_F)$ value.

The curve of the density of electronic states for cubic WC (Fig. 15b) is on the whole similar to the corresponding curves of cubic carbides of other transition metals MC ($M = Ti, Zr, Nb, Ta$) and contains a low-energy 2s(C) band with small contributions of s, p and d states of tungsten, a ground-state valence-binding band formed due to the hybridisation of 2p(C) and 5d(W) states and a high-energy band largely formed by the 5d(W) states with an admixture of 6s(W) states. As compared with the $N(E)$ curve of TaC carbide (a typical non-stoichiometric carbide, the closest to WC), the 2s(C) and 2p(C)–5d(W) bands of the cubic tungsten carbide are somewhat broadened due to the smaller WC unit cell parameter.

The band structure of W_2C is intermediate between the band structure of bcc metallic tungsten and hexagonal WC. The main difference in the density-of-states curves of hexagonal W_2C (Fig. 15c) and hexagonal and cubic monocarbides (see Fig. 15a,b) is that W_2C has narrower bands; hence, the hybridised valence-binding and metal 5d(W) bands have the density of states much higher as compared with monocarbides WC. The density of electronic states at the Fermi level is also higher for W_2C as compared with higher hexagonal and cubic WC, namely, the $N(E_F)$ values calculated⁶⁶ per unit cells of hexagonal and cubic WC and also for lower hexagonal carbide W_2C are 0.78, 0.86 and 2.17 eV⁻¹ (10.6 , 11.7 and 29.5 Ry⁻¹), respectively.

Based on the results of band structure calculations, the unit cell parameters, the compression bulk modulus B (also conventionally designated as K) and the Debye temperature θ_D were calculated for these carbides. The modulus of elasticity of hexagonal WC is 655 GPa (6.55 Mbar), which substantially exceeds that of lower carbide W_2C (490 GPa).⁶⁶ For hexagonal WC, the same authors showed a different calculated value of modulus of elasticity equal to 699 GPa (Ref. 67). The B values are 60%–70% higher than the value 413 GPa (4.13 Mbar) found for the same carbide.⁴⁶ The lowest bulk compression modulus equal to 375 GPa, was obtained⁶⁶ for cubic WC; the unit cell parameter a_{B1} was calculated to be 7.98 a.u. (0.422 nm). The small modulus of elasticity of this carbide is associated with its metastable state, because the energy of valence electrons in cubic WC is higher than that in hexagonal carbide by ~ 12.2 eV (~ 0.9 Ry).^{5,66,68}

As noted above, the measurements of the positron lifetime allowed the vacancies to be revealed in the carbon and metal sublattices of irradiated hexagonal carbide WC.⁴⁷ Taking into account this experimental result, an attempt was undertaken⁷⁰ to elucidate how the metal and carbon vacancies affect the WC band structure. The calculations were performed using a self-consistent *ab initio* total potential method (LMTO-TP). The simulations of stoichiometric and defective carbides involved the use of a super-cell formed by eight tungsten-sublattice and eight carbon-sublattice sites which are occupied according to the stoichiometries W_8C_8 (WC), W_8C_7 ($WC_{0.875}$) and W_7C_8 ($W_{0.875}C$). Figure 16 shows the calculated⁷⁰ total density of electronic states for tungsten carbides. According to earlier calculations,^{46,65–68} the valence band of the hexagonal stoichiometric monocarbide consists of two subbands separated by a forbidden gap. The lower subband A is largely formed by states 2s(C), while the subband B of a larger energy is formed by states 2p(C)–5d(W), i.e., is hybridised. The Fermi level [$E_F = 25.3$ eV, $N(E_F) = 0.23$ eV⁻¹ per unit cell] is located near the minimum of the density-of-states curve (Fig. 16a). Upon the introduction of a carbon vacancy, a

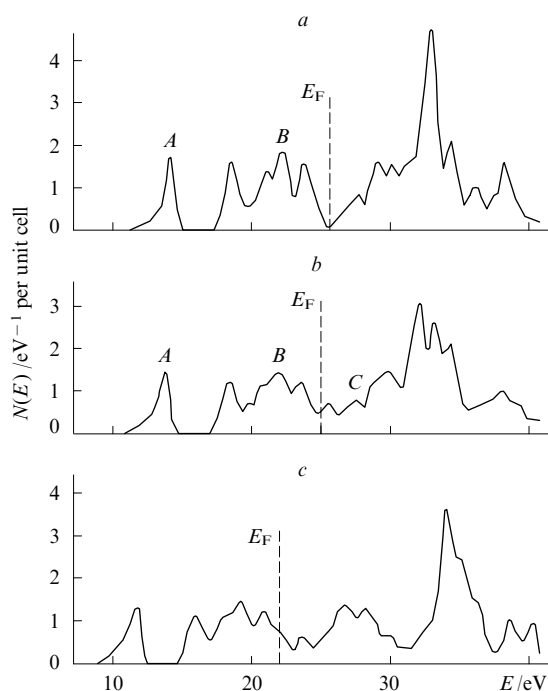


Figure 16. The effect of vacancies on the total density of electronic states $N(E)$ of hexagonal tungsten carbide according to LMTO-TP calculations.⁷⁰

(a) Stoichiometric carbide WC, (b) carbide $\text{WC}_{0.875}$ (W_8C_7) with carbon vacancies, (c) carbide $\text{W}_{0.875}\text{C}$ (W_7C_8) with vacancies in the tungsten sublattice.

vacancy peak C appears a little higher than the Fermi level, the density of states on the Fermi level $N(E_F)$ increases up to 0.61 eV^{-1} per unit cell and the band B acquires its fine structure (Fig. 16b). The presence of a vacancy in the tungsten sublattice also results in both the appearance in the Fermi level vicinity of a small vacancy peak and the increase in $N(E_F)$ up to 0.69 eV^{-1} per unit cell (Fig. 16c). The introduction of a carbon or a tungsten vacancy reduces E_F to 25.0 and 22.0 eV, respectively. The calculated⁷⁰ distribution of electronic density in the spheres of the tungsten and carbon vacancies and the charges of these vacancies ($q_{\square\text{C}} = 0.67e$, $q_{\square\text{W}} = 0.51e$) are in qualitative agreement with the positron lifetime in these vacancies:⁴⁷ the charge of a carbon vacancy is higher, hence, the positron lifetime in it is shorter as compared with the vacancy in the tungsten sublattice ($\tau_{\square\text{C}} = 136$ and $\tau_{\square\text{W}} = 175$ ps, respectively).

According to the results of calculations,^{46, 64–68, 70} the band structure of studied tungsten carbides is basically the same, *viz.*, it contains three main bands, namely, the low-energy 2s(C) band, the ground-state hybridised valence binding band 2p(C)–5d(W) and the high-energy band formed largely by the 5d states of tungsten.

V. Methods of synthesis of tungsten carbides and WC–Co alloys with different grain sizes

Polycrystalline metal carbides are usually synthesised by the powder metallurgy methods, which are described in detail in monographs.^{3, 4} Different synthetic methods are also described.^{71–73} The most popular methods are those that involve the direct synthesis from a metal and carbon or from the compounds containing the metal (for example, metal oxides or chlorides) and carbon (*e.g.*, a hydrocarbon or CO).

A conventional method of the synthesis of hexagonal carbide WC involves heating of tungstic acid (H_2WO_4) or ammonium tungstate $(\text{NH}_4)_2\text{WO}_4$ in a mixture of hydrogen and methane at 1020–1270 K. When tungstic acid is used, the metal is completely

reduced even before the carburisation. The carbothermal reduction of WO_3 by carbon in the inert or reductive atmosphere proceeds in a similar way. Tungsten carbide synthesised by carbothermal reduction usually contains traces of oxygen and oxycarbides; therefore, synthesis of a pure substance requires that the latter be additionally annealed at a temperature not lower than 1800 K.

The purest hexagonal WC samples are synthesised by the solid-phase vacuum sintering of metallic tungsten and carbon (gas black) at a temperature not lower than 1400 K. Hexagonal carbide W_2C is synthesised by the solid-phase vacuum sintering of tungsten and carbon powders at 850–900 K. However, the solid-state carburisation at this low temperature proceeds only in the presence of hydrogen or a gaseous hydrocarbon; moreover, the final product contains a relatively high amount of free carbon. Synthesis of a single-phase WC powder with the grain size of 5–6 μm from the metallic tungsten powder in a mixture of hydrogen with methane has been described;⁷⁴ at 2300–2500 K and a gas mixture with ≤ 2 vol.% of methane, WC with the free carbon content < 0.1 mass % could be obtained. High temperature (up to ~ 2400 K) is required in those cases where the solid-state sintering is carried out in vacuum, although the carburisation starts at 1400 K.

Tungsten carbides can also be synthesised using the following methods: deposition from the gas phase in the reaction of $\text{W}(\text{CO})_6$ or tungsten chloride with a mixture of a hydrocarbon and hydrogen, thermal decomposition of various precursors,⁷⁵ self-propagating high-temperature synthesis and mechanochemical synthesis.⁷⁶ For example,⁷⁷ a mixture of carbon (black) and tungsten powder with the grain size of up to 10 μm was ground in a cam-type mill; during the grinding, the average load in the ball impact zone was 10^8 – 10^9 Pa and the quantity of mechanical energy absorbed by the powder during the grinding reached 30 kJ g^{-1} . As a result of such treatment, lower hexagonal tungsten carbide was obtained. Mechanochemical synthesis of carbides from elementary tungsten and carbon in a planetary ball mill with the use of an inert copper matrix was described;⁷⁸ according to authors' estimates, the average size of W_2C and WC particles formed did not exceed 0.5 μm .

We have already mentioned that hexagonal carbide WC is not the hardest and most refractory among carbides. Its melting point (~ 3060 K) is lower as compared with TiC, ZrC, HfC, NbC and TaC, and its hardness at 300 K (according to different sources, from 18 to 22 GPa) is lower as compared with non-stoichiometric carbides TiC_y , ZrC_y , HfC_y , VC_y , NbC_y , TaC_y at the same temperature.^{3, 4} However, the hardness of WC is sufficiently stable, *e.g.*, as a result of carbide heating from 300 to 1300 K, the microhardness H_V of hexagonal WC decreased from ~ 18 to ~ 12 GPa,⁷⁹ whereas H_V of carbides of other metals decreased under the same conditions from their maximum values to 3–8 GPa (Fig. 17). The increase in temperature from 300 to 1100 K is accompanied by a more pronounced decrease (approximately three-fold) in the WC hardness; however, the hardness of other carbides undergoes a still sharper decrease (approximately five-fold) in the same temperature range.⁸⁰ The sharp decrease in the WC hardness with the increase in the temperature follows from the experimental results,⁸¹ which, nonetheless, substantially differ from those given by other authors^{79, 80} (the same study⁸¹ also shows the hardness value for vanadium monocarbide at ~ 900 –1500 K, which is lower as compared with that found in other literature sources). Apparently, the value of WC hardness measured in the study cited (Ref. 81) is severely underestimated. Moreover, note that, as compared with other carbides, WC has a modulus of elasticity higher by a factor of 1.5–2 [~ 700 GPa (see Ref. 82)] and a thermal expansion coefficient lower by a factor of $1.5 [(5-6) \times 10^{-6} \text{ K}^{-1}]$ (see Ref. 82)].

The mentioned properties of WC and their temperature stability during the heating up to 900–1000 K determined its application as the basis of wear-resistant hard alloys that are used in metal-working and drilling operations. The direct use of WC for

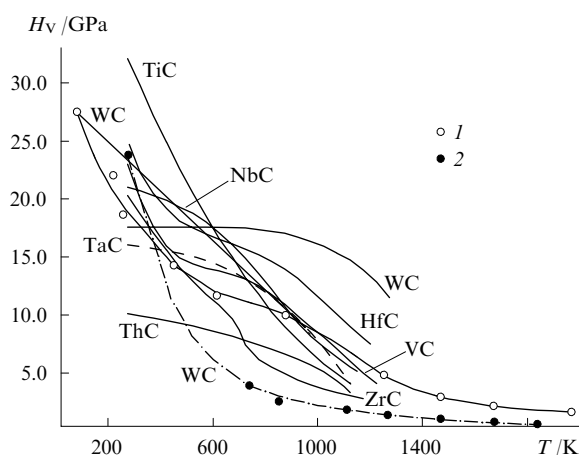


Figure 17. The effect of temperature on the Vickers hardness of hexagonal WC and carbides of transition metals.⁷⁹ For comparison, the known $H_V(T)$ dependences of monocarbide WC (1)⁸⁰ and (2)⁸¹ are shown (see text).

these purposes is impossible because of its brittleness and sintering only at very high temperatures. Hence, for a given carbide to be applied in practice, it should be imparted certain viscosity without sacrifice in its hardness. This is achieved by using a metal binder together with WC that provides the plasticity of the composite material and, at the same time, has sufficiently high strength, melting point and impact elasticity.

The choice of a metal for the binder is restricted by the following conditions: this should withstand carburisation and in its molten state should adequately wet the carbide to be modified. Moreover, it is necessary that the carbide and the binding metal be soluble in each other. This provides their strong adhesion. For the case of WC, it is cobalt that best satisfies the mentioned requirements; that is why the first hard alloys that have found wide use in the industry were synthesised in the WC–Co system.[¶]

1. Hard alloys WC–Co

According to the phase diagram of the ternary W–Co–C system (see Fig. 12), at the low carbon content, the ternary compounds of the η -carbide type or the solid solution $\text{Co}_3\text{W}_3\text{C}_y$ based on η -carbides $\text{Co}_4\text{W}_2\text{C}$ and $\text{Co}_7\text{W}_4\text{C}$ can be formed. With further decrease in the carbon content, in the $\text{Co}_3\text{W}_3\text{C}_y$ solid solution, the triple phase diagram shows the appearance of a carbide with the approximate composition of $\text{Co}_6\text{W}_6\text{C}_y$. The mentioned ternary compounds and solid solutions exhibit enhanced brittleness; hence, in the synthesis of hard alloys, those compositions are used that lie in the WC–Co cross-section region where no ternary compounds can be formed. In commercial WC–Co alloys, the cobalt content varies from 4 to 18 mass % depending on their application.

The most important traditional operation in the technology of hard alloys is sintering of an item pressed from a powder mixture with an addition of a plasticiser^{83,84} at 1600–1800 K. During the sintering of a WC–Co alloy, a certain amount of liquid phase, namely, molten cobalt, is formed. The wetting angle of WC with cobalt is zero, *i.e.*, molten cobalt completely wets the tungsten carbide grains and partly dissolves them; they crystallise upon

subsequent cooling. In the sintering of a hard alloy, the following temperature intervals are considered:

- at 470–670 K, the plasticiser is removed;
- at 670–970 K, the admixtures of tungsten and cobalt oxides are reduced;
- at 1050–1400 K, individual carbide grains are welded together in their contact points;
- at 1400–1570 K, a solid solution of tungsten carbide in cobalt is formed, the sample shrinks and all cobalt passes to the liquid phase;
- at 1550–1670 K, due to the migration of carbide grains in the liquid phase, the sample acquires its final compact shape;
- the temperature increase up to 1770–1800 K is accompanied by additional dissolution of the WC grains in cobalt, on the one hand, and the growth of carbide grains due to the recrystallisation *via* the liquid phase, on the other hand; simultaneously, complete degassing of the alloy occurs;
- during cooling after the exposure at the maximum sintering temperature, the dissolved tungsten carbide deposits from the liquid phase onto the surface of carbide grains, which results in their growth.

In the ideal case, the sintered WC–Co alloy is two-phase, containing only WC grains and the metal binder between them. At a deficit or an excess of carbon, the alloy becomes three-phase and contains additionally either an η -phase of $\text{Co}_3\text{W}_3\text{C}_y$ (at carbon deficit) or graphite inclusions (at carbon excess). The graphite inclusions as well as the presence of very coarse (several times larger than the average size) WC grains substantially reduce the alloy service life.⁸⁵

The average size of carbide phase grains increases noticeably upon sintering as compared with the grains in the original WC powder. Fine-grain alloys exhibit better performance and the use of fine-grain mixtures for the sintering allows higher quality alloys to be obtained. All other conditions being equal, the grain size in an alloy decreases with the decrease in the cobalt content due to the decrease in the liquid phase content and the deceleration of the grain growth by recrystallisation *via* the liquid phase; the grain size also decreases at a low content of carbon, which, however, results in the appearance of the brittle η -phase. Deceleration of the growth of carbide-phase grains in WC–Co alloys is achieved by their doping with other carbides. The most efficient dopant in this respect is vanadium carbide. Upon introduction of only 0.3 mass % of vanadium carbide, the average grain size of the carbide phase in fine-grain alloys is $\sim 1 \mu\text{m}$. To obtain fine-grain alloys, it is standard practice to include the long-term (up to 48 h) grinding of WC and Co powders in ethanol at the stage of mixture preparation.⁸⁶

Over the past 20 years, the methods of synthesis of various substances and materials in the nanocrystalline state have been actively developed. In this state, the size of particles (grains, crystallites) does not exceed 40 nm.^{87–90} Substances with particles measuring 40–100 nm are called submicrocrystalline.^{89–91} Monographs^{87–90} describe different methods of the synthesis of nanocrystalline powders and compact nanomaterials, the peculiarities of their microstructures, the methods of certification of nanomaterials, the effect of the particle (grain) size on the physical properties of substances. The manifestations of nanoscale effects in the structure and properties of metals, compounds and materials were reviewed.^{92,93}

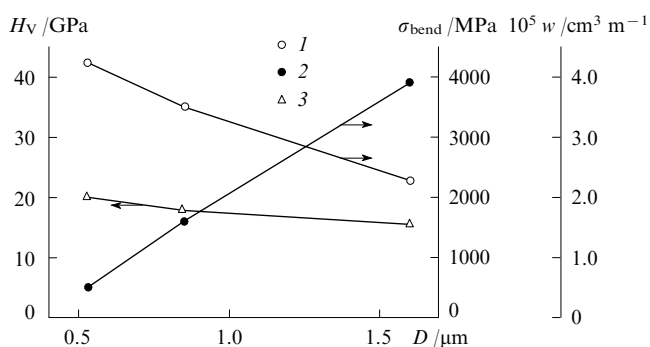
2. Nanostructured hard alloys

The most promising way to increase the production of nanostructured alloys with the reduced sintering temperature and the enhanced (due to the superfine-grain structure) hardness, strength, fracture toughness (crack-resistance) is to use nano- and submicrocrystalline carbides as the components of these alloys.^{94,95} The decrease in the WC particle size even in the micron scale is accompanied by a noticeable increase in the wear resistance of WC–Co alloys, as well as the increase in their hardness and the compression and bending strength (Table 3, Fig. 18).^{97,98}

[¶] For the brief analysis of the data published from 1918 to 1923 on the development of hard alloys based on tungsten carbide in which such metals as Fe, Ni and Co were used as the binder, see a review.¹⁵ The author of this review, K. Schrüter, in 1925 patented the alloys WC–M (M = Co, Ni, Fe) in the USA with the priority from 1923. Later, similar alloys were developed in Sweden, Austria and other countries. In Russia, hard alloys based on tungsten carbide were manufactured under a trademark ‘pobedit’.

Table 3. The effect of the WC grain size on certain properties of hard alloys WC–Co.⁹⁶

Alloy composition (mass %)	Grain size / μm	Rockwell hardness /HRA	Density / g cm^{-3}	Bending strength /MPa	Compression strength /MPa	Modulus of elasticity /GPa	Relative wear resistance (%)
97WC–3Co	1–2	92.5–93.2	15.3	1590	5860	641	100
94WC–6Co	0.5–1.0	92.5–93.1	15.0	1790	5930	614	100
94WC–6Co	1–2	91.7–92.2	15.0	2000	5450	648	58
94WC–6Co	2–5	90.5–91.5	15.0	2210	5170	641	25
90WC–10Co	0.5–1.0	90.7–91.3	14.6	3100	5170	620	22
90WC–10Co	2–5	87.4–88.2	14.5	2760	4000	552	7

**Figure 18.** (1) Bending strength σ_{bend} , (2) wear rate (wear resistance) w and (3) hardness H_V as a function of the grain size D of the carbide phase of hard alloys WC–6 mass % Co.⁹⁸

The only exclusion known is the decrease in the bending strength of WC–6 mass % Co alloys with the decrease in the grain size (see Table 3). The results of other studies demonstrate that the mechanical properties always improve with the transition from coarse-grain to fine-grain WC–Co alloys. For example, upon sintering of WC–15 mass % Co nanopowders with the average particle size of 970, 490 and 30 nm at 1690 K the resulting alloys with the average grain size of 1350, 950 and 620 nm exhibited hardness of 13.8, 14.7 and 17.0 GPa, respectively.⁹⁴ A hard alloy WC–10 mass % of Co with the carbide phase of superfine structure (the WC grain size is smaller than 0.5 μm) exhibits microhardness of 19.3 GPa and a bending strength of 3890 MPa, whereas the same characteristics of a similar alloy with the grain size of 0.5–1.0 μm are 17.8 GPa and 3780 MPa.⁹⁹ Hard alloys WC–6 mass % Co manufactured by ‘Krupp Widia GmbH’, which contain carbide-phase grains measuring 1.4–1.8, 0.8–0.9 and 0.5–0.6 μm , exhibit the bending strength of 2000, 3000 and 3800 MPa, the hardness of 15.8, 18.0 and 20.4 GPa, the abrasive wear resistance of 1.26%, 2.08% and 2.78%, respectively. A similar improvement in the mechanical properties with the decrease in the carbide-phase grain size was observed for hard alloys with larger (up to 15 mass %) cobalt content. The strength characteristics of conventional (with micron-scale grains) hard alloys based on WC are discussed in a monograph.⁸⁵

Plasmochemical synthesis is among the most widely used chemical methods for obtaining fine-grain powders of nitrides and carbides.^{100,101} The main conditions for the production of fine-grain powders by this method are as follows: the reaction should proceed far from its equilibrium and the new-phase nucleation rate should be high as compared with the nuclei growth rate. Under real conditions of the plasmochemical synthesis, nanoparticles are produced upon fast cooling of the plasma flow in which the gas phase is condensed; this reduces the sizes of the particles formed and suppresses their coalescence upon collisions. The plasmochemical synthesis of carbides makes use of the low-temperature (3000–8000 K) hydrocarbon and argon plasma of the arc, glow, high-frequency and microwave discharges; elements and their halides and other compounds are used as the starting

substances.⁸⁷ The characteristics of the powders synthesised depend on the starting materials, the process of synthesis and the reactor type. The particles obtained in plasmochemical reactions represent single crystals, have regular shapes and the sizes from 10 to 100–200 nm (and higher).

The plasmochemical synthesis is characterised by high rates of formation and condensation of substances, its efficiency is sufficiently high. The major disadvantages of this method are as follows: the wide size distribution of particles and, as a consequence, the presence of sufficiently coarse (up to 1–5 μm) particles, which means that the selectivity of the process is low, as well as high content of impurities in the resulting powder. To date, fine-grain powders of titanium, niobium, tantalum and tungsten carbides have been synthesised by the plasmochemical method.^{87,101–104} For instance, the synthesis of a submicrocrystalline WC powder with a specific surface area of 15 $\text{m}^2 \text{g}^{-1}$ and a particle size not exceeding 300 nm,[†] which was conducted in an argon–hydrogen plasma from methane and tungsten hexafluoride, was reported.¹⁰⁴

Synthesis of fine-grain tungsten carbide powders with the use of an arc plasmatron is described.¹⁰⁵ The plasmochemical synthesis produced a substance of the W–C–O system with a definite carbon-to-oxygen ratio, while the synthesis of the single-phase carbide as such was carried out in a tube furnace by the reduction of this product with hydrogen and CO. The specific surface area of synthesised WC varied from 5–6 to 50 $\text{m}^2 \text{g}^{-1}$. To produce the WC–Co furnace mixture, a cobalt powder with a specific surface area of 8–10 $\text{m}^2 \text{g}^{-1}$, which was synthesised by plasmochemical reduction of the oxide, was used. Sintering of the furnace mixture involved its hot pressing at 1370–1670 K and 10–50 MPa. The WC grain size in the samples sintered in the solid phase was ~ 100 nm.

A design of an electro-arc plasmatron for the plasmochemical synthesis (hydrogen plasma with the temperature of 3000–4000 K) of nanocrystalline powders of refractory compounds including tungsten carbide with the particle sizes from 10 to 100 nm was reported.¹⁰⁶

Low-temperature gas-phase synthesis of WC nanopowders is described.^{107,108} A two-step process was originally proposed¹⁰⁷ which included reduction of tungsten (its nanopowder) from tungstic acid salts, *i.e.*, the reductive decomposition of the precursor, followed by carburisation of tungsten in a CO-containing gas mixture. The synthesis produced a WC powder with the average grain size of 8 nm when conducted at 900–950 K and metastable lower carbide W_2C with particle measuring 13–19 nm when conducted at 600–800 K. A more straightforward one-step synthesis of the nanocrystalline WC carbide powder was described:¹⁰⁸ an H_2/CO gas mixture (2:1 or 1:1 molar ratios) was passed through ammonium tungstate or tungsten oxide powder at 800–1000 K; this directly led to the formation of nanocrystalline WC with particles < 10 nm. One important

[†] Note that WC has a density $\rho = 15.6 \text{ g cm}^{-3}$; hence, the average particle size (diameter) in a powder of the total specific surface area $S_{\text{sp}} = 15 \text{ m}^2 \text{g}^{-1}$ should be $D = 6/\rho S_{\text{sp}} \approx 30$ nm, *i.e.*, 10 times smaller than reported.¹⁰⁴

parameter of the single-step synthesis is the heating rate, which should provide the kinetic balance between the reduction and carburisation reactions. The heating rate of 2 deg min^{-1} is close to the optimum; moreover, heating even up to 1000 K resulted merely in a minor coarsening of WC particles as compared with heating to 800 K.

Mechanochemical synthesis in a cam-type mill produced hexagonal W_2C with the average particle size of 10 nm from a powder mixture of tungsten with the average particle size of up to 10 μm and carbon.⁷⁷

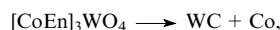
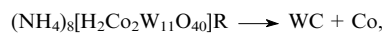
To preserve the positive effect achieved due to the use of nanocrystalline powders for the production of hard alloys, the WC particles should retain small sizes during their sintering. In our studies,^{109–111} we used the X-ray diffraction and magnetic susceptibility measurements to follow the changes in the thermal stability of a WC nanopowder that was obtained by the plasmachemical synthesis from WO_3 and propane at $\sim 3300\text{--}3800 \text{ K}$ in hydrogen plasma with the additional annealing in argon atmosphere at $1100\text{--}1300 \text{ K}$. The average particle size in the nanopowder was 50–55 nm. According to our studies, the particles in this powder retained the stable size when annealed in the temperature range from 300 to 1200 K, while the relaxation of microstresses in them began at $\sim 600 \text{ K}$ and ended at $\sim 900 \text{ K}$.

The fine-grain structure of hard WC–Co alloys synthesised from WC powders is determined not only by the small size of the furnace mixture particles, but also by the way their sintering proceeds. Upon formation of the liquid phase, first, the smallest particles and, then, medium size particles pass to the melt, while coarser particles survive. Insofar as most nanoparticles are of the medium size, the number of crystallisation centres in the alloy will be sufficiently high. In the recrystallisation, tungsten carbide deposits on the surface of non-dissolved WC particles. Due to the excessive surface energy of small particles, they acquire a thicker layer of deposited tungsten carbide as compared with coarse particles. As a result, the size of carbide-phase particles levels off. In an ordinary hard alloy, the number of crystallisation centres is substantially smaller than in an alloy synthesised from the WC nanopowder; hence, a nanocrystalline alloy would have a more fine-grain and uniform structure as compared with an ordinary alloy. However, it should be borne in mind that the growth of grains in nanocrystalline compositions WC–Co can occur at $\sim 1070 \text{ K}$,¹¹² *i.e.*, below the eutectic temperature of the W–Co–C system, which is equal to $\sim 1600 \text{ K}$ (nanopowders of WC–15 mass % Co with the average particle size of 30 nm were studied;¹¹² the liquid phase appeared at $\sim 1420 \text{ K}$ during sintering). This means that, during the liquid-phase sintering of WC–Co nanopowders, the initial growth of carbide-phase grains occurs in the range of solid-phase sintering temperatures, whereas the subsequent liquid-phase sintering only leads to the coarsening of WC grains.¹¹³

Also note that the most compact (non-porous) alloys can be obtained provided the furnace mixture is not monodisperse, because obviously the total volume of a sample cannot be filled without voids with unisized particles. More compact packing is achieved due to the presence of different-sized particles in the furnace mixture, where the finer particles occupy the voids between the coarser particles. Analysis of the three-dimensional packing of spherical particles has shown¹¹⁴ that a very high degree of the free space filling (~ 0.9) can be reached for their bimodal size distribution where, along with medium-size particles (D) that have the maximum share, the fraction of particles with a diameter $\sim 0.1D$ is fairly high. In other words, the size-distribution curve of the particles should possess two maxima, the first of which (abundance) corresponds to the particles with the medium size D , while the second corresponds to the particles with the size $\sim 0.1D$.

Analysis of the literature data has shown that nanocrystalline or submicrocrystalline tungsten carbide can be synthesised by different methods. However, for the production of nanostructured hard alloys WC–Co, it is better that not only tungsten

carbide, but the whole composition mixture WC–Co be in the nanocrystalline state. Such a mixture can be obtained by thermolysis of various precursors.⁷⁵ Particularly, heating can induce the following decomposition reactions resulting in the formation of WC and metallic cobalt:



where R and En are alkyl and ethylenediamine, respectively.

Modern technologies of the production of nanocomposite mixtures WC–Co include several consecutive operations, namely, deposition from colloid solutions, cryogenic sputtering and drying, carbothermal reduction. Thus an efficient method for the production of nanocrystalline compositions of tungsten carbide and cobalt for manufacturing hard alloys is based on the co-deposition of WC and Co precursors from colloid solutions.^{115, 116} According to this method, colloid solutions of tungsten and cobalt salts {*e.g.*, $(\text{NH}_4)_6[\text{H}_2\text{W}_{12}\text{O}_{40}] \cdot 4 \text{H}_2\text{O}$, CoCl_2 , $\text{Co}(\text{NO}_3)_2$, $\text{Co}(\text{CH}_3\text{COO})_2$ } are dried by sputtering, then the obtained powder is subjected to the low-temperature carbothermal reduction in the fluidised bed and thus retains its high-dispersion state. This technology was patented¹¹⁷ as the ‘Spray Conversion Process (SCP)’. Insofar as the synthesis starts in the solution, the components (W and Co) are mixed on the molecular level, which favours the formations of an amorphous carburised powder.

The grain growth can be inhibited and the WC solubility in cobalt can be suppressed by adding up to 1 mass % of non-stoichiometric vanadium carbide to the mixture. The alloy obtained from this nanocrystalline composition demonstrates the optimum combination of high hardness and high strength; for example, its Vickers hardness reached 21.5 GPa, whereas the maximum hardness of an alloy with the same composition, which was obtained from a conventional WC powder, did not exceed 19.5 GPa.^{115–118} The increase in the hardness and the decrease in WC grain size correlate with the increase in the vanadium carbide content in the alloy. Figure 19 illustrates the size distribution of grains in a sample of the WC–6 mass % Co alloy obtained from a nanocomposite mixture prepared by the deposition method described above and containing 0.83 mass % of vanadium carbide, and in a sintered sample of a conventional alloy WC–6 mass % Co containing 0.32 mass % of VC. As is seen, the average size of WC grains in the alloy synthesised from the

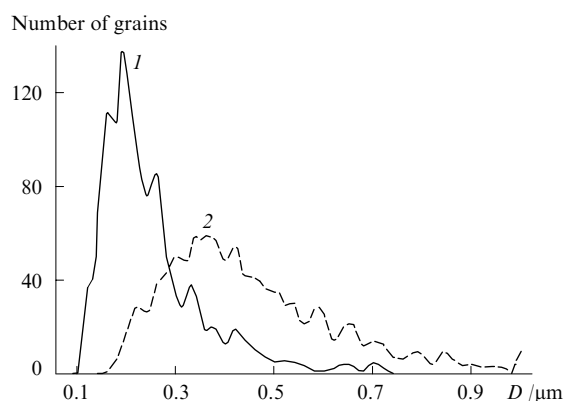


Figure 19. Size distribution of grains in WC–6 mass % Co alloy samples.¹¹⁹

(1) Alloy sintered from a nanocomposite mixture of WC, Co and 0.83 mass % of VC, which was obtained by the co-deposition from colloid solution followed by drying and carbothermal reduction; the sample contained 1000 grains; (2) conventional fine-grain alloys WC–6 mass % Co with 0.32 mass % of VC; the studied sample contained 948 grains.

amorphous nanocomposite powder is 250 nm, whereas an ordinary alloy has the grains almost twice larger (450 nm).

It was shown^{119, 120} that each nanocomposite WC–Co particle with a size of $\sim 75 \mu\text{m}$ consists of several millions of nanocrystalline WC grains measuring $< 50 \text{ nm}$, which are distributed throughout the cobalt matrix (Fig. 20). Sintering of a nanocomposite tungsten carbide mixture with 6.8 mass % of Co and 1 mass % of vanadium carbide produced the alloys which contained 60% of the WC grains measuring $< 250 \text{ nm}$ and 20% measuring $< 170 \text{ nm}$. A structure with still finer grains was obtained for an alloy which, in addition to tungsten carbide, contained 9.4 mass % of Co, 0.8 mass % of Cr_3C_2 and 0.4 mass % of VC_y . Upon its sintering at 1670 K, 60% of the tungsten carbide grains were $< 140 \text{ nm}$ and 20% were $< 80 \text{ nm}$. A comparison of the nanoalloy with ordinary polycrystalline alloys of equal hardness have shown,¹²⁰ that the crack resistance of the nanoalloy is higher by a factor of 1.2–1.4 as compared with ordinary coarse-grain alloy.

The described nanocrystalline WC–Co composite powder with the carbide grain size of 20–40 nm is manufactured on the commercial scale in the USA as NANOCARBTM. For the deposition of protective coatings by the thermal sputtering method, the nanocomposite multimodal (containing several frac-

tions of carbide grains, viz., from 8 to 50 nm) WC–Co powder NANOMYTETM was used.

Synthesis of a one-phase nanocrystalline WC powder by grinding tungsten and carbon in a ball mill at room temperature for $2.95 \times 10^5 \text{ s}$ is described;¹²¹ the increase in the grinding time to $4.32 \times 10^5 \text{ s}$ afforded a nanopowder with the average grain size $< 5 \text{ nm}$. Then different amounts of cobalt were added to the WC nanopowder, and grinding was continued for $2.6 \times 10^5 \text{ s}$. The resulting nanocomposite mixtures WC–Co contained different amounts of cobalt, and the particles with the average size $< 5 \text{ nm}$ represented WC covered with a cobalt layer. Its pressing and hot sintering produced an alloy, which contained the carbide phase grains with the average size of $\sim 100 \text{ nm}$. The hardness and the elasticity modulus of the alloys, which contained from 5 mass % to 12 mass % of Co varied in the ranges of 20–12 and 740–580 GPa, respectively.

It was already mentioned that the initial and the most active growth of carbide phase grains occurs in the sintering of WC–Co nanopowders in the temperature range of solid-state sintering. To decelerate the growth of grains in this region, it was proposed¹²² to synthesise the nanostructured hard alloys WC–Co in an electric arc discharge. In this case, the stage of compacting of the nanopowder mixture is combined with its fast sintering and subsequent cooling of the sintered sample. The heating and cooling rates in this method are sufficiently high to avoid the sintering in the solid state and prevent the grain growth during the cooling. Thus a hard alloy was obtained¹²² from a nanopowder of tungsten carbide containing 10 mass % of Co prepared by the SCP technology (see Refs 115–117) and had, on average, 50-nm coherent-scattering regions (according to X-ray diffraction data) or the average particle size of 200 nm (according to the data from scanning electron microscopy). The compacting pressure reached 300 MPa. When a current pulse was passed for several microseconds through a sample with the mass of 2.5 g, the energy (3 kJ g^{-1}) was liberated, which led to sintering. As a result, a hard alloy was obtained that had a density equal to 95% of its theoretical value and contained only WC and a fcc solid solution of tungsten carbide in cobalt. The average grain size in the carbide phase of this alloy was 120 nm according to data from electron microscopy; the measured modulus of elasticity was 550 GPa.¹²²

A hard alloy WC–Co synthesised from a tungsten carbide powder with 30–50-nm particles¹²³ had a more uniform fine-grain structure and exhibited higher hardness and strength as compared with common hard alloys of the same composition. It was mentioned that the introduction of 3 mass %–5 mass % of tungsten carbide nanopowder to the standard furnace mixture containing coarse ($1\text{--}4 \mu\text{m}$) WC grains levels off the deviations in the hardness and strength of the resulting WC–Co alloy, i.e., stabilises the hard-alloy properties.

A virtually ideal version of mechanochemical synthesis, which is coupled with the synthesis of a nanocomposite mixture, was described.¹²⁴ A mixture of coarse ($\sim 75 \mu\text{m}$) tungsten, graphite and cobalt powders was ground in an argon-filled ball mill for 100 h; the resulting nanocomposite WC–Co mixture contained cobalt and tungsten-carbide grains with the average diameter of 11–12 nm. In the hard alloy, which was obtained by cold pressing of the mixture followed by its sintering at 1310 K, most WC grain had a size $< 200 \text{ nm}$, i.e., were several times smaller as compared with conventional alloys of the same composition. The sintered hard-alloy samples demonstrated the hardness of $\sim 18 \text{ GPa}$ and the relative density equal to 80% of the theoretical value. The possibility of sintering of a nanocomposite WC–Co powder mixture at lower temperatures as compared with coarse-grain mixtures is determined by the lower melting point of nanocrystalline cobalt as compared with coarse-grain cobalt.

Bearing in mind that even a small amount of non-stoichiometric vanadium carbide inhibits the growth of the carbide phase grains during the sintering, it was proposed¹²⁵ to synthesise $\text{V}_8\text{C}_7 + \text{WC}$ powder mixtures in the first stage of the synthesis of WC–VC–Co alloys. Joint grinding of WC and V_8C_7 powders

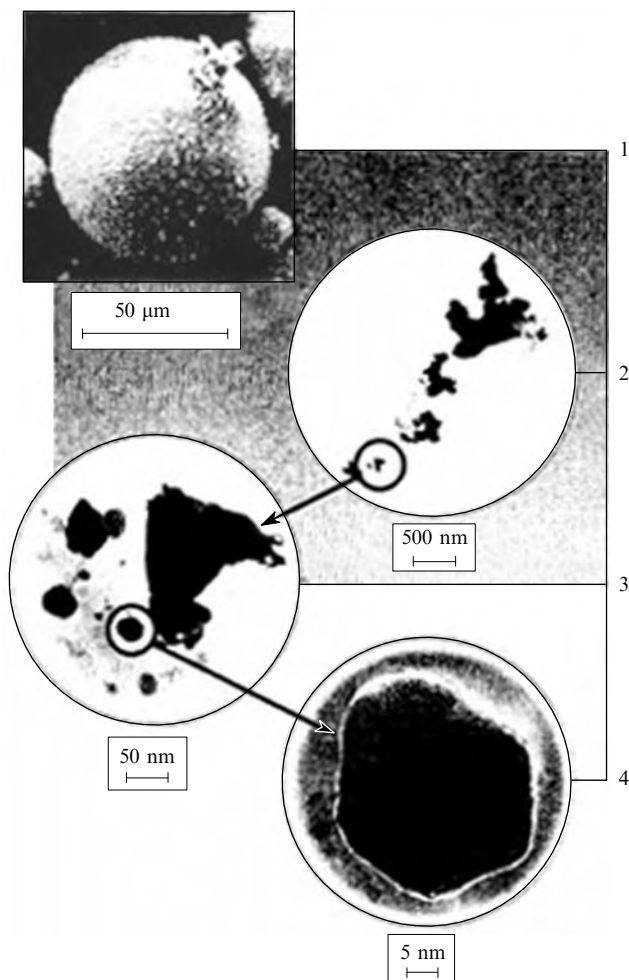


Figure 20. Distribution of WC grains in coarse particles of the amorphous nanocomposite mixture WC–6 mass % Co with 0.83 mass % of VC, which was obtained by the deposition from a colloid solution followed by drying and carbothermal reduction.^{119, 120}

(1) A particle of a composite powder WC–Co measuring $75 \mu\text{m}$, (2) particle fragments after grinding of the powder, (3) a polycrystalline cluster formed by WC grains in a cobalt matrix, (4) a WC grain measuring 30 nm.

with an addition of 0.5 mass % of Co for 48 h followed by their 3-h exposure at 1470 K to form their mixed (V,W)C carbide produced a mixture with the average particle size of 1.4 μm . Joint grinding of vanadium oxide, tungsten carbide and carbon was also carried out, which was followed by the carburisation of the resulting mixture at ~ 1470 K in the H_2/Ar atmosphere. In this case, the obtained powder had the particles with the average size of 1.8 μm .

The synthetic methods, the structure and mechanical properties of fine-grain hard alloys based on tungsten carbides were discussed briefly in a review.¹²⁶ Studies devoted to the microstructure, hardness and fracture toughness of hard WC–Co alloys¹²⁷ have shown that the hardness increases with a decrease in the thickness of the metal binder layer. It was also noted that the hardness measurements carried out at low loads or using a nanoindenter overestimate its value by ~ 2 GPa. The effects of the microstructure and the grain size of alloys WC–6 mass % of Co on their hardness in the temperature range from 80 to 1170 K was studied.¹²⁸ The examined alloys had the microstructure typical of ordinary hard WC–Co alloys (Fig. 21). Figure 22 illustrates the changes in the hardness H_V of alloys with the average grain size of 0.6, 1.4 and 3.6 μm as a function of the temperature. It is evident that the alloys with a fine-grain structure are harder throughout this temperature range.

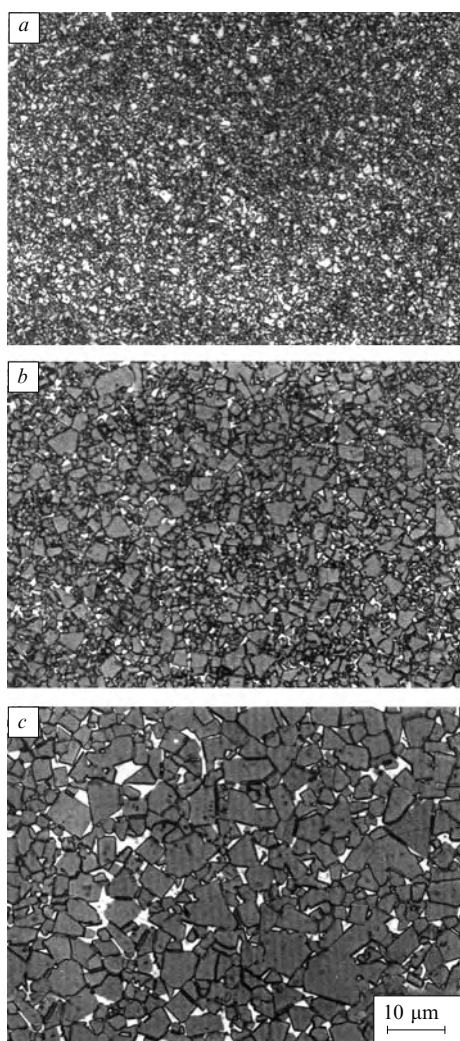


Figure 21. A typical microstructure of hard alloys WC–6 mass % Co with the average size of carbide phase grains of 0.6 (a), 1.4 (b) and 3.6 μm (c).¹²⁸

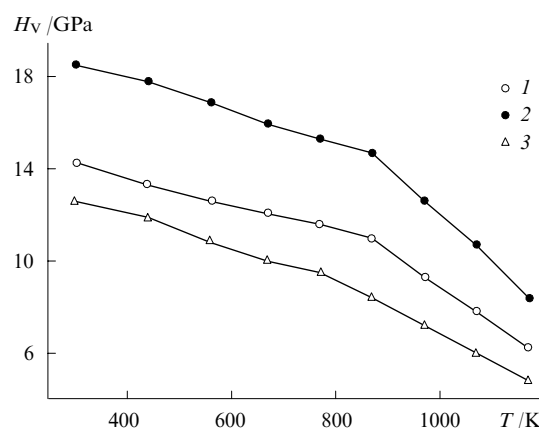
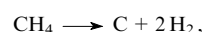


Figure 22. The effect of temperature of the Vickers hardness of WC–6 mass % Co alloys with the average size of carbide phase grains of 1.4 (1), 0.6 (2) and 3.6 μm (3).¹²⁸ The measurements were performed under a load of 6 kg.

Recently, nanopowders of the WC–Co system came into use for synthesising nanocomposites that contain a diamond phase.^{129,130} A nanopowder WC–15 mass % of Co with tungsten carbide grains measuring 100 nm on average was pressed into samples of 8-mm diameter under a pressure of 100 and 300 MPa.¹²⁹ The samples were first heated to 1170 K in a hydrogen atmosphere to remove the oxide film and then sintered in vacuum at 1270–1470 K with 30-min exposure at the maximum sintering temperature. By varying the sintering time at the lowest temperature used, one could control the size and the arrangement of pores in the sample. Then, the samples were kept for 3 h at 1170 K in a flow of $\text{H}_2 + \text{CH}_4$ gas mixture to infiltrate the gas into the pores, after which they were simultaneously subjected to impact of high temperatures and pressures in order to reduce methane to carbon and transform carbon (graphite) into the diamond phase. The resulting superhard nanocomposite material contained ~ 45 vol.% of the diamond phase.¹²⁹ The diamond phase content in the synthesised nanocomposite seems to be significantly overrated.

A somewhat different method for the synthesis of WC–Co–diamond nanocomposites was proposed.¹³⁰ The initial mixture represented a powder mixture of WC with 15 mass % of Co; the average size of WC particles was 100 nm. The samples compacted under a pressure of 200 MPa were heated to 870 K in a hydrogen atmosphere to remove the oxide film and then sintered in vacuum at 1370 K for 30 min. The resulting porous samples with the 70% relative density were subjected to electrochemical etching in an aqueous $\text{NaC}_4\text{H}_5\text{O}_6$ solution. After the etching, the samples were washed with water, dried and then saturated with a gas mixture $\text{H}_2 + \text{CH}_4$, which contained 15% of methane. The infiltration of the gas into pores was carried out at 1170 K for 4 h. Then hydrostatic pressure of 8 GPa was applied at 1770 K to decompose methane in a catalytic reaction



deposit carbon on the pore walls and transform it from the graphite state into the diamond state and also to condense the samples. The hardness of samples near their edges reached 32 ± 3 GPa, which was five times higher than in the bulk.

Thus, nowadays, there are different methods for the synthesis of nano- or submicrocrystalline tungsten carbides, WC–Co composite nanopowders and nanostructured hard WC–Co alloys. The available data suggest (see Table 3, Fig. 18) that the decrease in the size of carbide grains in hard WC–Co alloys is accompanied by noticeable increase in the abrasive wear resistance (by a factor of 2–3). Indeed, when drilling the printed circuit boards, the drills made of ultradispersed hard alloys prove to be

2–3 times more stable as compared with those made of standard alloys.¹²⁶ Therefore, it is reasonable to use the hard alloys with untradispersed and nanocrystalline structures, which combine the enhanced wear resistance, strength and fracture toughness, in those operations that require high wear resistance. However, it deserves mentioning that for ordinary alloys the same and even greater effect of the increase in the wear resistance can be achieved by the deposition of a wear-resistant coating.¹³¹ This should be taken into account when assessing the economic profits associated with the use of nanostructured hard alloys.

VI. Conclusion

Hexagonal tungsten carbide is the most extensively used among all carbides of Group IV–VI transition metals. Originally, in the W–C system, only two hexagonal carbides W_2C_y (β - W_2C) and WC (δ -WC) were known, which despite their similar symmetry differ significantly, namely, lower carbide W_2C_y has a noticeable homogeneity region $WC_{0.34}–WC_{0.50}$, while hexagonal monocarbide δ -WC can have only the stoichiometric composition and contains no vacancies in the carbon sublattice. The non-stoichiometry of a disordered lower carbide W_2C_y , which is at equilibrium from 2700 K up to the melting point, is a prerequisite for its ordering with respect to both atoms and vacancies at lower temperatures. According to the neutron diffraction analysis, with decrease in the temperature, the following disorder–order transformation takes place in β - W_2C carbide:



The earlier concepts on the two consecutive transformations, *viz.*, the disorder–order transformation to form the orthorhombic β' - W_2C phase of the PbO_2 type

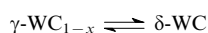


and the order–disorder transformation to form the trigonal β'' - W_2C phase of the $C6$ type



were not confirmed by the neutron diffraction analysis of the W_2C structure.

One peculiarity of lower tungsten carbide is that at 1523 K it undergoes the eutectoid decomposition to give tungsten and δ -WC and thus does not exist at lower temperatures. In the 1960s, an additional compound highly non-stoichiometric with respect to carbon, namely, cubic carbide γ - WC_{1-x} was discovered in the W–C system. The region of the existence of equilibrium of this carbide is very wide with respect to composition (from $WC_{0.58–0.59}$ to $WC_{1.00}$) and very narrow with respect to temperature (from ~ 3060 to $\sim 2990–3020$ K); however, due to quenching from high temperature, it can be preserved in the metastable state at 300 K. The temperature of the equilibrium transformation



is 3000–3010 K; however, the temperature of the non-equilibrium transformation of the quenched cubic carbide γ - WC_{1-x} to give hexagonal δ -WC, which occurs on heating, is still unknown.

Studies on the W–C system are also important from the practical viewpoint, because tungsten carbide is used in the production of hard alloys applied in the metal working and drilling. The traditional basis for such alloys is hexagonal stoichiometric carbide WC (δ -WC); to date, no attempts were undertaken to use cubic carbide γ - $WC_{1.0}$ of the stoichiometric composition or non-stoichiometric cubic carbide γ - WC_{1-x} for these purposes. The cubic structure of tungsten carbide can apparently be stabilised by the addition of other cubic carbides, for example, VC_y . The use of cubic tungsten carbide with VC_y additives as the basis for hard alloys can also provide the thermal stability of the carbide phase and the fine-grain structure of the alloy.

Yet another direction in the application of tungsten carbide, which was actively developed in the past 20 years, concerns the nanostructured hard alloys. In the systems W–C and W–C–Co, the nanostructured carbides or nanocomposites of the WC–Co and WC–Co–diamond types were obtained. Their synthesis became possible due to the use of new and, as a rule, combined synthetic methods and non-traditional procedures such as co-deposition of tungsten and cobalt from colloid solutions, thermal decomposition of precursors, plasmochemical reduction, mechano-synthesis, *etc.* The particle sizes in nanocomposites can be very low (10–40 nm); however, the problem of the conservation of the small particles during sintering of a hard alloy is not yet solved completely. Nonetheless, the microstructure of newly developed ultradispersed hard alloys contains carbide-phase grains with the average size of 100–250 nm, which provides the noticeable increase in their hardness, wear resistance and other performance characteristics. The introduction of small amounts of vanadium carbide favours the retention of small-sized grains in nanostructured hard alloys.

On the whole, the studies of tungsten carbides and the related phase equilibria in both the W–C system and more complex systems containing tungsten carbides contribute to the development of fundamental concepts on the nature of refractory compounds of transition metals and serve as the basis for their wide application in the future.

This review has been written with the financial support of the Russian Foundation for Basic Research (Project No. 06-03-32047a).

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^e — *Power Metall. Met. Ceram. (Engl. Transl.)*

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^h — *J. Theor. Exp. Phys. Lett. (Engl. Transl.)*

Discreteness of nanostructures and critical dimensions of nanoclusters

I P Suzdalev, P I Suzdalev

Contents

I. Introduction	637
II. Critical dimensions of nanoclusters and nanostructures	638
III. Critical characteristics and properties of nanoclusters and nanostructures	652

Abstract. Theoretical models and experimental data related to the formulation of the discreteness concept for nanoclusters and nanostructures are analysed. The discreteness is shown to be due to the existence of critical sizes of nanoclusters determined by the magic numbers of atoms and thermodynamic parameters. Such nanoclusters exhibit the highest stability in the formation of nanostructures and specific properties. The bibliography includes 116 references.

I. Introduction

There are a few types of discreteness of matter, *e.g.*, discreteness on the atomic level, the elementary particle level and the atomic-molecular level. For instance, the atomic-molecular structure is discrete on the atomic level (of the order of 10^{-1} nm). This manifests itself in individual electronic, optical, magnetic properties of matter on this level of discreteness and in, *e.g.*, the form of X-ray diffraction, electron diffraction and in the onset of co-operative mechanical, thermal, optical, electronic and magnetic properties in the formation of condensed state. The structure and properties of matter on various levels of discreteness have been a subject of atomic physics and quantum chemistry, physics and chemistry of condensed state and physical chemistry. Discreteness of matter on a lower, elementary particle level (of the order of 10^{-6} nm) has been studied by nuclear physicists and chemists.

There is yet another level of discreteness of matter. Some features of the supramolecular structures and nanoclusters of size 1–100 nm also indicate the formation of the most stable clusters (nanoparticles) of particular sizes, which can be treated as manifestation of specific discreteness level.

In addition to the spatial discreteness level in heterogeneous nanostructures involving nanopores, nanotemplates, nanoclusters, *etc.*, discreteness governed by the physicochemical properties of matter emerges. On the one hand, this is a consequence of the microscopic approach and the effect of the atomic or electronic structure of matter on the formation and properties of nanoclusters of size 1–10 nm on going from the local energy levels to the band structure. On the other hand, the laws of thermody-

namics and the effect of the surface dictate the formation of stable nanoclusters of the most probable sizes from 1 to 50 nm and thus the appearance of nanostructures with discrete nanocluster size distributions. (Of course, the case in point are the most probable cluster sizes against the background of overall continuous nanocluster size distribution in nanostructures.) Nanostructures built of the critical-size nanoclusters possess novel co-operative properties.^{1–6}

The aim of this review is to elucidate the discreteness and conditions for formation of critical-size nanoclusters and to consider the properties of such nanoclusters as well as nanostructures, nanomaterials and nanodevices based on them. It should be noted that the functions characterising the state of clusters are determined by not only the cluster size, but also the presence of defects, by the electronic, magnetic and other factors which were ignored in our models.

The review consists of two main parts. The first part is devoted to the formation of critical-size nanoclusters and nanostructures based on them in various media. In the second part we will consider the properties of such nanostructures and nanomaterials.

The first part concerns the mechanisms of nanocluster formation in the gas, liquid and solid phases. The formation of critical-size nanoclusters in the gas phase is considered using the thermodynamic (pressure and temperature dependences) and microscopic (with inclusion of triatomic collisions and the effect of the magic number of atoms in filling the electron shells) approaches and the close packing principle. For the liquid phase (solutions and colloidal systems) we consider the formation of molecular clusters, colloidal clusters and critical-size nanoclusters in a nanopore or a reverse micelle based on the thermodynamic approach and the principle of close packing of atoms.

The formation of mesoporous silica and alumina is also associated with the existence of nanoparticles of characteristic discrete sizes. Solid-phase reaction studies revealed not only the formation of critical-size nanoclusters with the primary structure, but also the existence of aggregates of the critical-size clusters, namely, superclusters that form hierarchical secondary or ternary structures. Using the thermodynamic approach, it is possible to determine the critical cluster sizes corresponding to the onset of sintering and the formation of a nanostructure.

The second part is devoted to those properties of nanostructures that are due to discreteness. We will consider the thermal properties related to the existence of critical cluster sizes at which melting begins and transition to the solid–liquid state occurs. Then, we will discuss the mechanical properties. At certain critical value of the defect concentration, nanoclusters can behave as superhard or superplastic materials. These properties can be controlled by varying the cluster surface area. The conducting and optical properties of nanoclusters and nanostructures are due to

I P Suzdalev, P I Suzdalev N N Semenov Institute of Chemical Physics, Russian Academy of Sciences, ul. Kosygina 4, 119991 Moscow, Russian Federation. Fax (7-495) 137 83 18, tel. (7-495) 939 71 01, e-mail: suzdalev@chph.ras.ru (I P Suzdalev), tel. (7-495) 930 21 01 (P I Suzdalev)

Received 13 January 2006

Uspekhi Khimii 75 (8) 715–752 (2006); translated by A M Raevskiy

the existence of the critical cluster size for one-electron transfer and the critical sizes governed by the occurrence of a plasmon (in the case of optical absorption in metals) or a polaron (in the case of semiconductor luminescence). Laser emission is also related to the maximum and minimum sizes of semiconductor clusters. The electromagnetic properties including the giant magnetoresistance are determined by the critical size of superparamagnetic clusters, the magnetic field magnitude and the ratio of the cluster size to the mean free path of an electron (in the case of electron conduction). Tunnelling magnetisation parameters are characterised by the critical values of external magnetic field. Finally, magnetic phase transitions in clusters can be governed by the critical cluster sizes.

With allowance for specific properties of nanoclusters, nanostructures can be considered as a specific form of matter that is discrete on the cluster (or supramolecular) level.

II. Critical dimensions of nanoclusters and nanostructures

1. Critical sizes of nanoclusters in the gas phase

a. Critical cluster size and nucleation

The metal, oxide, carbon, noble gas and small-molecule (*e.g.*, water) clusters are formed by condensation in atomic beams or vapours. Clustering studies are carried out using the dynamic approach with account of triatomic collisions (in particular, the molecular dynamics or Monte Carlo methods) or the thermodynamic approach.

The formation of a cluster can take a time exceeding 10^{-13} s; the process depends mainly on the kinetic energy of the cluster; however, even the times of the order of 10^{-9} s (*i.e.*, characteristic of a single computer operation) are too short to study the whole history of cluster formation.⁷ The finite size of a stable cluster can be estimated using the thermodynamic approach by minimising the changes in the Gibbs free energy depending on the size of the cluster formed upon the gas–liquid phase transition

$$n A(\text{gas}, P) = A_n(\text{liquid cluster}).$$

In this case one has⁸

$$\Delta G = 4\pi r^2 \alpha - \frac{4}{3}\pi r^3 n R T \ln \frac{P_r}{P_\infty}, \quad (1)$$

where r is the radius of the cluster, α is the surface tension of the cluster, R is the gas constant, n is the number of atoms in the cluster, P_r is the gas pressure above the cluster surface and P_∞ is the pressure above the flat surface. Supersaturation in the system is given by the ratio

$$\Phi = \frac{P_r}{P_\infty}.$$

Clustering occurs at

$$\Phi_{\text{cr}} = \frac{P_{\text{cr}}}{P_\infty}.$$

The smallest critical size (a smaller cluster is unstable due to thermal fluctuations) can be determined from the equation

$$r_{\text{cr}} = \frac{2\alpha m}{\rho k T \ln \Phi_{\text{cr}}}, \quad (2)$$

where m is the atomic or molecular mass, ρ is the cluster density and k is the Boltzmann constant.

The critical characteristic size (diameter) of a water cluster d_{cr} equals 1.6 nm at $\Phi = 4$, which corresponds to about 90 molecules.⁸ The thermodynamic approach gives larger sizes of, *e.g.*, stable alkali metal or aluminium clusters comprising the magic numbers of atoms or noble gas clusters. The size of thermodynamically stable alkali metal clusters can be estimated from Eqn (2). With allowance for the molecular mass, density and surface tension (it is ten times higher than the surface tension for water) differences, an alkali metal cluster should be an order of

magnitude larger than the water cluster and comprise thousands of atoms. However, the most stable clusters with the magic-number-determined sizes only comprise about tens of atoms (see below).

b. Critical nanocluster sizes governed by the electronic and atomic structure

Isolated (ligand-free) clusters are studied using atomic beam methods with supersonic sources. Here, atoms are produced by evaporation of substances on raising the temperature of the environment or by laser ablation from the surface of a solid. A cluster is formed due to the pressure drop and sharp cooling of the environment. Clusters are separated by sizes (masses) in, *e.g.*, time-of-flight mass spectrometers.

Alkali metal nanoclusters. The alkali metal clusters have a simple electronic structure, namely, each atom has one s-electron in addition to the filled electron shells. Such s^1 -clusters are formed in atomic and molecular beams in high vacuum. They are ligand-free, being convenient objects for studying the electronic properties of nanoscale structures (size 1–2 nm). As for molecules, here the key measurable and interpretable parameters are the ionisation energy, electron affinity, dissociation energy and optical absorption of clusters. By studying these characteristics it is possible to construct models for description of the cluster properties.

Ionisation of s^1 -clusters. The ionisation energy (or potential), E_i , of a cluster is minimum in the following process



The E_i value is determined by varying the energy of a laser or some other ionisation source. The formation of charged clusters of particular sizes can be detected using mass spectrometers. The ionisation potential decreases with an increase in the cluster size.⁹ This correlation can be explained using the classical model of a metal drop and the metallic shell (quantum) model. The latter model gives the magic numbers of the metal atoms that form clusters characterised by the higher ionisation potentials and stability.

The classical model correctly predicts the trends in the change in the cluster size, but it seems to be inaccurate in the case of small clusters for which the quantum size effects were established. Here, the shell model is more appropriate, which considers the motion of an s^1 -electron in the effective potential produced by other electrons and ions in the cluster.

In the shell model, which is also called the ‘jellium model’, the cluster-forming ions produce an averaged positive background for the motion of an electron. The shell model for a cluster is constructed similarly to the shell model for an atom. Solving the one-electron Schrödinger equation in the potential field gives the energy levels (eigenvalues of the electron energy). As a result, the energy levels of the clusters with one free electron should be characterised by the principal quantum number N , the number of radial wave functions ($N-1$) and the angular momentum l with a degeneration degree of $2(2l+1)$. This model^{10,11} predicts the closed-shell electronic structure for 1s-, 1p-, 1d-, 2s-, 1f-, 2p-, 1g-, *etc.*, clusters comprising $n = 2(2l+1) = 2, 8, 18, 20, 34, 40, 58, \text{etc.}$, atoms (or having the same numbers of free electrons). These numbers are called the magic numbers.

Ionisation energy measurements for clusters of various sizes provide a method of direct investigation of the cluster shell structure; the filled electron shells should correspond to the highest stability and ionisation energy.

The ionisation energies of potassium, sodium and silver clusters of various size are presented in Fig. 1. The E_i show clearly seen oscillations for the even (higher E_i values) and odd (lower E_i values) atom numbers in the clusters and maxima at $n = 8$ and 20, which confirms the shell structure of these clusters. The shell structure is most pronounced for silver clusters due to strong electron coupling and, correspondingly, higher potential for the

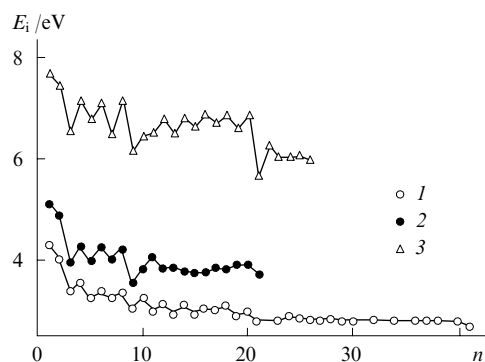


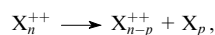
Figure 1. Ionisation energies of potassium (1), sodium (2) and silver (3) nanoclusters.⁹

motion of electrons (deeper potential well), which leads to greater separation of the energy levels.

Fragmentation of s^1 -clusters. Once excited by, e.g., laser radiation, clusters can undergo fragmentation into either isolated atoms or smaller clusters by the evaporation or fission mechanisms (similarly to transformations in atomic nucleus); in this case, the drop model is applicable. Additionally, the cluster dissociation can proceed by the monomolecular mechanism or be accompanied by cascade transformations. The stability of a cluster composed of n atoms is governed by the redistribution of the energy absorbed over a total of $(3n-6)$ vibrational degrees of freedom followed by fixation of a particular cluster breakdown channel and the excited-state lifetimes. The results of cluster stability studies using both the metallic drop model and the shell model indicate a common trend, namely, an increase in the binding energy with an increase in the cluster size.

Monomolecular dissociation studies of singly charged clusters also revealed discrete magic numbers of the atoms in the cluster. For instance, the dissociation energy decreases for the Na_n^+ and K_n^+ clusters comprising $n = 9$ and 21 atoms, which corresponds to 8 and 20 electrons in the filled electron shells, respectively. Clusters containing an even number of electrons are highly stable, which is indicative of electron pairing effects. These effects are more characteristic of Na_n^+ rather than K_n^+ , because for sodium the potential well in the electron field is deeper than for potassium and, hence, the energy differences between the sodium energy levels are larger (greater level – level separation).

Monomolecular dissociation of doubly charged cluster ions is a more complex process compared to the dissociation of singly charged nanoclusters, because it includes not only evaporation, but also fission of clusters. Two possible dissociation mechanisms involve retention of two charges on one fragment



or acquisition of one charge on each fragment



If one cluster fragment remains doubly charged, the potential energy surface has no potential barrier. If both fragments become charged, repulsion between them produces a Coulomb barrier. The fragments are separated upon formation of a transition state. This process is often called the Coulomb fission.

Signals of small doubly charged clusters X_n^{++} are often indistinguishable in the mass spectra; signals of the critical-size clusters (n_c) suitable for Coulomb fission are observed.¹² Usually, it is assumed that small doubly charged clusters of size less than n_c are unstable because the repulsive energy of the positively charged fragments exceeds the binding energy in the cluster. Therefore, the critical cluster size is governed by the dynamics of monomolecular dissociation. In the case of large neutral clusters ($n > 30$), evaporation dominates the Coulomb fission. For clusters of intermedi-

ate sizes ($26 < n < 30$), evaporation and fission ‘coexist’. This points that the height of the Coulomb barrier approximately equals the binding energy. For small clusters ($n < 24$) the Coulomb barrier becomes higher than the binding energy and the doubly charged clusters can no longer exist. The critical sizes of the doubly charged clusters of the first-row elements are as follow:⁹

Element	Na	K	Cs	Au	Ag
n_c	24	17	19	3	5

Aluminium clusters. Aluminium clusters are of interest as models with free electron gas that consists of s^2 - and p^1 -electrons and provides a metallic type of conductivity. Aluminium is widely used as structural material; this makes corresponding reactivity studies topical. Similarly to the alkali metal clusters, the state of aluminium clusters is characterised by the ionisation energy, dissociation energy, polarisation and reactivity that is determined in the reactions with other molecules. Answering the question of applicability of the electron shell model (‘jellium model’) to aluminium clusters requires analysis of all these characteristics.

Ionisation energy of aluminium clusters. Figure 2 presents the results of ionisation energy calculations for Al_n (n from 2 to 70) clusters from the following equation

$$E_i(r, z) = E_{i\infty} + \left(z + \frac{3}{8}\right) \frac{e^2}{r}, \quad (5)$$

where $E_i(r, z)$ and $E_{i\infty}$ are the ionisation energies of the cluster of radius r and charge z and the flat metallic surface, respectively, and e is the electron charge. The open circles denote experimental data and the dashed line shows the prediction of the metallic spherical drop model.

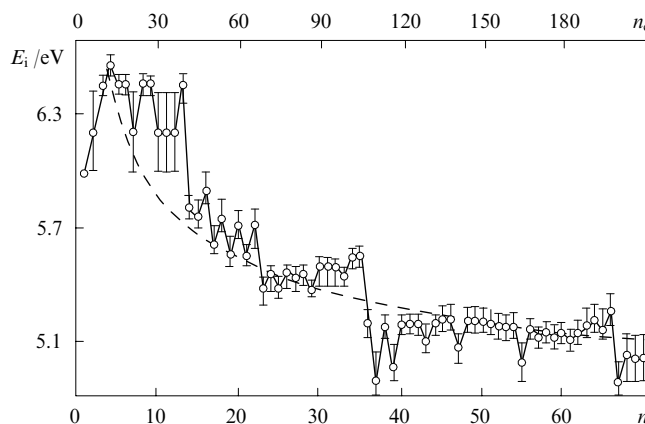


Figure 2. Ionisation energies of Al_n clusters obtained after photoionisation.¹³

The clusters with $n = 7, 14, 23, 36$ and 67 are characterised by abrupt changes in E_i . According to the electron shell model, closed shells are formed at the electron numbers equal to 20, 40, 58, 70, 92, 138 and 198. A decrease in E_i should be expected for the clusters with one or two extra electrons (in addition to the filled shell), i.e., at the electron numbers 21, 42, etc. Taking account of the fact that the aluminium atom has s^2p^1 valence electrons leads to agreement between the experimental data and the predictions of the shell model, because the number of free electrons for aluminium clusters is $3n$. However, no agreement is obtained for larger clusters ($n > 30$).

Yet another feature of aluminium clusters compared to the alkali metal clusters consists in considerable deviation of the calculated ionisation energy (work function of an electron in a metallic sphere) from the experimental values for small clusters

(see Fig. 2). This can be explained by different effect of the conduction band in the alkali metal and aluminium clusters with an increase in the cluster size. The ionisation energies of alkali metal clusters with half-filled s-bands decrease as the cluster size increases. For the s^2p^1 -clusters, the p-band top initially decreases with an increase in the cluster size (ionisation energy increases) and then increases similarly to the situation for the alkali metal clusters. Agreement with the predictions of the classical drop model approximately begins with a 25-atom cluster.

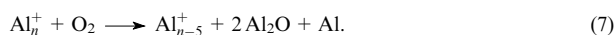
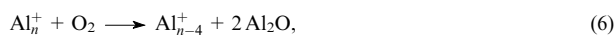
Dissociation of aluminium clusters. Aluminium clusters mainly dissociate by evaporation rather than fission, namely, monomolecular dissociation with evaporation of aluminium atoms or ions occurs. In this case one can expect an increase in the binding energy per atom with an increase in the cluster size.

A dissociation study¹⁴ showed that the Al_n clusters with $n = 7$ and 14 are more stable than clusters with neighbouring n values. The mass spectra exhibit clearly seen signals of the stable clusters Al_7^+ and Al_{14}^+ . The magic numbers $n = 7$ and 14 differ from those found for the alkali metal clusters, but agree with the shell model. Indeed, depending on the type of the potential for the motion of electrons, at $n = 8, 18, 20, 34, 40, 58, 68$ and 92 the set of closed shells includes 1p, 1d, 2s, 1f, 2p, 1g, 2d and 3s for the 'rectangular well' potential or $n = 8, 20, 40, 70$ for the harmonic oscillator potential. The aluminium atom has a valence of three and therefore the Al_7^+ cluster has twenty valence electrons, namely, $7 \times 3 - 1$ (with allowance for the cluster charge). This gives the first magic number, 7. Analogously, the closed shell of Al_{14}^+ cluster has forty-one valence electrons. Of course, the aluminium cluster has a more complex configuration compared to alkali metals because the interaction of the s- and p-valence electrons occurs.

The electron shell scheme also describes the oxidised aluminium clusters with $O=O$ or $O=Al$ bonds that reduce the number of valence electrons in the cluster by two. For instance, the cluster $Al_{15}O_2^+$ is more stable than other oxidised aluminium clusters. Here, the number of valence electrons in the closed electron shell is $3 \times 15 - 1$ (with allowance for the cluster charge) $- 4$ (two electrons per oxygen atom) = 40. The dissociation energy increases as the cluster size increases.

Reactivity of aluminium clusters. The interaction of aluminium clusters with hydrogen or oxygen molecules is an important cluster characteristic. Studies of these reactions can be useful in order to relate the shape of a cluster to its reactivity. The majority of experimental data point that the activation barriers to the reactions involving clusters are higher than the corresponding parameters for bulk material.¹⁴

Now we will consider the best studied reactions of aluminium clusters with oxygen as examples. Reactions of neutral clusters result in Al_nO_2 . Aluminium atoms or dimers react rapidly; the reactivity initially decreases with an increase in the cluster size and then increases. Reactions of positively charged clusters comprised of at most seven Al_2O^+ particles with oxygen produce Al_nO^+ cations as the major product. Possible reactions of larger clusters are shown below:



Here, the activation barriers are of the order of a few tenths of an electronvolt at $n = 3-25$.

Bulk aluminium is readily (almost barrierlessly) oxidised, *i.e.*, clusters are less reactive than bulk material. Reactions of negatively charged clusters with an excess of oxygen lead to stable products in the form of 13-, 23- and 37-atom clusters. This indicates that the shell structure of clusters affects their reactivities, namely, Al_{13}^- , Al_{23}^- and Al_{37}^- have 40, 70 and 112 valence electrons respectively that form closed electron shells in the harmonic oscillator potential. The shape of a cluster is also related to its reactivity. For instance, calculations of Al_7^+ cluster predict a distorted octahedral configuration in which all atoms are equidistant from the centre of mass in such a fashion that they

seemingly are on the surface of a sphere. This cluster is characterised by a closed spherical electron shell with 20 valence electrons. The next closed-shell structure is an icosahedral cluster Al_{13} . A feature of this stable structure is a large energy difference between the filled and unfilled orbitals, which ensures a low reactivity of this system.

Mercury clusters. Mercury clusters provide a unique possibility of studying an insulator-conductor transition. The mercury atom has a closed electron shell ($[Xe]4f^{14}5d^{10}6s^2$) and can be considered as a building block for forming the van der Waals bonds. At the same time, bulk mercury is a metal. Transition from the van der Waals to the metal bonds is accompanied by an increase in the cluster size and in the latter case the metal atom has a $[Xe]4f^{14}5d^{10}6s^{1.46}p^{0.6}$ configuration.

Similarly to alkali metals, silver and aluminium, the ionisation energy serves the key indicator of the properties of mercury. In Fig. 3 the results of ionisation energy measurements for Hg_n clusters (n from 1 to 43) are plotted *vs.* $1/r$.

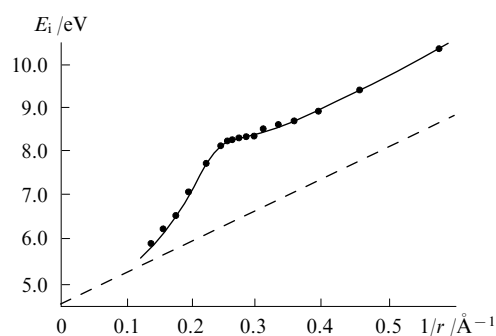


Figure 3. Ionisation energies of clusters Hg_n plotted *vs.* inverse cluster radius.¹⁵

Dashed line corresponds to the relation for bulk material [$E_i(n \rightarrow \infty) \approx \phi + (e^2/r)$].

Mercury clusters with $n \leq 13$ are characterised by a decrease in E_i with increasing the cluster size. But in this case the E_i energies are appreciably different from the values predicted by the spherical metallic drop model. Moreover, extrapolation of the ionisation energy to $n \rightarrow \infty$ gives a value of 6.5 eV, which much exceeds the work function of an electron in bulk material (4.49 eV). At $n > 13$, the E_{in} sharply decreases and the experimental data approach the results obtained by the spherical metallic drop model.

The ionisation energy was determined from the results of Hartree-Fock MO energy calculations,¹⁶

$$E_{in} = E_n(v_t - 1) - E_n(v_t), \quad (8)$$

where $E_n(v_t)$ is the total electronic energy of an n -atom cluster with v_t valence electrons. It was found that

$$E_{in} = -\varepsilon_{HOS}(n) + \frac{e^2}{2r}, \quad (9)$$

where $\varepsilon_{HOS}(n)$ is the energy of the highest occupied shell. The existence of a critical cluster size (n_c) is assumed, *e.g.*, $n_c = 13$; at $n < 13$, the electron is localised on the atom, whereas at $n_c > 13$, it is delocalised. Thus, an increase in the cluster size is accompanied by an abrupt transition from insulator to conductor. The first term in Eqn (9) describes the changes in the ionisation energy due to the changes in the electronic structure for different cluster sizes and the second term describes the electrostatic contribution after shift of the energy levels upon ionisation $v_t \rightarrow (v_t - 1)$. At $n < n_c$, the atom emits electrons (Fig. 4) and thus the energy of the highest occupied level approaches the energy of the atom, whereas at $n > n_c$ electrons are delocalised and the $\varepsilon_{HOS}(n)$ value should be treated as the energy of the highest occupied MO (HOMO).¹⁶

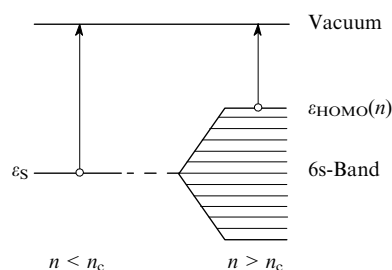


Figure 4. Scheme describing ionisation for localised ($n < n_c$) and delocalised $n > n_c$ electronic states of Hg_n clusters.

Carbon clusters. A distinctive feature of carbon clusters consists in strong atom–atom interactions. Clustering of carbon atoms occurs much easier compared to all other elements, which is substantiated by, *e.g.*, the formation of carbon black in thermolysis of any carbon-containing structures. Carbon is one of the most abundant elements in the Universe (it ranks fourth after hydrogen, helium and oxygen). Additionally, this is the first stable element produced by thermonuclear fusion. Red giant stars emit a huge amount of carbon to interstellar space, and interstellar dust probably consists of carbon clusters. The clusters in question are also of interest as objects for basic research. In laboratories, they are produced by laser vaporisation or arc evaporation of carbon followed by mass separation using mass spectrometers. The mass spectrum obtained has a bimodal character, namely, one mode corresponds to small clusters (number of atoms $n < 24$) and the other mode ($n > 24$) corresponds to fullerenes.

Small carbon clusters. The mass spectra of small carbon clusters show a period of four carbon atoms, which manifests itself in the even–odd oscillations of the line intensities of the clusters synthesised.^{17–20} The magic numbers of the carbon atoms can be readily determined from the spectra (C_n , $n = 7, 15, 19$ and 23). Such mass spectra are obtained after ionisation of the neutral clusters synthesised by the laser vaporisation method by exposure to UV light. Photoinduced fragmentation studies showed that the process mainly results in neutral clusters C_3 . Larger particles can undergo fragmentation into C_5 clusters.

According to quantum-chemical calculations, neutral carbon clusters should have a chain structure up to nine atoms long, which then transforms into a ring. Taking into account the fact that a covalently bonded cluster tends to reduce the number of free bonds, the cluster shape is governed by the following factors: an increase in the number of carbon–carbon bonds in the cluster (although each succeeding bond is weaker than the preceding one), a change in the number of free bonds and production of strain upon formation of the ring-type structure. The C_3 cluster is considered linear.²¹ The formation of a carbon ring structure is accompanied by disappearance of free carbon bonds and production of additional strain in the cluster.

Ring-type structures are characteristic of larger clusters. The chain-to-ring transition should occur at $n = 10$; the even-numbered clusters tend to form rings at low temperatures.²²

The predicted (calculated) stabilities of particular forms of carbon clusters and transitions from chain to ring-type structures were also observed in the experiments involving the photoelectron spectra of negatively charged clusters.²³

Signals of C_3 clusters were detected in the optical spectra of comets. The signals of C_3 and C_5 clusters were observed in the spectra of interstellar space in the vicinity of some stars; vibrational spectroscopy data confirm the chain structure of the clusters.

The shapes of larger carbon clusters are calculated based on a certain quantum-mechanical model, *e.g.*, the Hartree–Fock model or the density of states approximation.²⁴ According to calculations, three isomers of C_{20} cluster can exist, namely, a ring-type, a bowl-shaped and a fullerene-like structure (Fig. 5).

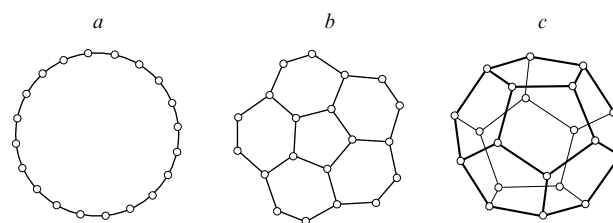


Figure 5. Ring-type (a), bowl-shaped (b) and fullerene-like (c) isomers of C_{20} .

In principle, the smallest fullerene is a dodecahedron comprising twenty carbon atoms that form twelve pentagonal faces. The laser ablation experiments result only in ring-type clusters. Besides, calculations predict the existence of a bowl-shaped cluster with a graphite-like structure and a minimum number of free bonds. Yet another stable structure is a tetrahedral structure C_{28} . According to calculations, the C_{28} cluster behaves as a superatom with an effective valence of four and high reactivity to both encapsulation of metal atoms and *exo*-attachment of other atoms. Experiments with this cluster revealed the possibility of encapsulating an uranium atom; this structure is denoted by $\text{U}@C_{28}$.²⁴ Additionally, the scandium, titanium, zirconium, and hafnium atoms can be encapsulated inside the C_{28} . The existence of exohedral polymers of the $C_{28}\text{H}_4$ type was predicted.²⁵

Fullerenes. The first representatives of large carbon clusters, namely, fullerenes were discovered by Kroto, Smalley and Curl in 1985. Investigations were initiated by Kroto who used laser vaporisation and mass spectroscopy for production and study of small carbon clusters. He paid attention to a single spectral peak, which appeared under particular conditions for production of carbon clusters. This peak corresponded to the C_{60} cluster, which was called fullerene.^{26,27}

In the structure of C_{60} (Fig. 6), pentagons are embedded into hexagonal graphite sheets for which sp^2 -hybridisation is allowed. As a result, a hollow structure is formed, which has no free bonds and is stabilised through π -bonds. Equivalence of all atoms, unstrained character and the possibility of isolating all pentagons make the 5/6-ring structure of the C_{60} cluster unique. The next (in size) stable fullerene is C_{70} .

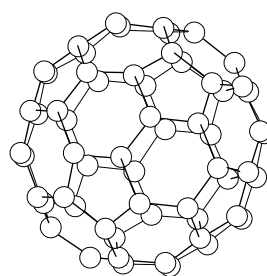


Figure 6. Structure of C_{60} cluster.

Formation of fullerenes. The first question that should be answered is as to how stable ordered structures are formed under high-temperature laser vaporisation and chaotic plasma conditions? Probably, graphite species removed by laser form hollow structures, but it is also not impossible that the fullerene formation mechanism is similar to the mechanism of carbon black formation. The kinetic models for growth of clusters from carbon atoms and cluster radicals present in plasma were elaborated.²⁸

The most energetically favourable shape of small cluster radicals is a linear chain. Such chains interact with one another, grow in plasma up to 20–30 atoms long and then undergo

spontaneous transformations to polycyclic aromatic rings or graphite sheets. These structures are preferred because the average coordination number of the carbon atom increases, but they also contain numerous free bonds. It is the decrease in the number of free bonds that makes the growth of such structures energetically favourable. If the density of carbon atoms is high, clusters will have reactive termini whose curvature is appropriate the most energetically favourable arrangement of transient states including matching of the edges of rolled sheets and formation of fullerenes of size up to the size of macroscopic carbon black particles. Such a random plasma process also permits formation of larger fullerenes, *e.g.*, C₁₈₀, C₂₄₀ or C₅₄₀, which can theoretically be stable.

Effective studies of the structure and properties of C₆₀ and heavier fullerenes became possible after the elaboration and improvement of the method for production of sufficient amounts of fullerenes by Kratschmer *et al.*²⁹ An arc discharge using graphite electrodes in helium atmosphere produces carbon black, which is then dissolved in benzene or toluene. Crystallisation of the solution gives gramme amounts of C₆₀/C₇₀ mixture in a 3 : 1 ratio and heavier fullerenes (2%).³⁰

Fragmentation of fullerenes. As mentioned above, fragmentation of small carbon clusters involves detachment of C₃ clusters. Fragmentation of fullerenes occurs by detachment of C₂ fragments owing to stability of the even-numbered clusters.^{31,32}

Based on the kinetic energies of products, the following estimates of the binding energy of C₂ with C₅₈⁺, C₆₀⁺ and C₆₂⁺ were obtained: 4.6 eV for C₅₈⁺, C₆₀⁺ and only 3 eV for C₆₂⁺ (see Ref. 33).

The C_n⁺ shell comprising five-membered rings loses a C₂ unit and transforms to the C_{n-2} shell. The fused five-membered rings transform to six-membered ones and two six-membered rings above and below these five-membered rings transform to five-membered rings. As a result, the total number of five-membered rings remains unchanged, as required for a closed shell upon the loss of a six-membered ring. This mechanism implies a fast surface reorganisation in order to join two five-membered rings.

The ionisation energies and the electron affinity energies of fullerenes (starting with C₆₀) do not show large-amplitude oscillations as in the case of metal clusters. This is probably due to rather large sizes of the former (*n* = 60).³⁴

Generally, the experimental data are in agreement with the spherical metal model, that is, an increase in the fullerene size causes a decrease in the ionisation energies and an increase in the electron affinity energies (*E*_A) that approach the calculated value of 5.37 eV. The average electronegativity (*E*_i + *E*_A)/2 = 5.2 ± 0.2 eV obtained from experimental data agrees with the results of calculations. The slopes of the plots of *E*_i and *E*_A vs. cluster size decrease on going to heavier fullerenes. One should expect deviations from the spherical drop model for those fullerenes (especially, heavy ones) whose shape differs from a sphere.

Taking account of symmetrical closed structure of fullerenes, an impression may be formed of these compounds as low-reactive species. However, this is not the case. Fullerenes react with, *e.g.*, metals and fluorine to form a variety of derivatives that can be classified into different structural types. These are endohedral fullerenes containing one or a few metal atoms inside the fullerene cage, exohedral fullerenes with functional groups attached from the outside of the fullerene cage and substitution fullerenes in which one or several carbon atoms of the fullerene cage are replaced by some metal atom(s).⁶

Noble gas clusters. Noble gas atoms have spherically symmetric electron shells. This is the reason for specific properties of the noble gas clusters. Here, clustering is due to the van der Waals forces that are responsible for the formation of molecular crystals at low temperatures (except helium atoms).

The interaction between two noble gas atoms separated by a distance *R* can be described by the Lennard-Jones potential

$$V_{LJ}(R) = \varepsilon \left[\left(\frac{R}{R_0} \right)^{-12} - 2 \left(\frac{R}{R_0} \right)^{-6} \right], \quad (10)$$

where ε is the depth of the potential well in the field in which atoms move, with a minimum at the distance *R*₀. This interaction can be treated as a contact of soft, weakly attracting spheres. The first term in Eqn (10) corresponds to repulsion between the filled orbitals and can be described by the Morse exponential potential. The second term corresponds to attraction of induced dipoles. The first excited electron state lies between 10 (for Xe) and 20 eV (for He); therefore, crystals formed from noble gas atoms are colourless and transparent.

The ground state of neutral noble gas clusters was simulated using the potential of pair interactions.³⁵

Figure 7 presents the most stable configurations of clusters of various size obtained from calculations. The cluster structures correspond to an isosceles triangle (*n* = 3), a tetrahedron (*n* = 4) and a trigonal bipyramid (*n* = 5). At *n* = 7, five-fold (pentagonal) symmetry arises, which is not observed for infinite crystal lattices. The most stable icosahedral structures begin with *n* = 13. Further increase in the cluster size leads to stable structures with *n* = 55, 147, 309, 561, ... The number of the nearest neighbours of an atom in icosahedron is larger than for all other crystal lattice symmetries. This is the reason for enhanced stability of icosahedral structures. Thus, the noble gas clusters obey the principle of close packing of atoms. As a consequence, the most stable clusters are formed and the magic numbers of atoms arise, namely, *n* = 13, 55, 147, 561, ...

Transition metal clusters. In contrast to the clusters considered above, transition metal clusters have a more complex electronic structure because it is formed by d- or f-electrons. The stability and reactivity of such clusters are governed by two series of magic numbers. One of them is related to the electron shell (as for alkali metal clusters) and the other is associated with the geometric factor (close packing), as for the noble gas clusters. Additionally, the ability of atoms to be in different oxidation states is of

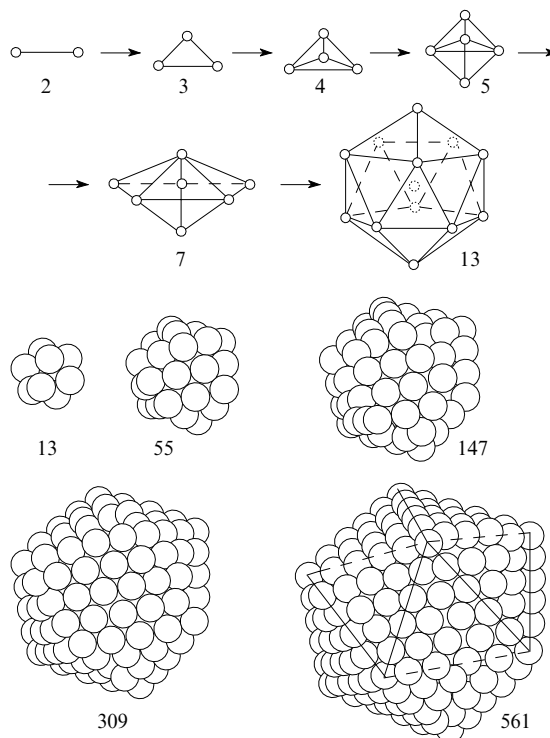


Figure 7. Model structures of noble gas clusters of different sizes. Shown are the numbers of atoms in the structures.

particular value for the transition metals clusters. This factor is responsible for large deviations of the cluster structure from the shell model and difficulties in prediction of the critical sizes of stable clusters using the microscopic approach.

2. Critical sizes of liquid-phase clusters

The formation of liquid-phase nanoclusters (from liquid phase, solutions or melts) can be considered using the thermodynamic or microscopic approach. Both approaches give the critical nucleation and stabilisation sizes for clusters with sizes of a few nanometres. Additionally, by applying the microscopic approach in studies of clustering from solutions and cluster stabilisation by ligands, it is possible to find the most stable clusters comprising the magic numbers of atoms that manifest themselves to the greatest extent in the formation of molecular clusters.

a. Thermodynamics of cluster nucleation

Clusters nucleated from the liquid phase (in, *e.g.*, formation of micellar colloids) have a minimum critical size that is determined by the reagent concentrations, presence of stabilising ligands, surfactants, *etc.* In contrast to nucleation in an infinite volume, cluster nucleation in the closed volume of a nanopore or reverse micelle (see, *e.g.*, Ref. 36) leads to formation of clusters of minimum and maximum critical sizes. Such processes proceed faster than in the macroscopic space and the cluster size is controlled by the size of the closed volume. The minimum size of a nanocluster formed in a closed pore as a result of nucleation from solution or melt can be determined from the equation

$$n_{\min} = \frac{32\alpha^3}{3\rho^2\Delta\mu^3}, \quad (11)$$

where α is the density of the surface energy of the cluster, ρ is the density of the cluster and $\Delta\mu$ is the change in the chemical potential in the cluster formation. The maximum size can be determined from the relation

$$n_{\max} \approx \frac{n_0\Delta\mu}{2 + \Delta\mu}, \quad (12)$$

where n_0 is the number of atoms in the nanopore, involved in clustering (*i.e.*, the nanocluster size should increase with an increase in the nanopore size). At the same time the minimum critical size of a nucleus in the pore is governed by the thermodynamics of nucleation and by the initial concentration of the cluster-forming atoms in the pore space. As the pore size increases, a number of smaller clusters are formed. The rate of nucleation in the nanopore increases owing to a decrease in the potential barrier to nucleation (ΔG) caused by the effect of the pore wall (heterogeneity factor $K < 1$)

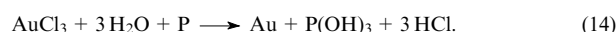
$$\Delta G = \frac{16\pi\alpha^3 K}{3\rho^2\Delta\mu^2}. \quad (13)$$

Thus, isolated nanoclusters of the critical sizes from one to a few nanometres³⁶ depending on the nanopore size and initial reagent concentration can form in porous materials with pore sizes of up to 10 nm.

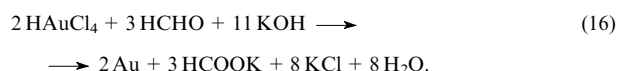
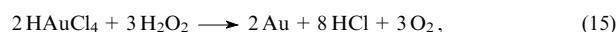
b. Colloidal clusters and nanosystems

Colloidal nanosystems comprise metal and metal oxide sols, conventional and reverse micelles, microemulsions, nanoclusters in micelles and colloidal crystals.

Sols and sol formation. Metal sols are prepared in solutions after reduction reactions. In 1857 (see Ref. 37), Faraday obtained a red gold sol with cluster sizes from 2 to 50 nm by the reaction

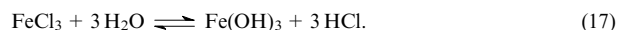


Later on, Zsigmondy (see Ref. 37) synthesised monodisperse gold sols with variable cluster sizes by reducing gold salts with hydrogen peroxide and formaldehyde



The reduction involves two stages, (i) nucleation and (ii) growth of the new phase. By controlling the second stage it is possible to form a yellow (size 20 nm), red (40 nm) and blue (100 nm) gold sols.

Oxide sols are formed in the condensation reactions. An example is provided by the widely used hydrolysis of inorganic metal salts



Such sols can exist in the liquid phase for long without precipitation or coagulation due to involvement in Brownian motion of molecules in the solution, weak cluster–cluster interactions, charge repulsion and passivation of the surface. The size of sols formed is determined by the reaction conditions, the nature of the solvent and stabiliser, reaction duration and temperature and to a great extent by the supersaturation of solutions.^{37, 38}

The formation of nanoclusters is related to nucleation (homogeneous or heterogeneous) from solution. An increase in the nanocluster sizes to the maximum critical values [see Eqns (11) and (12)] and the prevention of coagulation are controlled by the surface tension that can be varied by passivating the surface. The range of possible passivators includes thiols, triphenylphosphine and its derivatives, phenanthroline, *etc.*, and various surfactants. In particular, the gold nanoclusters in the sol, prepared by reactions (14)–(16) and passivated by alkanethiols represented metal nanoclusters coated with a dense thiol monolayer. The monolayer self-assembles, which is accompanied by a change in the alkyl chain length in alkanethiols and in the thiol/metal ratio and affects the size of the metal nanocluster.

Colloidal gold clusters thus formed are octahedral or icosahedral single crystals with the face-centered cubic lattice.³⁹ This substantiates the fact that the formation and stabilisation of nanoclusters of the critical sizes obey the close packing principle (similarly to noble gases and molecular clusters). Silver, palladium and platinum sols were also obtained.

Drying silicon hydroxide sols and metal hydroxides or alcohols causes the formation of gel structures, *e.g.*, the known silica gel $n\text{SiO}_2 \cdot m\text{H}_2\text{O}$ or alkoxides Zr(OPr)_4 , Ti(OBu)_4 , Al(OPr)_3 . The sol–gel technique is employed for the preparation of nanomaterials and nanoceramics used in optical, electronic and magnetic devices and for the synthesis of catalysts. Gels are then used as matrices for preparation of nanomaterials, *e.g.*, catalysts coated with metal oxide clusters.

Micelles. Micelles are formed using surfactants that can adsorb on the interface thus reducing the interfacial tension. A surfactant molecule consists of a hydrophobic part and a polar group. The hydrophobic part includes hydrocarbon radicals $\text{C}_n\text{H}_{2n+1}$, $\text{C}_n\text{H}_{2n-1}$, $\text{C}_n\text{H}_{2n+1}\text{C}_6\text{H}_4$, *etc.*, containing at least eight carbon atoms. Depending on the nature of the hydrophilic group, surfactants are classified into cationic (containing primary, secondary, tertiary amines and quaternary ammonium bases), anionic (containing carboxyl, sulfoester, sulfonic acid groups, *etc.*) and non-ionic. The action of surfactants in aqueous solutions is based on structuring of the water molecules surrounding the nonpolar hydrocarbon radicals of the surfactants, which should cause a decrease in the entropy of the system. Since any system tends to a maximum entropy, at a certain critical micelle concentration (CMC) the water molecules and surfactant ions form associates that are called micelles (according to McBen's definition³⁷). Thus, micelles are also characterised by a critical size governed by the structuring of water and the surface tension.

Micelle formation causes a portion of structured water to release; this is accompanied by an increase in the entropy and a decrease in the free energy of the system. The presence of micelles in solution can be determined from the dependences of the surface tension, conductivity, density, viscosity, light scattering and other characteristics on the surfactant concentration. The CMC value

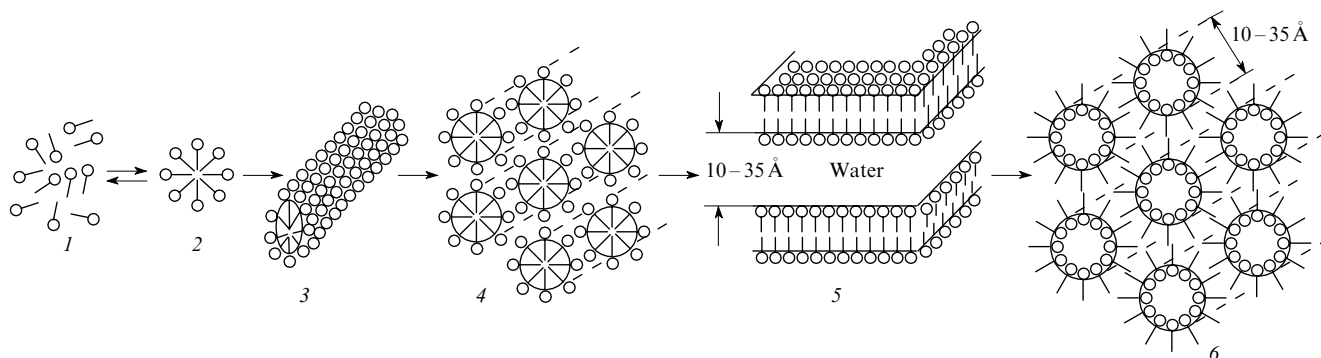


Figure 8. Structures organised as a result of the action of surfactants.

Surfactant monomers (1), micelle (2), cylindrical micelle (3), hexagonally packed cylindrical micelles (4), lamellar micelle (5) and hexagonally packed reverse micelles containing water molecules (6).

depends on the nature of the surfactant, the length of the hydrocarbon radical, the electrolyte and the pH value of the solution. The longer the hydrocarbon radical and the lower the polarity of the polar group the lower the CMC.

At the surfactant concentrations close to CMC, micelles represent spherical particles in which the polar groups contact water and the hydrophobic radicals form a nonpolar nucleus inside the micelles. There are various types of micelles, such as spherical, cylindrical, hexagonally packed and lamellar ones (Fig. 8).

Thus, micellar systems can exist in the form of one-, two- and three-dimensional nanostructures comprising tens to hundreds of molecules.

The molecules of the same surfactant can form different types of micelles in polar (*e.g.*, water) and in nonpolar solvents. Here, micelle formation at the surfactant concentrations higher than the CMC is due to the interaction between the polar groups of the surfactant. Hydrophobic (fatty) fragments of the surfactant molecules are directed outside the micelle and the polar groups are inside. As a result, a nanoreservoir is formed within the micelle, which can be filled with, *e.g.*, water. Such micelles are termed reverse micelles (see Fig. 8). Conventional and reverse micelles can be treated as oil nanodroplets in water and water nanodroplets in oil, respectively.

A valuable property of micelles is the ability to solubilise (*i.e.*, considerably enhance the solubility) hydrocarbons in aqueous micellar solutions or in solutions of reverse micelles in polar liquids. Solubilisation causes the formation of stable isotropic systems called microemulsions. The properties of substances significantly change upon solubilisation in micelles; as a consequence, the rates of chemical reactions also change. This phenomenon is called micellar catalysis. It is widely used in chemistry, biology, medicine and various technological processes.

The properties of microemulsions are to a great extent determined by the size and shape of the components of the dispersed phase and by the properties of the interfacial adsorption layers formed by the surfactant molecules. Microemulsions are characterised by high mobility and large interface surface area and can serve a medium for carrying out many chemical syntheses, *e.g.*, the syntheses of metal, oxide and metal chalcogenide nanoclusters.

Clusterisation in microemulsions. In a microemulsion system the dispersed droplets constantly collide, coalesce and split again, which results in the continuous exchange of their contents. The exchange occurring by collisions of nanodroplets or micelles is controlled by diffusion. It is governed by the interaction between the surfactant adsorption layers and by the flexibility of the interface. Reverse micelles and reverse emulsions are widely used for the synthesis of nanoclusters; here, the inner volume of the reverse micelle serves as a nanoreactor. This is achieved by mixing two identical reverse microemulsion systems, aqueous phases containing, *e.g.*, substances A and B that can react to give a

poorly soluble compound C. Coalescence of micelles is accompanied by exchange of A and B and thus formation of the new compound C (Fig. 9).

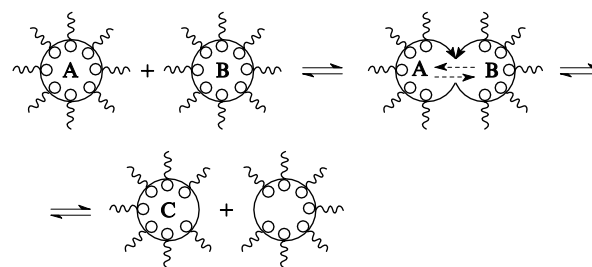


Figure 9. Scheme of reactions in reverse micelles.

Metal clusters can also be prepared by introducing a reducing agent (hydrogen or hydrazine) into a microemulsion containing a metal salt or by passing CO_2 or H_2S through emulsion. This procedure was used to obtain platinum, palladium, rhodium and iridium nanoclusters with the nanoparticle size 3–5 nm and bimetallic platinum/palladium clusters. Metal and semiconductor nanoclusters (*e.g.*, CdS, CdSe, CdTe, SnO_2 , TiO_2 , Fe_2O_3 , MoS_2 , HgS, InAs, GaP, GaAs, BiI_3 , SiO_2 , high-temperature ceramics, *etc.*) were prepared by the synthesis in reverse micelles.^{36,37}

The course of the nanocluster formation in microemulsions is affected by various factors. First of all, this is the aqueous phase/surfactant ratio in the nanosystem

$$W = \frac{[\text{H}_2\text{O}]}{[\text{Surfactant}]} \quad (18)$$

This is followed by the structure and properties of the solubilised aqueous phase, the microemulsion dynamics, the average reactant concentration in the aqueous phase and the nature of the surfactant. The sizes of the clusters formed in the cavity of a reverse micelle can be controlled by varying the size of the micelle. A linear dependence of the cluster size on W in the formation of CdS clusters was established.⁴⁰ A similar dependence was obtained in a study of the nucleation of metal oxides in nanopores.³⁶

The size of a cluster synthesised in reverse micelle depends on the nature of the surfactant. For instance, the nanosystem stabilised with sodium di(2-ethylhexyl)sulfosuccinate (AOT) was characterised by a smaller cluster size compared to the system stabilised with polyethylene glycol *p*-(*tert*-octyl)phenyl ether with $n = 10$ (Triton X-100).

Synthesis in reverse micelles offers considerable prospects for the preparation of nanoclusters of various chemical composition and shape. In particular, copper clusters of various shape can be obtained using water micelles stabilised with $\text{Cu}(\text{AOT})_2$ and

Na(AOT) in isooctane. They are mixed with a microemulsion of Na(AOT)-stabilised sodium borohydride. Mixing of the microemulsions leads to reduction of copper, the size of the copper cluster being dependent on W .⁴¹

At $W < 4$, the system contains only spherical droplets whose size is proportional to W . In the range from 1 to 12 nm the cluster diameter (d) obeys a linear relation $d \sim aW$. As the water content increases ($4 < W < 5.5$), micelles lose their spherical shape. As a result, spherical nanoclusters ($d = 8, 2$ and 12 nm) and cylindrical clusters 12 and 18.5 nm long are formed in the microemulsion system. Further increase in W ($5.5 < W < 11$) is accompanied by the formation of a continuous phase containing spherical nanoclusters ($d = 6.7\text{--}9.5$ nm) and rod-like nanoclusters of diameter 9.5 nm and length 22.6 nm. At $W > 11$, a lamellar structure built of rods of diameter $10\text{--}30$ nm and length $300\text{--}1500$ nm is formed. The synthesis of asymmetrical (rod-like, disk-shaped and ellipsoidal) clusters is of great scientific and practical interest. Using reverse micelles and emulsions, it is possible to prepare nanocomposites of the core-shell type.⁴²

Formation of micelles based on block copolymers. A block copolymer includes blocks characterised by strongly different solubilities. In particular, a diblock copolymer containing a hydrophilic and a hydrophobic component can form both simple spherical micelles and complex lamellar or two-phase structures in water. However, the block-copolymer-based micelles differ from the micelles prepared using simple surfactants by greater critical radii (from 7 to 15 nm) and higher stability.⁴³ A general scheme of preparation of such micelles is shown in Fig. 10.

Spherical micelles formed in a block-selective solvent consist of a core including an insoluble segment and a shell formed from the soluble block. Structural stabilisation of micelles occurs through polymerisation or cross-linking of the molecular fragments of the core or the shell and formation of the core- or shell-linked micelles, respectively. If the nanosystem is formed in the solid phase, the nature and size of aggregates depends on the relative size of each block and the molecular mass of the block copolymer. If a diblock copolymer has a short soluble block and a long insoluble block, twisted truncated micelles, vesicles, cylindrical elongated or flattened aggregates are formed; otherwise, spherical aggregates called star-like micelles are formed. In lyotropic systems it is possible to vary the solvent. For instance, an increase in the concentration of the block-selective solvent with respect to the concentration of the solvent affecting both blocks causes the formation of vesicles and cylinders.

Thus, the lyotropic system provides additional opportunities for controlling the formation of nanoscale objects.

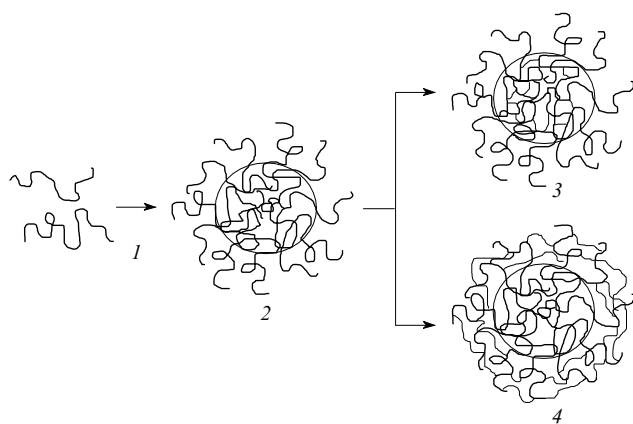


Figure 10. Scheme of micelle formation involving block copolymers. Dissolution of monomeric block copolymers in block selective sorbent (1), formation of micellar aggregate (2), formation of cross-links in the block copolymer core (3) and formation of cross-links in the block copolymer shell (4).

Organisation and self-organisation of colloidal structures. Self-organisation and evolution of a colloidal nanosystem is due to the presence of a well-developed surface and thermodynamic instability of colloidal clusters. The excess free energy resulting from the existence of an interface between the dispersed phase and the dispersive medium stimulates various processes resulting in a decrease in the Helmholtz free energy (F). Ignoring the chemical potential, one can write

$$dF = -TdS + d(\alpha s), \quad (19)$$

where α is the surface tension and s is the surface area of the phase boundary. The thermodynamic condition $dF < 0$ can be met by reducing the interface surface area $\alpha ds < 0$ or the interface energy $\alpha ds < 0$; this is accompanied by a change in the entropy of the system. As the interface surface area decreases, the average cluster size increases and the colloid can undergo phase separation into two phases, solid and liquid. Coalescence of clusters is precluded by the energy barrier originating from electrostatic repulsion (E_{el}). For instance, if $E_{el} \gg kT$, the system is stable against aggregation and no larger particles are formed. At $E_{el} \ll kT$, each intercluster collision will lead to aggregation with the rate limited by the diffusion rate in the dispersive medium.

As the concentration of the electrolyte decreases, the coagulation rate decreases (slow coagulation). Coagulation of sols produces aggregates the fractal dimension of which depends on the type of coagulation. The fractal dimension of the aggregates obtained under slow coagulation exceeds that of the aggregates obtained under fast coagulation conditions, which indicates a better organisation in the former case. Long-range cluster-cluster interaction causes the formation of macroscopic ensembles that exhibit the phase stability. Such ordered objects were called periodic colloidal structures.⁴⁴

Surfactant solutions are appropriate for not only self-organisation of molecules in micelles, but also organisation of ordered nanostructures built of the metal and metal oxide clusters prepared by micellar technique. In particular, chemical reactions involving conventional and reverse micelles are widely used for the synthesis of colloidal clusters of 1 to 10 nm size. For instance, Ag_2S clusters are prepared using microemulsions containing two types of reverse micelles, with Na_2S and Ag -surfactant. Collisions, coalescence and exchange of the contents of the aqueous phases lead to formation of Ag_2S clusters whose size is controlled by the micelle size. The cluster size increases from 3 to 5.8 nm in the range mentioned above as the size of the reverse micelle increases,⁴⁵ which is consistent with the model of nucleation in a closed pore.

To release the nanoclusters from the micelle, the latter is destroyed by thiols, the resulting clusters are dissolved in appropriate solvents (e.g., benzene), the solution is filtered and then the solvent is evaporated. This procedure allows one to prepare monodisperse nanoclusters of size up to 10 nm passivated by thiols (e.g., dodecanethiol). Then, ordered nanostructures (colloidal crystals) are formed from these clusters immobilised on certain supports. Two- and three-dimensional colloidal crystals were synthesised from metallic gold, cobalt and silver clusters as well as from the metal oxide and metal chalcogenide clusters.³⁶ Alkanethiols, alkylphosphines and dithiols are used as nanocluster surface passivators.

Figure 11 presents photomicrographs of the Ag_2S nanostructure formed from passivated nanoclusters of size 5.8 nm. Like a conventional crystal, it can contain dislocations and defects. Two-dimensional nanostructures are close-packed monolayers and three-dimensional structures have a face-centred cubic lattice. The clusters assemble into crystals under the action of weak van der Waals interactions similarly to crystallisation of molecular clusters or noble gas clusters. Apparently, weak intercluster interactions are necessary for the formation of ordered nanostructures.

Yet another important condition for organisation of ordered cluster crystals is undoubtedly the monodisperse character of

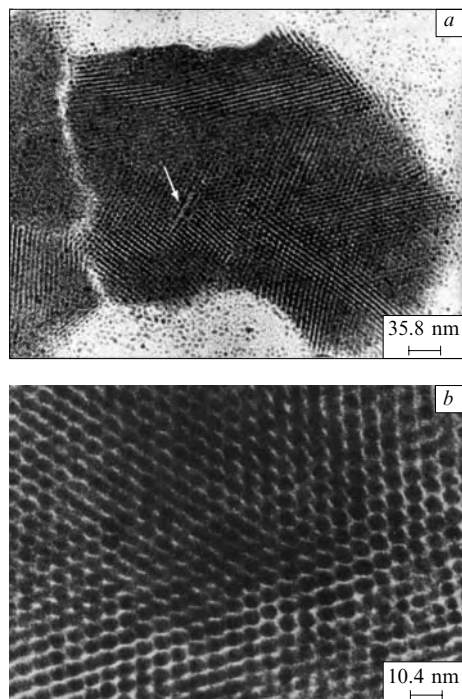


Figure 11. Ag₂S nanostructure micrographs obtained at different magnification.⁴⁵

White arrow points to a defect in the crystal structure of colloidal crystal.

clusters. Colloidal clusters are used as key elements in nanoelectronics and nanooptics, as well as nanomagnets; because of this, requirements for the strength and stability of such structures become more stringent. Here, it would be more appropriate to work with covalent bonds and covalent crystals. However, the latter cannot be obtained by the methods employed in the crystallisation of colloidal nanocrystals (namely, by coating a substrate followed by evaporation). Ordered nanostructures with monodisperse nanopore or nanofibre size are prepared by template methods using micelles (templates) that set the size of the nanosystem. In this connection the formation of mesoporous silica and alumina is a characteristic manifestation of discrete critical sizes.

Mesoporous silica. Mesoporous silica is prepared by polycondensation of silicon compounds, *e.g.*, tetramethoxysilane or tetraethoxysilane (TEOS) in the presence of surfactant molecules that form a micelle and play the role of a template.⁴⁶ In particular, this procedure is used for fabrication of the family of molecular sieves M41S.⁴⁷ Hydrolysis of TEOS causes the formation of silicas on the surface of surfactant micelles. An example of the material for the micelle and template is provided by cetyltrimethylammonium bromide C₁₆H₃₃NMe₃Br. The phase diagram of the water–C₁₆H₃₃NMe₃Br system is shown in Fig. 12.

Bifunctional C₁₆H₃₃NMe₃Br molecules are amphiphilic, *i.e.*, they contain hydrophilic groups and hydrophobic tails that are directed to the centre of the micelle. The shape of micelles and the degree of micelle formation depend on the surfactant concentration. At high concentrations, the surfactant molecules aggregate to form liquid-crystalline (LC) phases with temperature-dependent structures. Removal of organic micelle template results in mesoporous silica with monodisperse pore size. The pore size can be varied by varying the hydrocarbon chain length in the surfactant molecule. For instance, the pore size in the nanosystem synthesised using C_nH_{2n+1}NMe₃Br (where $n = 8, 10, 12, 14, 18$) as template increases by 0.45 nm as the n value changes by 2.

Silica-based nanostructures also include critical-size particles determined by the principles of close (hexagonal or cubic) pack-

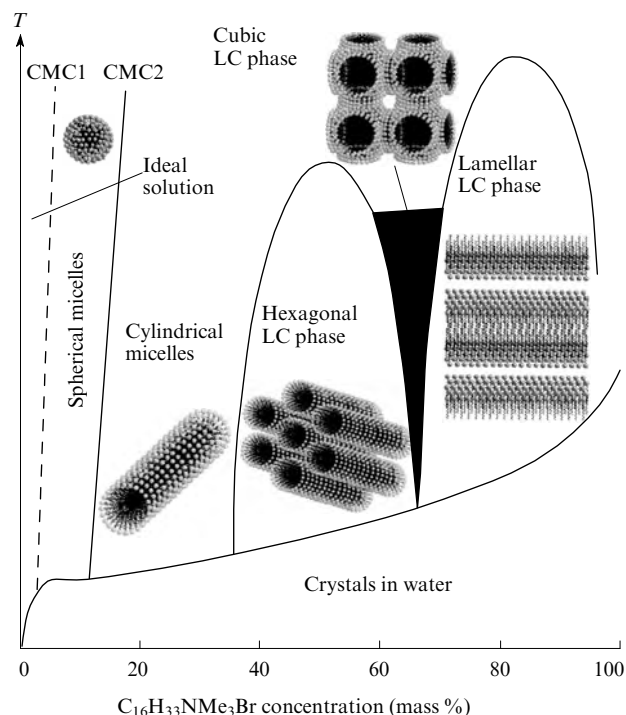


Figure 12. Phase diagram for the H₂O–C₁₆H₃₃NMe₃Br system with two critical micelle concentrations (CMC1 and CMC2).

ing. With block copolymers as templates, the pore size increases; using triblock copolymers, one can prepare pores 5–30 nm in diameter and nanostructures with hexagonal packing.

Mesoporous silicon films deposited from the mesophase (prepared similarly) to bulk material are of the greatest interest. In such films, mesopores represent channels aligned with the substrate surface due to minimisation of the film–substrate interaction energy. For instance, the widely used MCM-41 films have the (100) orientation; they can be prepared on the (110)-oriented silicon substrates.

Porous alumina. Anodic oxidation of high-purity alumina foil produces monodisperse alumina that self-assembles into a nanostructure with nanopores of size from 15 to 100 nm depending on the voltage applied (30 to 150 V).⁴⁸ Alumina membranes thus obtained serve as templates for fabricating, *e.g.*, nanowires. The fact that porous alumina is formed in various electrolytes has long been known,⁴⁹ however fabrication of material with controllable monodisperse nanopore size distribution and assembling templates began only recently. Electrolytic anodic oxidation of alumina surface followed by etching leads to the formation of an ordered hexagonal system of nanopores (channels).

Electrolytic anodisation is schematically shown in Fig. 13. The first stage of oxidation proceeds in an acidic medium and results in the formation of Al₂O₃ nanoclusters that form a discrete ordered structure on polished aluminium surface. The ‘bottom’ clusters merge with organised pore network of the same size in metallic aluminium. After etching of the oxide clusters the aluminium surface is covered with a hexagonally patterned network of pores with monodisperse size distribution. In the second stage of electrolytic oxidation the hexagonal pattern of the surface acts as a template for the growth of an oxide nanostructure that includes cylindrical nanopores with walls 10–30 nm thick and nanopores of size ranging from > 10 to 20 nm the surface of which is coated with alumina. The next stage involves removal of aluminium by, *e.g.*, mercury chloride. This results in an Al₂O₃ membrane with a honeycomb structure and closed channels that can be opened chemically or by using an ion beam. SEM images of such a membrane are presented in Fig. 14. The images show a

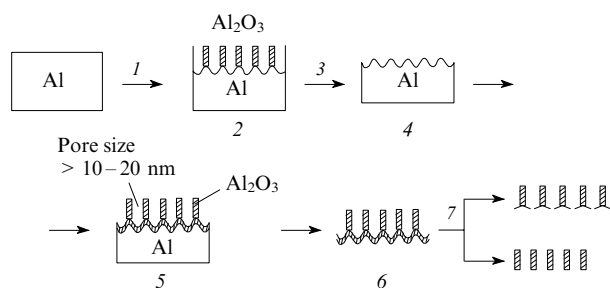


Figure 13. Scheme of fabrication of porous aluminium.⁴⁹ Purification of aluminium (1), first stage of anodic oxidation (2), etching (3), hexagonal organisation of surface pores (4), second stage of anodic oxidation involving formation of Al_2O_3 (5), surface etching (6) and pore opening by ion beam and chemical treatment (7).

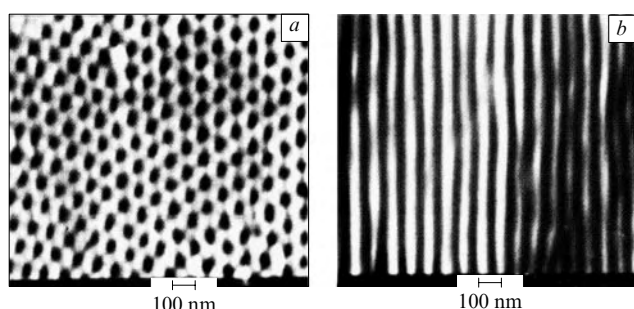


Figure 14. SEM images of Al_2O_3 coplanar (a) and normal to (b) the membrane surface.⁴⁸

patterned structure with monodisperse pores (channels). Deviations of geometric parameters from specified values can be due to structural defects.

c. Molecular clusters

Initially, ligand-stabilised molecular clusters have been the subject of studies in the fields of coordination and structural chemistry. At the same time unusual structure and properties of these species, originating from the presence of a core of metal atoms, gave an impetus to the development of a separate field of science, cluster chemistry, possessing its own computational, synthetic and other methods of investigation. Interest in this type of clusters increased in connection with the development of nanochemistry and nanotechnology, which permit preparation of nanomaterials and fabrication of nanodevices based on molecular clusters. In this Section we will consider the structure and properties of molecular clusters of size 1–3 nm. Molecular clusters with metal cores and clusters based on metal oxides will be described separately.

Molecular metal clusters. The core of a molecular cluster is formed in accordance with the packing pattern of metal complexes and the principle of closest packing of atoms.⁵⁰

The largest molecular clusters are synthesised based on noble metals, palladium and platinum. The formation of their cores obeys the principle of closest packing of atoms.^{51,52}

The number of atoms in a nanocluster constructed in the form of regular 12-vertex polyhedron (cuboctahedron, icosahedron or anticuboctahedron) can be calculated from the expression

$$n = \frac{1}{3}(10N^3 + 15N^2 + 11N + 3), \quad (20)$$

where N is the number of layers around the central atom. Thus, the smallest close-packed core contains 13 atoms, that is, one central atom and 12 atoms in the first layer. Relation (20) gives a set of ‘magic’ numbers of atoms $n = 13, 55, 147, 309, 561, 923, 1415,$

2057, 2869, etc. corresponding to the most stable cores of metal clusters (similarly to the noble gas clusters). Indeed, the following clusters are known: 13-atom (single-layer) clusters $[\text{Au}_{13}(\text{diphos})_6](\text{NO}_3)_4$ (diphos is $\text{Ph}_2\text{PCH}_2\text{CH}_2\text{PPh}_2$) and $[\text{Rh}_{13}(\text{CO})_{24}\text{H}_3]^{2-}$ with icosahedral and cuboctahedral cores, respectively (see, e.g., Ref. 36); 55-atom (two-layer) clusters $\text{Au}_{55}(\text{PPh}_3)_{12}\text{Cl}_6$, $\text{Rh}_{55}(\text{PPh}_3)_{12}\text{Cl}_6$, $\text{Pt}_{55}(\text{AsBu}_3)_{12}$, $\text{Ru}_{55}(\text{PBu}_3)_{12}\text{Cl}_{20}$ with cuboctahedral cores; a 309-atom (four-layer) cluster $\text{Pt}_{309}(\text{phen}')\text{O}_{30 \pm 10}$ [phen' is the sodium salt of 4,7-bis(phenylsulfate)-1,10-phenanthroline] with a cuboctahedral core; a 561-atom (five-layer) cluster $\text{Pd}_{561}(\text{phen})_{60}(\text{OAc})_{180}$ (phen is phenanthroline) with an icosahedral core; a 1415-atom (seven-layer) cluster $\text{Pd}_{1415}(\text{phen})_{60}\text{O}_{\sim 1100}$ and a 2057-atom (eight-layer) $\text{Pd}_{2057}(\text{phen})_{84}\text{O}_{\sim 1600}$ cluster. The structure of the $\text{Pd}_{561}(\text{phen})_{60}(\text{OAc})_{180}$ cluster is schematically shown in Fig. 15.⁵³

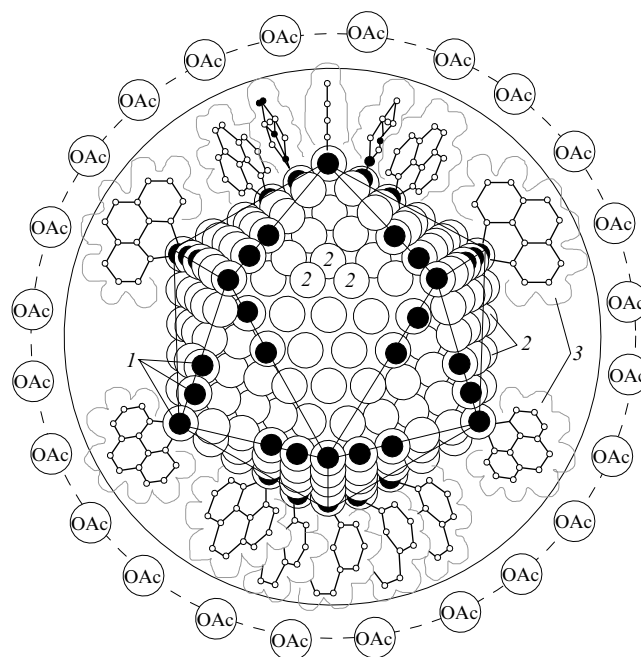


Figure 15. Structure of giant cluster $\text{Pd}_{561}(\text{phen})_{60}(\text{OAc})_{180}$.⁵³ (1) Surface palladium atoms bonded to bidentate phen ligands; (2) surface palladium atoms nonbonded to phen ligands; (3) phen ligands.

Molecular clusters based on metal oxides. The cores of molecular clusters based on metal oxides are built of $\{\text{MO}_x\}$ polyhedral units, where M stands for the metal in high oxidation state. Polyhedra can interact with one another and thus form clusters comprising tens and hundreds of metal atoms. Large clusters are known for tungsten, vanadium and molybdenum oxides, the last-named being the largest.^{54,55} Most molybdates possess a mixed valence and form basic units, $\{\text{Mo}_8\}$ and $\{\text{Mo}_{17}\}$, which are then used for constructing larger clusters. An important feature of such clusters is the presence of the large fragments $\{\text{Mo}_{17}\}$. By linking them through various electrophilic groups, e.g., $\{\text{MoO}_2\}^{2+}$, one can obtain very large clusters. Using other electrophilic ions, such as Fe^{III} or V^{IV} , it is possible to form giant-size cluster fragments with the $\{\text{Mo}_{57}\text{M}_6\}$ metal core (M is iron or vanadium in different oxidation states), which can act as giant building blocks. In particular, a compound $\{(\text{NH}_4)_{12}[\text{Mo}_{45}^{\text{VI}}\text{Mo}_6^{\text{V}}(\text{MoNO})_6\text{Fe}_6^{\text{III}}\text{Fe}_{1.5}^{\text{II}}(\text{OH})_3(\text{H}_2\text{O})_{30}] \cdot 64\text{H}_2\text{O}\}_n$ was obtained. It contains the cluster fragment $\{\text{Mo}_{57}\text{Fe}_6^{\text{III}}\}$, which is similar to the structures considered above.

Using the basic cluster blocks, one can continue the cluster buildup.⁵⁴ For instance, cluster anions $[\text{Mo}_{154}(\text{NO})_{14}\text{O}_{448} \cdot \text{H}_{14}(\text{H}_2\text{O})_{70}]^{28-}$ were obtained. This giant ring-type anion consists of 140 octahedral bipyramids $\{\text{MoO}_6\}$ and 14 pentagonal

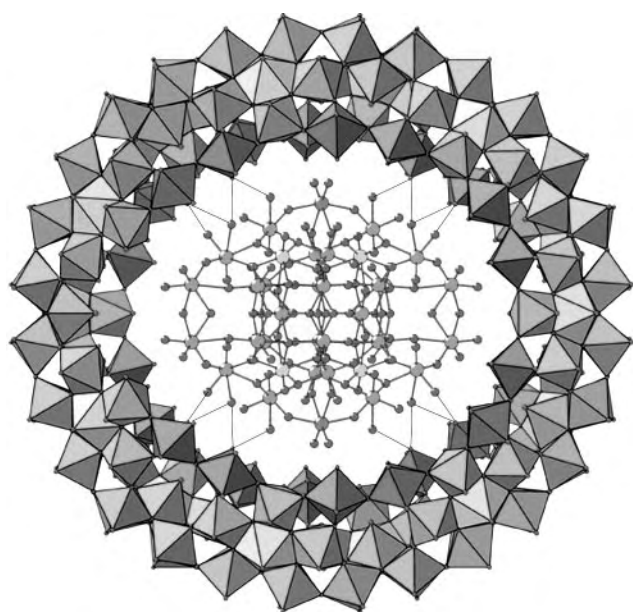


Figure 16. Structure of supramolecular system $\{\text{Mo}_{36}@\text{Mo}_{148}\}$ in polyhedral representation.⁵⁶

Light and dark octahedra denote $\{\text{Mo}_6\}$ and $\{\text{Mo}_8\}$ units, and pairs of $\{\text{Mo}_2\}$ units are given in gray.

bipyramids $\{\text{Mo}(\text{NO})\text{O}_6\}$. The equatorial diameter of the central cavity is ~ 2 nm. This anion can be treated as an assembly composed of 14 subunits. Each subunit is a $\{\text{Mo}_8\}$ fragment with the $\{\text{Mo}(\text{NO})\text{O}_6\}$ pentagonal pyramid at the centre. The $\{\text{Mo}(\text{NO})\text{O}_6\}$ unit shares vertices and edges with seven $\{\text{MoO}_6\}$ octahedra. Chains built of ring-type clusters can serve as ‘hosts’ for smaller ‘guest’ clusters, e.g., a $\{\text{Mo}_{36}\}$ cluster (Fig. 16). In this supramolecular nanocluster system $\{\text{Mo}_{36}@\text{Mo}_{148}\}$ the ‘host’ and the ‘guest’ are linked through 16 hydrogen bonds and four Na^+ cations arranged between the ‘host’ and the ‘guest’.

Giant ring-type clusters based on metal oxides possess some features differing them from the metal clusters. First of all, this is the presence of nanometre-sized cavities and the possibility of varying the nanoscale supramolecular organisation, well-developed hydrophilic surface suitable for sorption of various substances, e.g., activated charcoal, and replacement of the H_2O ligands by other molecules, which is accompanied by changes in the properties of the nanostructure. Finally, such systems are appropriate for modelling many catalytic reactions, because the composition of the surface of the cluster involved in the reaction is known with certainty.

Another group of molecular clusters based on metal oxides includes highly symmetric clusters (keplerates) with one central point⁵⁶ and layered structure. For example, giant spherical molecular clusters are built of 12-vertex icosahedra and pentagonal fragments.

The pentagonal fragments $\{(\text{Mo})\text{Mo}_5\}$ consist of the central pyramid MoO_7 which shares edges with five MoO_6 octahedra. In the presence of binuclear linkers $\{\text{Mo}_2^{\text{V}}\text{O}_4\}^{2+}$, an icosahedral molecular system is formed, which comprises 12 pentagons and 30 linkers. If the $\{\text{Mo}_2^{\text{V}}\text{O}_4\}^{2+}$ groups have acetate ions as bridging ligands, a spherical cluster of composition $[\text{Mo}_{72}^{\text{VI}}\text{Mo}_{60}^{\text{V}}\text{O}_{372} \cdot (\text{AcO})_{30}(\text{H}_2\text{O})_{72}]^{42-}$ is formed. Here, the central molybdenum atoms in the $\{(\text{Mo})\text{Mo}_5\}$ fragments occupy 12 vertices of an icosahedron and the $\{\text{Mo}_2^{\text{V}}\text{O}_4\}^{2+}$ groups form 30 edges of this polyhedron. Such clusters form polymer networks and serve as building blocks for constructing even larger aggregates. These blocks are sufficiently flexible and can change the shape upon minor changes of corresponding boundary conditions during the

synthesis; they can adjust the size and shape to one another. A giant oxomolybdate cluster composed of 386 metal atoms $\{\text{Mo}_{368}\}$ and 1880 non-metal atoms (ignoring hydrogen atoms) was synthesised.⁵⁷ The cluster similar in size to haemoglobin molecule was obtained by linking 64 $\{\text{Mo}_1\}$ fragments, 32 $\{\text{Mo}_2\}$ fragments and 40 $\{\text{Mo}(\text{Mo}_5)\}$ fragments. The formation of this cluster is accompanied by symmetry violation. The cluster structure includes a giant mixed-valence cluster anion (Fig. 17) $[\text{H}_x\{\text{Mo}(\text{Mo}_5)_8\{\text{Mo}(\text{Mo}_5)\}_{32}\{\text{Mo}_2\}_{16}\{\text{Mo}_2\}_8\{\text{Mo}_2\}_{8'}\{\text{Mo}_1\}_{164}\}]^{48-}$, where $\{\text{Mo}(\text{Mo}_5)_8\} \equiv \{\text{Mo}_6\text{O}_{21}(\text{H}_2\text{O})_6\}$, $\{\text{Mo}(\text{Mo}_5)\} \equiv \{\text{Mo}_6 \cdot \text{O}_{21}(\text{H}_2\text{O})_3(\text{SO}_4)\}$, $\{\text{Mo}_2\} \equiv \{\text{Mo}_2\text{O}_3(\text{H}_2\text{O})_2\}$, $\{\text{Mo}_2\}' \equiv \{\text{Mo}_2(\text{O})_2(\text{O}_{\text{br}})_3(\text{SO}_4)\}$, $\{\text{Mo}_2\}'' \equiv \{\text{Mo}_2(\text{O})_4(\text{O}_{\text{br}})(\text{SO}_4)\}$, $\{\text{Mo}_1\} \equiv \{\text{MoO}(\text{H}_2\text{O})\}$, $x \approx 16$.

Compound $\text{Na}_{48}[\text{H}_x\text{Mo}_{368}\text{O}_{1032}(\text{H}_2\text{O})_{240}(\text{SO}_4)_{48}] \cdot \text{ca.}1000 \text{ H}_2\text{O}$ crystallises in the $I4mm$ space group. Its unit cell contains two giant lemon-like cluster anions having an approximate symmetry D_4 with almost spherical central fragment $\{\text{Mo}_{288}\text{O}_{784}(\text{H}_2\text{O})_{192} \cdot (\text{SO}_4)_{32}\}$ (fragment B) and two ‘caps’ $\{\text{Mo}_{40}\text{O}_{124}(\text{H}_2\text{O})_{24}(\text{SO}_4)_8\}$ (fragments C). The B and C fragments have different local symmetry, D_{4d} and C_4 , respectively. The transition between two types of symmetry is shown in Fig. 17a. The anion consists of 6 building blocks mentioned above that form a cavity of size 2.5×4.0 nm, which can contain up to 400 water molecules. The use of giant ring-type and spherical molecular nanoclusters allows one to go to larger clusters possessing different properties on the one hand and to ‘tune’ the chemical reaction to proceed at the specified centres on the other hand. The use of such systems is also quite promising for carrying out the reaction inside the giant cluster cavity.

3. Critical dimensions of clusters formed in solid-phase reactions

Solid-phase nanoclusters are main structural units of any nanostructures. Processes resulting in the formation of solid-phase nanoclusters are not rare to occur. For instance, this can be melt or solution crystallisation, sintering, various martensite transformations, crystallisation from amorphous systems, formation of magnetic and ferroelectric domains and spinodal decomposition. All these processes obey the laws of thermodynamics and are accompanied by the ordering and self-organisation phenomena.^{58,59}

The fashion of assembling a condensed nanosystem from clusters strongly depends on the procedure for cluster formation. A nanostructure can be formed from individual clusters by compaction or nanostructuring of a bulk solid. These techniques are of great importance for the design of nanomaterials based on metals, alloys, oxides, ceramics, etc. In addition to the nanostructure formation studies, an important research aspect involves investigation of the mechanical, thermal, electronic and magnetic properties that are responsible for the quality and field of application of many structural materials.

a. Cluster nucleation in solids

Thermal decomposition of a metal compound at temperatures above certain critical (threshold) temperature is accompanied by the formation of a mobile reactive medium in which metal oxide (e.g., iron oxide) nanoclusters nucleate. The formation of clusters can be treated as nucleation from individual atoms in solution or melt within a confined volume (e.g., in a pore volume). The volume can be controlled by diffusion, which prevents the concentration fluctuation of the bulk medium (due to the change in the cluster size) from travelling a distance longer than $L \sim (Dt)^{1/2}$ (D is the diffusion coefficient) during the nucleation time (t). Here, it is this distance that can be considered as the size of the cell in which the cluster is confined; the components of the bulk medium cannot escape this cell.

For a system of non-contacting clusters the dependence of the Gibbs free energy (ΔG_{fc}) on the cluster radius (r) for one cluster in the course of atomic nucleation is given by

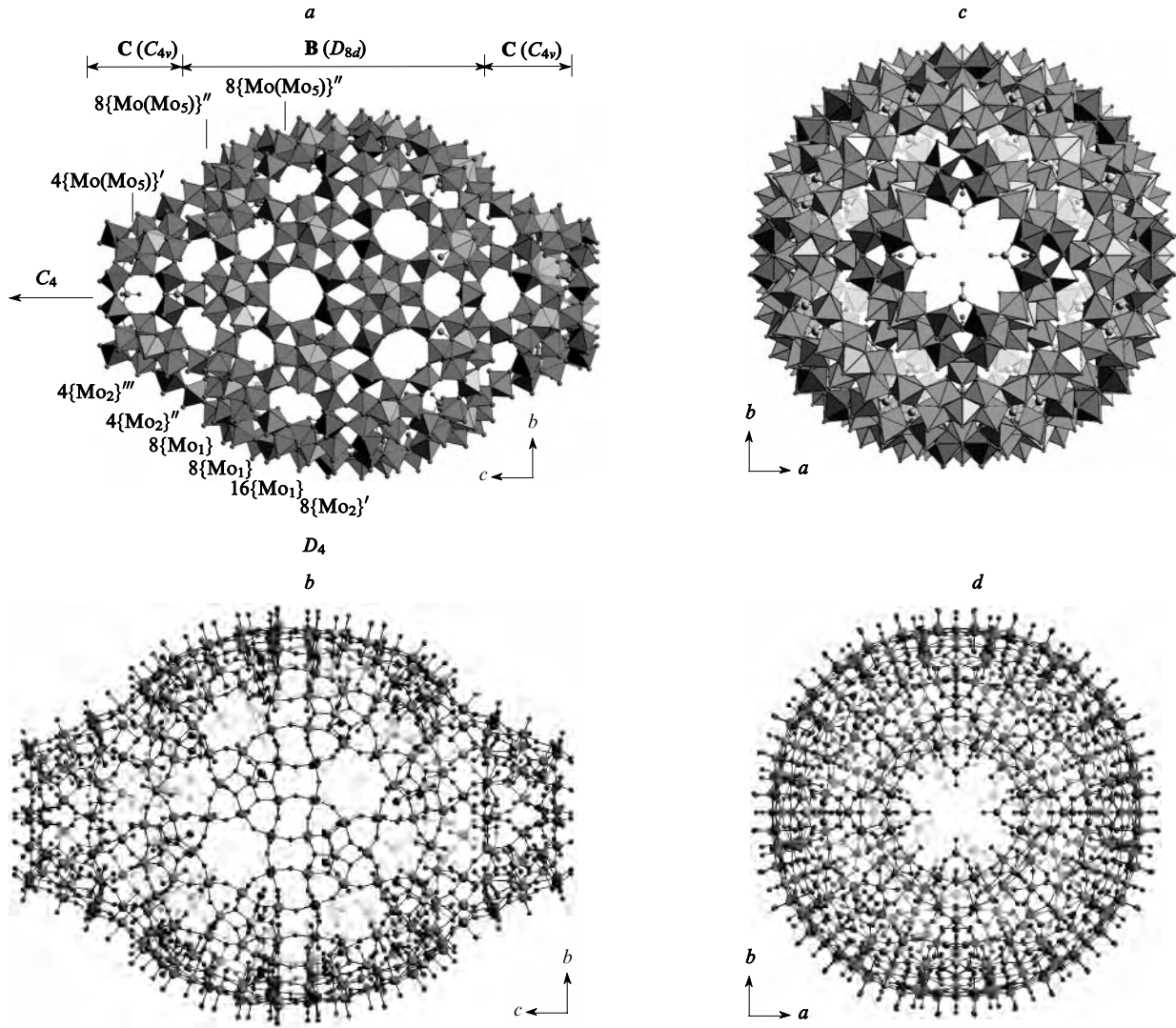


Figure 17. Structure of the $\{\text{Mo}_{368}\}$ anion in crystals in polyhedral (*a, c*) and ball-and-stick (*b, d*) representation.⁵⁷ Shown are different building blocks and regions with different symmetry; the building blocks include $\{\text{Mo}_1\}$, $\{\text{Mo}_2\}$ and $\{\text{Mo}(\text{Mo}_5)\}$.

$$\Delta G_{\text{fc}} = 4\pi r^2 \alpha_c - \frac{4}{3} \pi r^3 \rho_c \Delta \mu_c, \quad (21)$$

where α_c is the density of the free surface energy of the cluster, ρ_c is the density of iron atoms in the cluster and $\Delta \mu_c$ is the change in the chemical potential of iron upon transfer of one atom from the bulk medium to the cluster structure. It should be noted that in this representation the surface energy is independent of the cluster size and fulfilment of relation (21) implies that the laws of thermodynamics are applicable up to a cluster size of 1 nm.

Let the mixture contain N atoms per cluster, let n_0 out of N atoms be the iron atoms and let $n_c = (4/3)\pi r^3 \rho$ iron atoms be in the cluster structure. Then, at $N \gg n_0$ one has

$$\Delta \mu_c = \Delta \mu_c^0 + \ln \frac{n_0 - n}{N}. \quad (22)$$

Here $\Delta \mu_c^0$ is the change in the standard chemical potential of iron upon transition of one iron atom to the cluster structure, measured in units of kT .

Initially, clusters do not contact one another. Denoting the volume and the surface area of the non-contacting cluster by $V_{\text{fc}} = (4/3)\pi r^3$ and $S_{\text{fc}} = 4\pi r^2$, respectively, expression (21) can be rewritten in the form

$$\Delta G_{\text{fc}} = \alpha S_{\text{fc}} - \left(\Delta \mu_c^0 + \ln \frac{n_0 - n}{N} \right) V_{\text{fc}}. \quad (23)$$

The function ΔG_{fc} has a maximum at $r = r_{\text{cr}}$ and a minimum at $r = r_{\text{max}}$ (Fig. 18).

Relation (23) characterises the stages of cluster nucleation and growth in a weakly interacting system of non-contacting

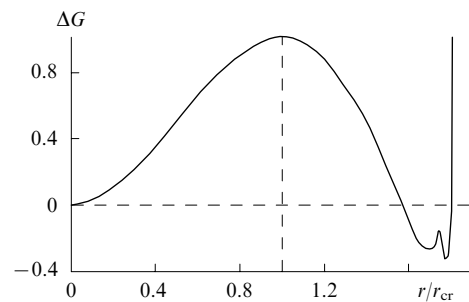


Figure 18. Change in the Gibbs free energy plotted vs. increase in cluster size upon nucleation and subsequent sintering for $r_{\text{f}} = 1.75 r_{\text{cr}}$.

clusters. As the cluster size increases, clusters contact one another, thus initiating the sintering. The onset of sintering indicates a strong interaction between clusters. If the distance, $2r_t$, between the centres of clusters is constant, the surface area S_{sc} and the volume V_{sc} of a cluster contacting k neighbours are quite correctly given by

$$S_{sc} = 4\pi r^2 + k2\pi r(r_t - r), \quad (24)$$

$$V_{sc} = \frac{4}{3}\pi r^3 + k\frac{1}{3}\pi r(-2r^3 + 3r^2r_t - r_t^3).$$

The change in the Gibbs free energy in the sintering stage (at $r > r_t$) is

$$\Delta G_{sc} = \alpha S_{sc} - \left(\Delta\mu^0 + \ln \frac{n_0 - n}{N} \right) \rho V_{sc}. \quad (25)$$

Thus, the profile of the change in the free energy of the system per cluster in the whole range of changes in this parameter is described by relation (23) at $r < r_t$ and by expression (25) at $r > r_t$.

Figure 18 presents the dependence $\Delta G(r/r_{cr})$ for $r_t = 1.75 r_{cr}$ shown as an example. The curve has three minima separated by two maxima. The minimum at $r = 0$ corresponds to the initial state of the bulk medium. After passing the point r_{cr} , the system goes to the first stable state $r = r_{max}$ and corresponds to the equilibrium state of non-contacting clusters (this is possible at $r_{max} < r_t$). The third minimum corresponds to the system where clusters are sintered and each cluster has k contacts. Correspondingly, the first maximum at $r = r_{cr}$ describes the potential barrier to nucleation and the second maximum corresponds to the potential barrier to sintering. The shape of the potential barrier to sintering for $k = 6$ at different r_t values is shown in Fig. 19. At $r_t = 1.7 r_{cr}$, sintering occurs barrierlessly; at $r_t = 1.75 r_{cr}$, i.e., at lower proportion of clusters in the system, transition to sintering involves the overcome of a potential barrier; if the proportion of clusters is even lower ($r_t = 1.8 r_{cr}$), sintering does not occur because it requires an increase in the free energy.

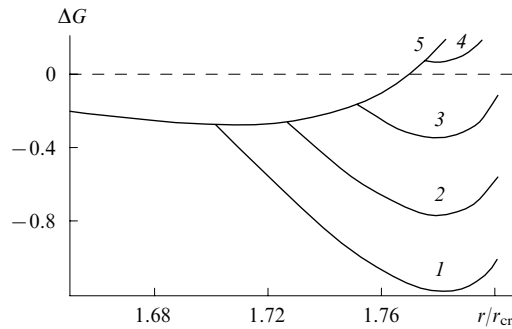


Figure 19. Change in the Gibbs free energy plotted vs. increase in cluster size during sintering at different r_t values. $r_t = 1.7 r_{cr}$ (1); $1.73 r_{cr}$ (2); $1.75 r_{cr}$ (3); $1.77 r_{cr}$ (4); $1.78 r_{cr}$ (5).

Thus, the formation of a nanosystem involves two main stages. The first stage is characterised by weak interaction between clusters (from nucleation to the onset of sintering), while the second stage is characterised by strong interaction between clusters (after the onset of sintering). A change in the character of intercluster interaction causes many properties of the nanosystem to change; in particular, strong intercluster interaction and sintering produce considerable interfacial stresses. They are generated in the formation of an intermediate neck due to the surface tension⁶⁰ and obey the dependence $P = \alpha/x$, where α is the surface tension and x is the neck radius in the sintering of clusters. Assuming that for iron oxide $\alpha \sim 1 \text{ N m}^{-1}$ and $x \sim 1 \text{ nm}$, we get $P \sim 10^9 \text{ Pa}$. The excess pressure is also produced in the presence of defects and dislocations at the interface and reaches

a value of the order of 10^9 Pa for clusters of size $\sim 10 \text{ nm}$. The stress and pressure in the system of strongly interacting nanoclusters are the key parameters responsible for the formation and properties of the nanostructure. Probably, solid-phase metal, oxide and chalcogenide nanoclusters can be prepared by low-temperature solid-phase reactions carried out at particular r_t and r_{max} values.

Atomic nucleation and subsequent sintering can be accompanied by cluster nucleation (aggregation of clusters). Indeed, analysis of the changes in the free energy of individual clusters nucleation (ΔG_{fa}) into an aggregate of radius R performed as above for atoms [see Eqn (21)] gives

$$\Delta G_{fa} = 4\pi R^2 \alpha_a - \frac{4}{3}\pi R^3 \rho_a \Delta\mu_a, \quad (26)$$

where α_a is the surface tension of the aggregate, $\Delta\mu_a$ is the chemical potential of aggregate formation and ρ_a is the density of the aggregate.

Let the mixture contain N atoms per aggregate, let n_0 out of N atoms be iron atoms and let $n_a = (4/3)\pi R^3 \rho_a$ iron atoms be in the aggregate structure. Then, at $N \gg n_0$ one has

$$\Delta\mu_a = \Delta\mu_a^0 + \ln \frac{n_0 - n}{N}. \quad (27)$$

Here $\Delta\mu_a^0$ is the change in the standard chemical potential of iron upon transition of one iron atom to the aggregate structure, measured in units of kT . Assuming that, similarly to individual clusters, the cluster aggregates do not contact one another in the initial stage and denoting the volume and the surface area of the non-contacting aggregate by $V_{fa} = (4/3)R^3$ and $S_{fa} = 4\pi R^2$, respectively, expression (27) can be rewritten in the form

$$\Delta G_{fa} = \alpha_a S_{fa} - \left(\Delta\mu_a^0 + \ln \frac{n_0 - n}{N} \right) V_{fa}. \quad (28)$$

The function ΔG_{fa} has a maximum at $R = R_{cr}$ and a minimum at $R = R_{max}$ like the corresponding function for the atomic nucleation of isolated cluster (see Fig. 18). However, the r_{cr} and R_{cr} values should be significantly different. Indeed, for a solid with strong covalent bond between iron and oxygen atoms the surface tension of the iron oxide cluster should be much higher than the surface tension of cluster aggregates due to weak van der Waals forces. The surface tension for such aggregates is unknown, but we can assume that the surface tension of the iron oxide nanocluster is of the order of 1 N m^{-1} (see Refs 61 and 62) and the surface tension of the cluster aggregate lies between 0.073 N m^{-1} (water) and 0.02 N m^{-1} (see Ref. 63) typical of large saturated hydrocarbon molecules; these boundary values are due to the hydrogen and van der Waals bonds, respectively. Then, comparing Eqns (23) and (28), one can expect an increase in R_{cr} by a factor of 15 to 50 compared to r_{cr} . A similar conclusion can also be drawn from comparing the energy of the bond between iron and oxygen atoms in iron oxide cluster ($\sim 2 \text{ eV}$ for the covalent bond) and the energy of the bond between noble gas atoms ($\sim 0.1 \text{ eV}$ for the van der Waals interaction). The bond between the noble gas atoms can be treated as an approximation to the bond between cluster aggregates. Cluster aggregation can occur not only by nucleation. The existence of superaggregates comprising a few aggregates formed in accordance with Eqn (28) and characterised by even lower surface tension and, correspondingly, larger critical radii seems not to be impossible.

b. Design of nanoclusters and nanostructures based on iron oxide complexes

The AFM images of the nanostructures formed from iron oxide clusters, obtained at the decomposition temperature of iron oxalate ($T_d = 210^\circ \text{C}$) are shown in Fig. 20.

The section profiles of the AFM image of a surface area of $600 \times 600 \text{ nm}$ along the lines 1 and 2 revealed the formation of two types of nanostructures in the course of thermal decomposition. These are large aggregates of size $\sim 300 \text{ nm}$ and smaller

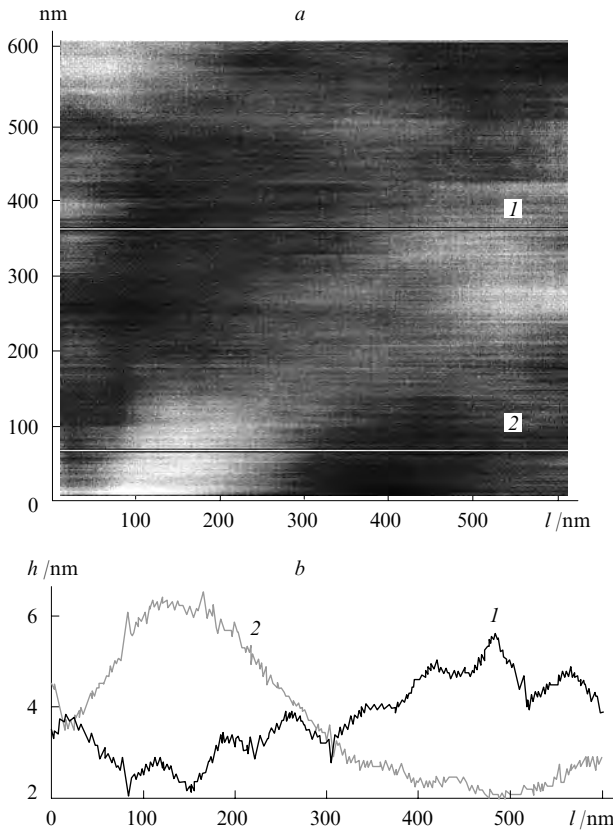


Figure 20. AFM image (a) of a nanostructure comprised of oxide iron nanoclusters, formed at iron oxalate decomposition temperature of 210 °C and profiles of the sections 1 and 2 (b).

aggregates of size 70–80 nm. Only one type of aggregates (of size 70–80 nm) was observed in a study of the region 300 × 300 nm. On both scales (especially, on the 300 × 300 nm scale) the AFM images show modulation of the aggregate profiles (roughness), which manifests itself as peaks (a total of 25–35 peaks) indicating that aggregates are composed of smaller particles, *i.e.*, nanoclusters whose limiting size was estimated at 2–3 nm. However, the AFM technique cannot look inside the cluster aggregate and determine its structure. To this end, ^{57}Fe Mössbauer spectroscopy was employed.

The Mössbauer spectra of the same nanostructure are shown in Fig. 21. At 4.2 K, the spectrum exhibits a magnetic hyperfine structure (HFS) characteristic of $\gamma\text{-Fe}_2\text{O}_3$. This structure was obtained using the simplest model involving two systems of magnetic HFS corresponding to the surface atoms and to the atoms in the cluster interior. Raising the temperature results in the spectrum diffusion, broadening of the lines of the magnetic HFS and a decrease in the magnetic induction at the nuclear site (B_{in}). Similar spectra are characteristic of superparamagnetic nanoclusters. This makes it possible to estimate the nanocluster size, from, *e.g.*, the simplest equation of superparamagnetism

$$\tau = \tau_0 \exp \frac{KV}{kT}, \quad (29)$$

where τ is relaxation time of the magnetic moment of the cluster, K is the magnetic anisotropy constant, V is the cluster volume and $\tau_0 = 10^{-9} - 10^{-10}$ s. The relaxation time τ was estimated using the slow relaxation model from the broadening of the components of the magnetic HFS.^{64,65} The spectra of nanoclusters measured at $T_d = 210$ °C were processed with the parameters $\Gamma = 0.62$ and 5.12 mm s^{-1} (Γ is the linewidth of the Mössbauer spectrum) determined from the spectra taken at $T = 4.2$ and 25 K, respectively. The value $\Delta\Gamma = 4.5 \text{ mm s}^{-1}$ at $T = 25$ K corresponds to

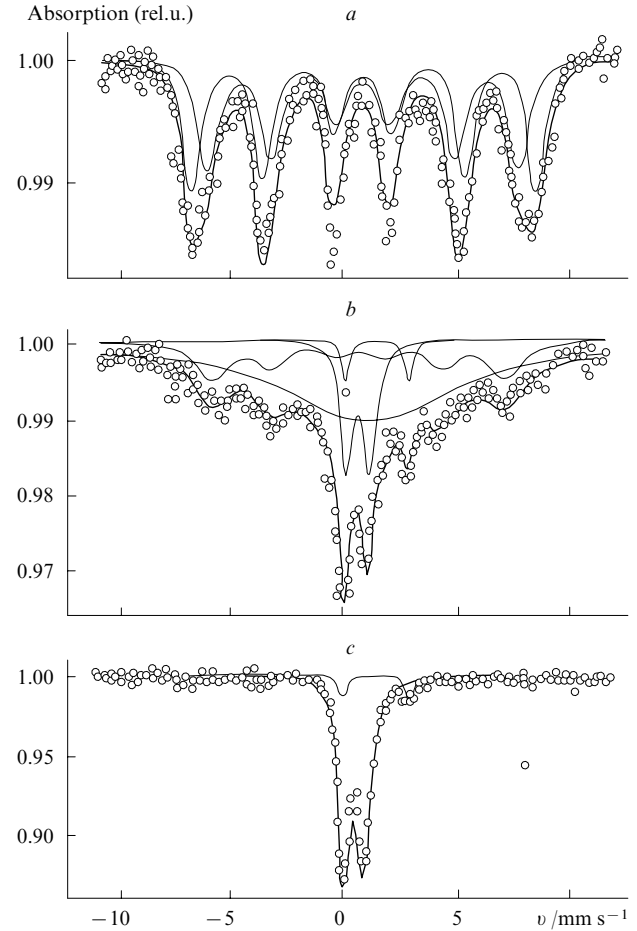


Figure 21. Mössbauer spectra of a nanostructure comprised of oxide iron nanoclusters, formed at iron oxalate decomposition temperature of 210 °C, obtained at 4.2 (a), 25 (b) and 80 K (c).

$\tau \approx 2.2 \times 10^{-9}$ s. Then for $\tau_0 = 10^{-9}$ at $T = 25$ K and $K = (1-2) \times 10^5 \text{ J m}^{-3}$ (see Ref. 66) the average cluster size is 1.4 to 1.7 nm. At 78 K, the τ value decreases and the Mössbauer spectrum exhibits only a quadrupole doublet.

An AFM study of larger clusters obtained at $T_d = 235$ °C revealed no formation of superaggregates including cluster aggregates. The size of the cluster aggregates was found to be nearly the same (~ 80 nm) as that of the nanoclusters obtained at $T_d = 210$ °C. The interior of these aggregates is difficult to see, but according to Mössbauer spectroscopy data, the nanostructure obtained at $T_d = 235$ °C is characterised by a higher superparamagnetic transition temperature (100 K); the nanocluster size was estimated at $\sim 4-7$ nm.

The AFM images become radically different for sintering of nanoclusters. The AFM images and profiles of nanoclusters in the initial stage of sintering ($T_d = 265$ °C) are shown in Fig. 22. The cluster size estimated in a study of a surface area of 500×500 nm in the system of strongly interacting clusters was 30 to 50 nm. A study on a larger scale (150×150 nm) and analysis of the profile of two contacting nanoclusters gave the half-width (14 nm) and height (6.4 nm) of a protrusion of the cluster. The Mössbauer spectra of this nanocluster structure (Fig. 23) are strongly different from similar spectra of two nanostructures considered above. Despite the absence of superparamagnetic relaxation, calculations for these large clusters using expression (29) lead to $\tau \gg 10^{-8}$ s and the spectra show a doublet characteristic of the paramagnetic or superparamagnetic state of the substance up to 100 K. Processing of the Mössbauer spectra obtained at $T = 78$ K revealed two magnetic hyperfine structures corresponding to $\alpha\text{-Fe}_2\text{O}_3$ and

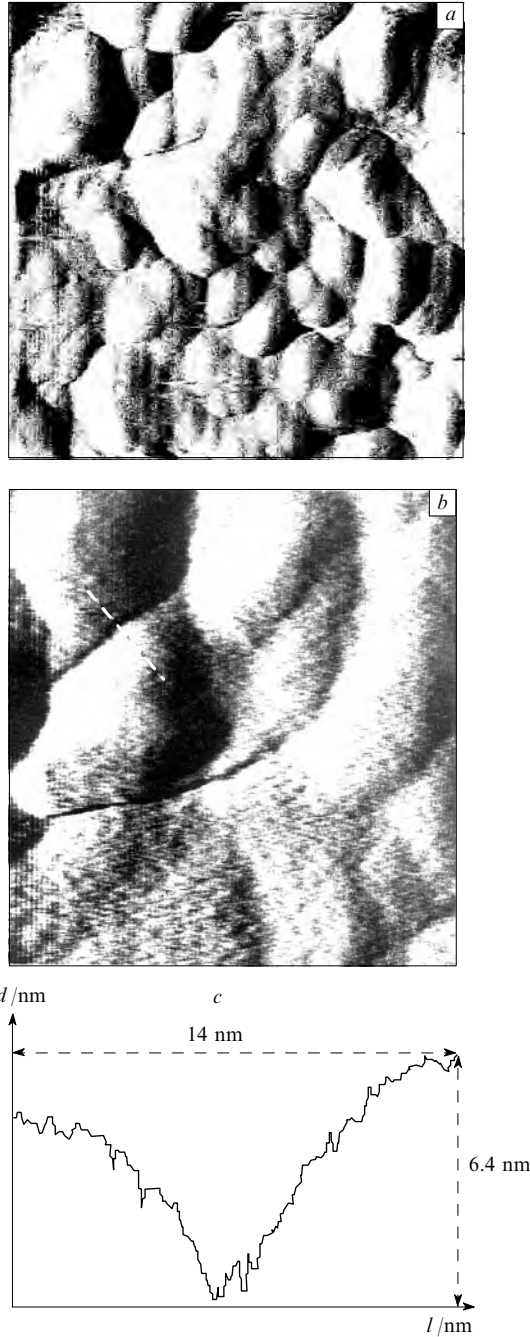


Figure 22. AFM image of a nanostructure comprised of iron oxide nanoclusters. Scan area 500×500 nm (a); scan area 150×150 nm (b) and surface profile along the dashed line shown in Fig. 22 b (c).

γ -Fe₂O₃. At 120 K and higher temperatures (up to room temperature), the Mössbauer spectra can exhibit one system of magnetic HFS and a quadrupole doublet. A characteristic feature of the series of the Mössbauer spectra with the magnetic HFS (see Fig. 23) is transformation of the magnetic HFS to the quadrupole doublet corresponding to the paramagnetic state of the substance at temperatures much below the Curie or Néel points ($T_C = 965$ K, $T_N = 865$ K) of bulk α -Fe₂O₃ and γ -Fe₂O₃, respectively. Interpretation of this result will be given below.

The AFM images of larger nanoclusters obtained at $T_d = 500$ °C showed the formation of a nanostructure comprising strongly interacting nanoclusters of size ~ 300 nm in the sintering

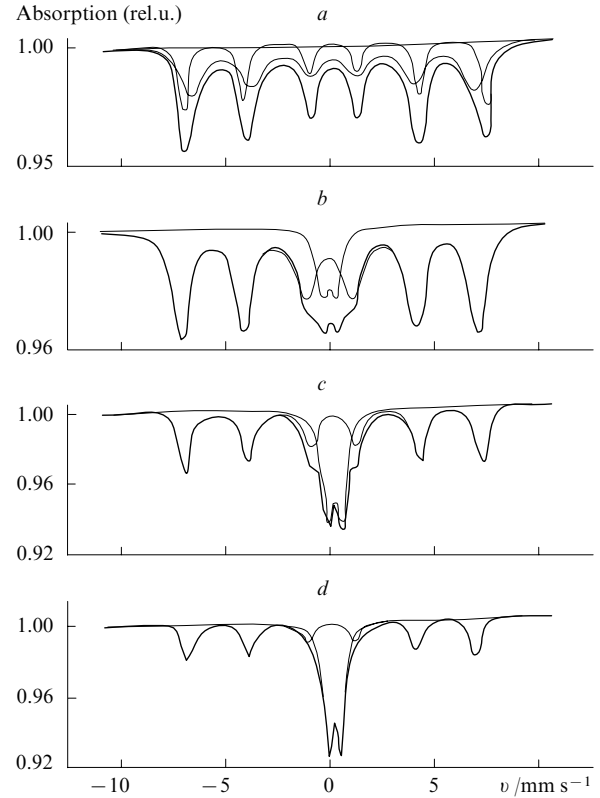


Figure 23. Mössbauer spectra of a nanostructure comprised of oxide iron nanoclusters, formed at iron oxalate decomposition temperature of 265 °C, recorded at 77 (a), 120 (b), 160 (c) and 300 K (d).

stage. The room-temperature Mössbauer spectra of this system correspond to bulk α -Fe₂O₃.

III. Critical characteristics and properties of nanoclusters and nanostructures

1. Thermal properties

a. Thermodynamics of cluster melting

The state of a cluster can be considered using a simple thermodynamic model, which makes it possible to predict a number of unusual properties.^{36, 67, 68} The free energy difference between the liquid and solid states of the cluster is given by

$$\Delta G = 4\pi r^2 \Delta\alpha + \frac{4}{3}\pi r^3 \rho \Delta\mu, \quad (30)$$

where $\Delta\alpha = \alpha_l - \alpha_s$ is the surface energy difference and $\Delta\mu = \mu_l - \mu_s$ is the chemical potential difference between the liquid and solid state of the cluster. Clearly, at melting $\Delta\alpha < 0$ and $\Delta\mu > 0$. The dependence $\Delta G = f(r)$ is shown in Fig. 24.

The critical cluster size corresponding to the solid–liquid transition ($\Delta G = 0$) is determined using the expression

$$r_{cr} = 3 \frac{\Delta\alpha}{\rho \Delta\mu}. \quad (31)$$

At $r < r_{cr}$, the cluster is in the liquid state. From Eqn (31) it follows that the solid–liquid transition state cannot occur for certain matrix atoms (at $\Delta\alpha = 0$), where the cluster does not yet form. At the same time a free cluster should be characterised by the maximum $\Delta\alpha$ value. Any intercluster interactions will cause a reduction of this value and, hence, the critical cluster size, which determines the region of possible fluctuations of the solid and liquid states.

The stability of a cluster can be characterised by the changes in the pressure $\delta P = P_0 - P$ or temperature $\delta T = T_0 - T$, which

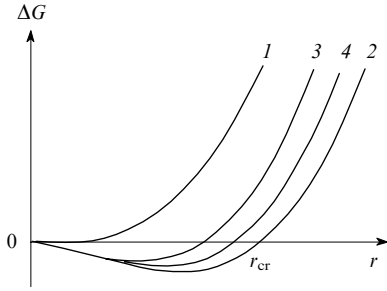


Figure 24. Change in the Gibbs free energy of an ensemble of atoms in a solid (1), isolated cluster (2) and a system of interacting clusters in the solid (3) and liquid (4) state plotted vs. cluster size. Interacting clusters (3) and clusters treated with surfactants (4).

correspond to a given $\Delta\mu = f(p, T)$ value. Due to these changes the phases equilibrate at a specified cluster size (P_0 and T_0 are respectively the pressure in the medium and the melting temperature of bulk material).

Replacing the function $\Delta\mu = f(P, T)$ by its expansion in powers of δp at the point P_0 with allowance for

$$\frac{\partial \mu_l}{\partial P} = V_l,$$

$$\frac{\partial \mu_s}{\partial P} = V_s$$

(V_l and V_s are the molecular volumes of the cluster in the liquid and solid state, respectively), one gets

$$\Delta\mu \approx -(V_l - V_s)\delta P. \quad (32)$$

Using the Clapeyron–Clausius relation

$$\frac{\partial P}{\partial T} = \frac{q}{T_0}(V_l - V_s), \quad (33)$$

where q is the latent heat of phase transition, one can write

$$\Delta\mu \approx -\frac{q\delta T}{T_0}. \quad (34)$$

Substituting Eqn (34) into expression (31), one gets a hyperbolic dependence of the changes in the phase transition temperature on the cluster radius

$$\frac{\delta T}{T_0} \approx -3 \frac{\Delta\alpha}{\rho q r}. \quad (35)$$

The relation (35) shows a decrease in the melting temperature with a decrease in the cluster size. Taking into account the plots presented in Fig. 24, we can suggest that at the specified temperature and pressure in the medium the initially stable cluster structure ($\Delta\mu > 0$) goes to a metastable state at $r < r_{cr}$.

A decrease in the melting temperature (down to room temperature) with a decrease in the cluster size was observed for gold, tin, CdS, etc. nanoclusters.^{69–71} Additionally, an electron microscopy study⁷⁰ of tin films revealed separation of the melting and freezing points of the cluster and the existence of a specific solid–liquid state characterised by enhanced mobility of clusters in the intermediate temperature range.

Specific features of the melting of clusters were studied taking iron oxide nanoclusters as an example. Figure 25 presents the results of a Mössbauer spectroscopy study of iron oxide nanoclusters obtained by solid-phase thermal decomposition of iron oxalate. The temperature dependence of the spectral area obtained for the γ -iron oxide nanocluster system shows a minimum at $T_d \approx 488$ K. The T_d value is related to the average size of the iron oxide cluster, namely, an increase in the cluster size from 1–2 to 6–8 nm causes T_d to increase from 488 to 508 K.

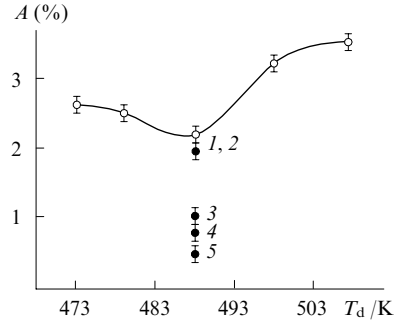


Figure 25. Mössbauer spectral area (A) for a nanosystem comprising iron oxide clusters formed upon decomposition of iron oxalate plotted vs. decomposition temperature T_d .

Open circles denote experimental data obtained in the absence, and closed circles, in the presence of surfactants: ethanol (1), isopropyl alcohol (2), Twin-65 (3), butanol (4) and sodium dodecylsulfate (5).

The right branch of the spectrum shown in Fig. 25 is associated with a decrease in the spectral area (on lowering T_d) and enhancement of atomic mobility in the cluster. It should be noted that the iron oxide spectra show no ‘broad component’ corresponding to the motion of the whole cluster as a result of, e.g., diffusion. The left branch of the $A = f(T_d)$ curve in Fig. 25 is associated with further reduction of T_d and, correspondingly, with a decrease in the cluster size up to breakdown of clusters into individual iron (Fe^{3+}) atoms, dimers and trimers (see Fig. 24, curve 1). Therefore, the minimum in the dependence curve $A = f(T_d)$ at $T_d = 488$ K is probably due to the onset of formation of the iron oxide clusters with reduced melting temperature.

As mentioned above, the state of the cluster surface is governed by the surface energy, and intercluster interactions should cause this parameter to decrease. Intercluster interactions also affect the intercluster atomic dynamics; however, they can weaken under the action of surfactants and the spectral area also considerably decreases upon the action of surfactants. Thus, weakening of intercluster interactions leads to enhancement of the cluster mobility and to a decrease in the melting temperature. Using relation (31), one can estimate the r_{cr} value corresponding to the onset of melting of γ -iron oxide clusters and compare it with the value found from the experimental Mössbauer spectra. With the following values for γ -iron oxide: $\rho = 5.18 \times 10^6 \text{ g m}^{-3}$ (see Ref. 63), $\Delta\alpha \approx 1 \text{ J m}^{-2}$ (see Ref. 62) and $q \approx 10^{-19} \text{ J m}^{-1}$ (see Ref. 63) one gets

$$r = \frac{aT_0}{\delta T}, \quad (36)$$

where $a = 0.1–1.0$ nm. At $T_m = 300$ K, one has $r = 0.1–1.2$ nm, which is in good agreement with the values 1–2 nm determined from the Mössbauer spectra.

Note also that the effect of adsorption-induced decrease in the strength of substances (Rehbinder effect), which manifests itself on the atom-molecular level owing to wetting and deformation of the surface under the action of surfactants, can be explained by the appearance of a specific solid–liquid transition state characterised by enhanced mobility of atoms.

b. Quantum-statistical model for cluster melting

The thermodynamic model for cluster melting is simple, but it provides no information concerning (i) the behaviour of the material the cluster is made of during transition from the solid to the liquid state, (ii) the predicted new solid–liquid state and (iii) the critical cluster size corresponding to the formation of this state.

Now we will consider some characteristics of the solid and liquid states. Unlike a solid, a liquid has a variable shape. The

liquid is inelastic and changes its shape under the action of weak forces. A solid exhibits an elastic response to the action of rather strong forces, but breaks down after an overload. The flow behaviour of the liquid implies the appearance of soft modes of atomic motions; most atomic vibration frequencies are much lower than the characteristic vibration frequencies of the atoms in the crystal lattice of a solid (10^{12} – 10^{13} s $^{-1}$). Applying this concept to clusters, one can expect that for a liquid cluster the density of states corresponds to lower frequencies and to lower frequencies of transitions between the states and shallow potential wells that limit such states. This allows the low-energy modes to execute slow motions that induce rearrangement and isomerisation of the liquid cluster. Yet another group of structural characteristics that differ for solids and liquids includes the angular and radial correlation functions. For solids, these functions show clearly seen peaks corresponding to the nearest and next-nearest neighbours. Liquids are characterised by a diffuse peak corresponding to the nearest neighbours and very weak peaks corresponding to more distant atoms. These criteria are also applicable to clusters when identifying the solid or liquid state. The difference between the solid and liquid states of a cluster can also be characterised by the ease of exchange in an atom or molecule with an identical species at another position of the cluster and, correspondingly, by the time taken for the process. For most materials, clusters are in the solid state at low temperatures and energies or in the liquid state at high temperatures and energies. Clusters can exist in some intermediate state ('slush') that differs from both the solid and liquid states and can be detected and studied in, *e.g.*, computer experiments.

The phase equilibrium in clusters can be studied using the thermodynamic and dynamic approaches, which depends on the characteristic times of computational procedures. In the case of static equilibrium one can employ the thermodynamic approach, namely, consider the change in the Helmholtz free energy (ΔF) of an ensemble of clusters comprising n atoms each,

$$\Delta F = \Delta E - T\Delta S, \quad (37)$$

where ΔE is the change in the internal energy upon the change in the state of the cluster material and the entropy S is calculated as follows:

$$S = kT \ln Z, \quad (38)$$

where

$$Z = \sum g_i \exp \frac{E_i}{kT} \quad (39)$$

is the partial function which sets the distribution over the states of the system and g_i describes the degeneracy of the energy level E_i . Quantum-statistical calculations of the function $Z = f(T)$ have been a subject of numerous studies. Knowing the partial function, one can determine almost all parameters of the equilibrium system with N states at a given temperature T . Since a cluster is characterised by a much smaller number n compared to a bulk solid, it is quite natural to expect that Z is calculable. For instance, knowing the vibrational and rotational energy levels of the cluster and the corresponding degeneracies, one can calculate the free energy of the cluster.

The energy distributions over the states of a solid and a liquid are significantly different. At low temperatures, the density of states for the solid is higher than for the liquid, but the situation reverses at high temperatures. The equilibrium transition from the solid to the liquid state occurs at the temperature T_{eq} . Therefore, at low temperatures the energy change ΔE is governed by the vibrational and rotational energy levels of the solid. As the temperature increases, the entropy factor (disordered motions characteristic of liquids) dominates. The T_{eq} value (or the melting point of the cluster) depends on the model for calculation of the states of the solid and liquid and on the number of states, *i.e.*, on the cluster size. At $T = T_{eq}$, both phases (solid and liquid) coexist

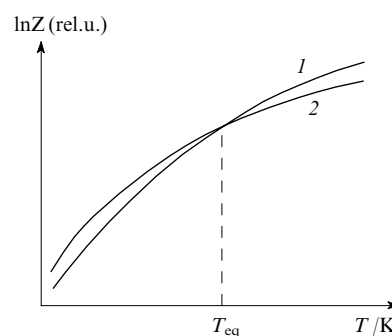


Figure 26. Partial functions (Z) of a solid (1) and liquid (2) cluster plotted vs. temperature.

in the system. The temperature dependence of $\ln Z$ for this model is shown in Fig. 26.

In fact, if we have a model for calculating the energy level and degeneracies, the energy and other thermodynamic parameters can be calculated as certain averaged thermodynamic characteristics that can be more reliable than those determined for individual energy levels and degeneracies.

In addition to the studies of the solid and liquid states of clusters it is of great interest to investigate the transient region and the conditions for stability of these two forms. Here, one should calculate their free energies and find minima corresponding to stable states. The free energy minimum is determined using the non-rigidity parameter of the cluster. The non-rigidity parameter (γ) can be determined, *e.g.*, phenomenologically by comparing two specified spectroscopic frequencies or on the microscopic level by establishing the degree of disorder and the density of defects. Both methods should give correct γ values for the limiting cases of rigid solid ($\gamma = 0$) and non-rigid liquid-like ($\gamma = 1$) states.⁷² After introduction of this new parameter of the energy of state the partial functions and the free energies become some functions of γ .

Calculations for the solid state can be carried out using the Einstein or Debye models or the harmonic oscillator model, which lead to qualitatively correct description of the equilibrium state of the cluster. Liquid state calculations are performed in the framework of the Gartenhaus–Schwartz model,⁷² which was initially proposed for the atomic nucleus. This pair interaction model applied to an n -atom cluster gives equidistant energy levels with a degree of degeneracy of $(3n-3)$. Analysis of the results obtained using this model showed that the density of cluster states changes differently as the temperature and energy increase; namely, the density of the liquid cluster states increases. Changes in the free energy $F(T, \gamma)$ with an increase in temperature should be studied taking into account the following: only low-lying levels of the solid cluster are populated at low temperatures; the free energy should be a monotonically increasing function of γ ; and the free energy of the solid state is lower than that of the liquid state. However, if the temperature increases, the free energy near the non-rigid limit of variation of the parameter γ decreases due to a greater contribution of the $T\Delta S$ term in the expression for the free energy (37) owing to a large number of the available non-rigid cluster forms. In this case near the non-rigid limit the changes in γ at certain temperature are given by

$$\frac{\partial F(T, \gamma)}{\partial \gamma} = 0.$$

This temperature was termed the freezing temperature (T_f). The solid state is stable only at temperatures below T_f . At temperatures above the freezing point, the function $F(T, \gamma)$ has two minima, one near $\gamma = 0$ and the other near $\gamma = 1$. Each minimum corresponds to a locally stable form, which can be compared with, *e.g.*, a stereoisomer. The system will contain two forms in the equilibrium, a solid and a liquid, with a ratio of

$$\frac{[\text{solid form}]}{[\text{liquid form}]} = K_{\text{eq}} = \exp\left(-\frac{\Delta F}{kT}\right), \quad (40)$$

where $\Delta F = F_{\text{liq}} - F_{\text{sol}}$.

These two forms exist in a dynamic equilibrium at which the cluster spends some time in the solid or in the liquid state. At the equilibrium temperature T_{eq} , one has $\Delta F = 0$ and the ratio (40) equals unity. At temperatures between T_f and T_{eq} the solid phase dominates and at temperatures above T_{eq} , the liquid state is preferred. As the temperature increases, the energy of the system decreases until the temperature reaches T_m . Above T_m , there exists only the liquid state of the cluster and the dependence $F(T, \gamma)$ is a monotonic function which decreases as γ increases.

The free energy is plotted vs. γ at different temperatures including T_f and T_m in Fig. 27. With these plots, one can imagine the cases where a cluster has a particular freezing temperature (only solid forms are stable below it) and a particular melting temperature (only liquid forms are stable above it). It should be noted that the melting and freezing temperatures of the cluster are different.

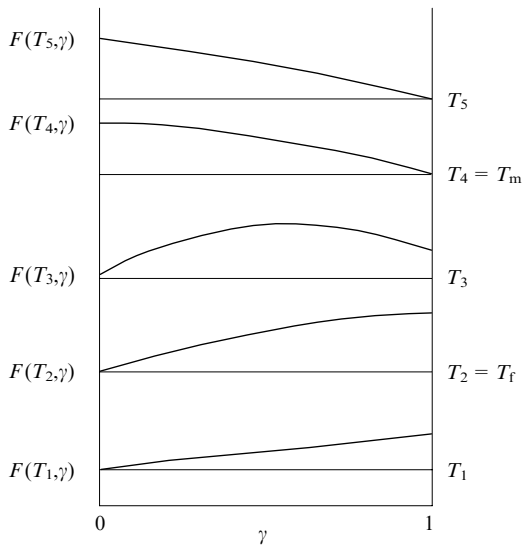


Figure 27. Free energy plotted vs. non-rigidity parameter γ for several temperatures.

In principle, the description given above is suitable for those clusters which can have well-distinguishable solid and liquid forms and spend in both states a considerable time sufficient to detect them. Actually, only a few clusters meet these conditions.⁷³ This was shown to be true for the simplest noble gas clusters Ar_7 , Ar_{13} , Ar_{15} and Ar_{19} . Other clusters, namely, Ar_8 and Ar_{14} are characterised by the potential energy surfaces having the shape of a potential well with large 'clapped-out' stair-steps which preclude the formation of stable solid or liquid states. Yet another type of clusters, Ar_{17} , rapidly fluctuates between the solid and the liquid states. Here, it is impossible to discuss the existence of the solid and liquid phases because only the 'slush' state is observed.

It is also interesting to consider the temporal aspect of the existence of the solid and liquid phases in clusters and transitions between them. How much time does it take to detect a phase? Of course, the question cannot be answered within the framework of the thermodynamic approach; one has to re-consider the dynamics of the process. All characteristics should be determined by the time necessary for equilibration of the process (relaxation time) and the measurement time. If the observation times are longer than the relaxation time, it is possible to obtain a time-averaged picture of individual phases; otherwise, pictures characteristic of a given temperature with variable phase ratio are obtained. Experimental data on the melting of clusters and existence of the

solid-liquid state corresponded to long observation times ($> 10^{-7}$ s). Similar data were obtained by measuring the spectral linewidths in the optical range. The lines of the probe molecules (e.g., carbazole) attached to argon clusters broadened and shifted to lower frequencies, which was interpreted as melting of argon clusters.⁷⁴

2. Defects and stresses in nanostructures

The appearance of numerous dislocations, defects and intercluster stresses in nanostructures is due to the presence of well-developed interfaces. The density of the interface boundaries (and dislocations associated with them) can be rather high, e.g., $\sim 10^{19} \text{ cm}^{-3}$ for a nanostructure comprised of 7 nm-clusters. Intercluster interactions or contacts between the cluster and its neighbours produce stresses and an excess pressure at the cluster boundaries. Additionally, assuming that the concentration of dislocations in a cluster is determined by the ratio of the cluster surface area to the cluster volume, the excess energy density of the cluster (ε_d) is³⁶

$$\varepsilon_d = \frac{Gb^2}{4\pi(1-\nu)} \ln \frac{R}{R_0} \frac{1}{r}, \quad (41)$$

where G is the shear modulus; b is the Burgers vector characterising the magnitude of the shift of the atoms of an edge dislocations ($b = a/\sqrt{2}$, a is the lattice constant); ν is the Poisson coefficient (usually, 0.3); R is the maximum distance at which the influence of dislocations is still retained; R_0 is the minimum dislocation size; and r is the cluster size.

Thus, in this approximation the excess energy density decreases as the cluster size increases and approaches zero for bulk material. It should be noted that the applicability of this approach to small-size nanoclusters is limited by the thickness of the surface layer of the cluster (which is equal to, e.g., the lattice constant a), i.e., Eqn (41) can be used only for calculating the excess energy of clusters at $r > a$.

When studying the influence of defects and dislocations on the properties of nanostructures, it is interesting to consider the relation between the size of the nanosystem and the density of defects in it. Here, it is convenient to use the thermodynamic approach, which takes into account the chemical potential and the excess energy of the cluster surface. The excess energy gives rise to excess pressure, which equals 1 GPa for 1 nm-clusters. The nanocluster is considered as being surrounded by atoms from the atomic structure and defects (impurity atoms, vacancies, dislocations). It is assumed that the key source of defects is the cluster surface and that defects can be redistributed between atoms inside the cluster, at interfaces and in the intercluster medium. The chemical potential of defects confined within the cluster can be written as

$$\mu_v = \mu_v^0(P) + kT \ln c_v, \quad (42)$$

where P and c_v are respectively the pressure and the defect concentration inside the cluster and μ_v^0 is the standard chemical potential. The chemical potential of the intercluster medium is given by

$$\mu_s = \mu_s^0(P_0) + kT \ln c_s, \quad (43)$$

where P_0 , c_s are respectively the pressure and the defect concentration in the intercluster medium and μ_s^0 is the standard chemical potential. At equilibrium

$$\mu_v = \mu_s, \quad (44)$$

it is assumed that the total number of defects in the nanostructure (c_0) is constant; therefore, the concentrations c_s and c_v are related to each other as follows:

$$c_s = c_0 - \frac{1}{q} c_v, \quad (45)$$

where $q(r) = (1 + R/r)^3 - 1$ (R is the thickness of a layer of the intercluster medium).

The pressure drop between the inside and outside of the cluster shifts the equilibrium in the nanosystem and one has

$$\mu_v^0(\delta P) = \mu_v^0(0) + \delta P v, \quad (46)$$

where v is the defect volume, $\delta P = P - P_0 = 2\alpha/r$ (α is the average surface tension); then one gets

$$\frac{c_v}{c_0} = \left\{ \frac{1}{q(r)} + \exp \left[\frac{\Delta\mu^0(P_0) + 2\alpha v/r}{kT} \right] \right\}^{-1}. \quad (47)$$

The dependence of c_v/c_0 on the cluster size in the r/a units (a is the lattice constant) is shown in Fig. 28. Calculations were carried out assuming $a = 2 \times 10^{-10}$ m for the metal and 5×10^{-10} m for the oxide, $\alpha = 1$ N m, the defect volume $v \sim a^3$ and $\Delta\mu^0 = 0$. The maximum defect concentrations were found for the cluster sizes ranging from 10 to 50 nm; therefore, such clusters have the highest excess energy. The model considered can be explained with ease as follows. In ~ 100 nm-clusters, the defect concentration is low due to the small specific surface area of these species. If the cluster size is < 10 nm, the specific surface area is large enough, but the surface pressure displaces defects from cluster volume; therefore, small clusters are defect-free objects, which was confirmed experimentally.

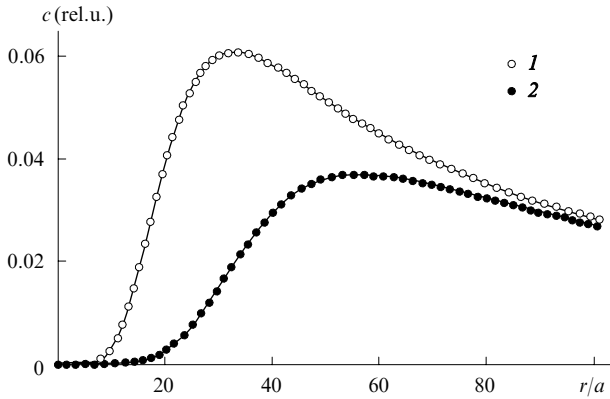


Figure 28. Defect concentration in cluster plotted vs. relative cluster radius for oxide (1) and metal (2) clusters.⁷⁵

The presence of defects in nanostructures and their relation to structural transformations in nanosystems can be determined by both macroscopic methods (by, *e.g.*, measuring the diffusion rate of a tracer through a macrolayer of a chemical substance or the total magnetic susceptibility of the nanosystem) and microscopic techniques (by, *e.g.*, positron annihilation or Mössbauer spectroscopy).^{76, 77}

3. Mechanical properties of nanoclusters and nanostructures

Among the mechanical properties of nanoclusters and nanostructures, high hardness and superplasticity should be pointed out. The hardness of a material characterises the resistance to plastic deformation and is measured by indenting with a harder material. The Vickers hardness (H_V), which is used in the text below for characterisation of nanomaterials, is measured from the depth of an indentation on the surface after unloading, being mainly determined by the yield point of the material σ . The grain size of a material is an important characteristic of the microhardness, which obeys the Hall–Petch law,^{78, 79}

$$\sigma = \sigma_0 + k d^{-1/2}, \quad (48)$$

where σ_0 is the internal stress, which precludes the motion of a dislocation in bulk material and k is a constant. At temperatures much lower than the melting point of the material, the Vickers hardness is proportional to the yield point. Then one has

$$H_V \approx H_0 + k d^{-1/2}, \quad (49)$$

where H_0 and k are constants.

If deformation occurs by diffusive slip, at temperatures that are much lower than the melting temperature the equation for the deformation rate has the form

$$\frac{d\varepsilon}{dt} = \frac{b\sigma v R D}{k_B T d^3}, \quad (50)$$

where b is the coefficient of proportionality, σ is the stress applied, v is the atomic volume, R is the grain boundary thickness and D is the grain boundary diffusion coefficient.⁸⁰

By extending the action range of Eqns (48)–(50) to nanostructures acting as grains, one can assume that the mechanical properties of nanostructures should be strongly different from those of bulk materials. A decrease in the cluster size should first of all affect the hardness of the nanostructure, which should also increase. At the same time of great importance for nanosized systems is the diffusive slip of nanocrystallites; intensification of this type of motion causes a considerable increase in the deformation rate. The stress–strain properties of a nanomaterial are determined by the relation between the yield point and the deformation rate; therefore, there should exist a critical cluster size corresponding to the maximum hardness of the nanomaterial. Yet another factor favouring an increase in the deformation rate is an increase in the diffusion coefficient with a decrease in the cluster size.

A nanostructure can be several times harder than coarse-grain materials. For instance, the hardness of metallic Ag, Cu, Pd, Se, Fe and Ni increased as the cluster size decreased to 4–6 nm according to the Hall–Petch law. However, if the nanocluster size is increased by annealing the same sample, the Hall–Petch law holds only for $d > 12–20$ nm.⁸¹

Superplasticity studies of metal oxides and ceramics are of great interest. Using the property of superplasticity, one can fabricate ceramic items of complex shape (*e.g.*, with internal cavities and variable curvature) with high accuracy. The superplasticity arises upon nanostructuring of materials; additionally, it increases if nanoparticles are dispersed within amorphous phase and the nanocrystalline grain boundaries are disoriented. Ceramics becomes superplastic at a grain size of less than 1 μm , and the grain size being retained with an increase in the temperature.⁸²

High strength and superplasticity can be explained using the ‘extremal’ dependence of the defect concentration and, hence, the excess energy on the cluster size (see Fig. 28). Indeed, nanosystems composed of small clusters (size less than 10 nm, ignoring diffusion mobility) contain a low proportion of defects and dislocations and exhibit record hardness. At the same time, nanosystems built of clusters of intermediate size ($10 < d < 100$ nm) have the maximum defect concentrations, which predetermines the record plasticities. Summing up, superhard materials should be fabricated using nanosystems containing nanoclusters with $d < 10$ nm, whereas superplastic materials should be prepared involving nanosystems comprising nanoclusters with $10 < d < 100$ nm.

4. Electronic-optical properties

a. The conductivity of nanostructures

Transition from a bulk material to a nanomaterial involves separation of electron energy bands into subbands and individual electron energy levels. Transition from individual atoms and molecules to nanoclusters is accompanied by broadening of energy levels and formation of energy band structure. The appearance of discrete electron energy levels is due to limitation of the mean free path of electrons and characterises the quantum confinement effects in nanoclusters. As the cluster size decreases, the quantum confinement effects cause a decrease in the conductivity and the appearance of a Coulomb barrier to one-electron

transitions between the energy levels separated by kT and higher energies. This barrier is determined by the energy of electrostatic interaction of the tip of a tunnelling microscope used for studying the one-electron conductivity of clusters,

$$E = \frac{e^2}{2C}, \quad (51)$$

where $C \sim r$ is capacitance of the cluster–tip system. This technique was employed to obtain stepwise I – V curves for clusters of size of a few nanometres. Here, the number and height of steps increase as the cluster size and temperature decrease. Starting from certain critical size, reduction of the cluster size is accompanied by the loss of metallic properties and transition to dielectric molecular state.

One-electron transitions between clusters can be induced by, *e.g.*, thermal excitation. Using parameters of such transitions, it is possible to estimate the critical cluster size. Namely, assuming that $C = d_{cr}$ in relation (51) and the electronic transition energy $E_e \geq kT$, the critical cluster size equals ~ 2 – 3 nm at 300 K and ~ 200 nm at 4.2 K. The estimate of the critical cluster size at low temperatures (17 nm) is nearly an order of magnitude larger than the size of a colloidal cluster. This is due to the appearance of electron energy bands in these clusters and inapplicability of the one-electron transition model. This estimate also much exceeds the results obtained at high temperatures for mercury.

Weakening of the conducting properties is also due to the scattering of conduction electrons by the cluster surface, which is enhanced with a decrease in the cluster size and thus hampers separation of the contribution of one-electron conductivity and determination of the corresponding critical cluster size. The formation of nanostructures from nanoclusters is accompanied by retention of the factors favouring a decrease in the number of charge carriers and their scattering by the intercluster boundaries. Additionally, new factors appear, which can induce the tunnelling electron transitions between adjacent nanoclusters, appearance of charges, *etc.* Nanomaterials prepared by compaction of metal nanoclusters exhibit a noticeable decrease in conductivity compared to that of bulk materials. However, this method of fabrication of nanostructured conducting materials offers no prospects for the design of nanomaterials with controllable electrophysical properties. This requires the use of solid state chemistry and cluster chemistry methods.

The conductivity of three-, two- and one-dimensional nanostructures. Promising methods of application of nanocluster structures as conducting materials involve the assembly of different-dimension nanostructures with molecularly controlled conductivities.

Organised conducting or semiconducting structures of atomic or molecular crystals are well known. However, it is difficult to force nanoclusters to form nanocrystals under normal conditions. In the text above we have considered the possibility of organisation of (i) silver, silver sulfide, *etc.* nanocrystals obtained by reverse micellar technique or (ii) ordered nanostructures based on semiconductor nano-islands or (iii) nanowires on epitaxial surface. An efficient method of fabrication of organised three-dimensional conducting cluster structures is provided by the crystallisation of ligand-stabilised semiconductor chalcogenide clusters of particular size. An array of clusters separated by the ligand shells can be schematically represented by a sequence of potential wells containing ground-state and excited-state electron energy levels. In the ground state the valence electrons are localised. In the excited state, tunnelling through dielectric medium is possible. This shows that the conductivity can be controlled by varying the intercluster distance using different ligands (such ligands are called spacers).

As an example, we will consider the change in the conductivity (the Coulomb barrier) for Au_{55} -based molecular cluster crystals with spacers of different length (Fig. 29).⁸³ The crystals studied showed a noticeable decrease in the conductivity (increase in the Coulomb barrier) with elongation of the spacer. These data

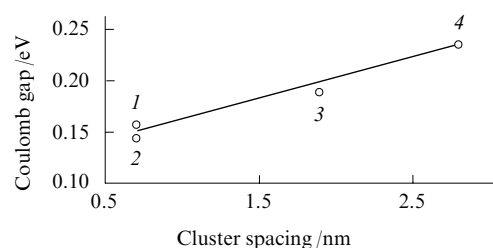
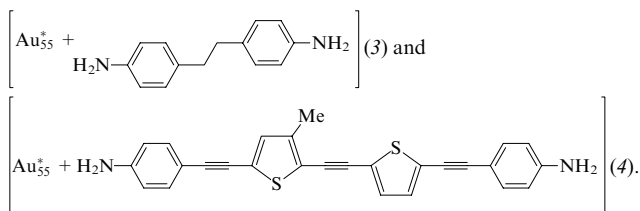


Figure 29. Correlation between cluster distance and Coulomb gap.⁸³ Open circles correspond to clusters (1, 2) and systems (3, 4):⁸³ $\text{Au}_{55}(\text{PPh}_3)_{12}\text{Cl}_6(\text{Au}_{55})$ (1), $\text{Au}_{55}(\text{Ph}_2\text{PC}_6\text{H}_4\text{SO}_3\text{Na} \cdot \text{H}_2\text{O})_{12}\text{Cl}_6(\text{Au}_{55}^*)$ (2),



confirm the efficiency of the concept of directed change in the conductivity of a molecular cluster crystal by varying the spacer.

One-dimensional cluster nanostructures can play the role of quantum wires; a feasible example is provided by carbon nanotubes. A method of fabrication of quantum wires based on nanoporous anodised alumina (the preparation of the material was considered above) also seems to be quite promising. Technologically, both the pore size and the pore length can be controlled on the nanometre length scale.⁸⁴ Filling pores with clusters provides a nanowire distribution density of 10^9 – 10^{10} per cm^2 and separation by dielectric alumina matrix. The main problem in fabricating such nanowires, that is, breakdown during the growth, can be solved by soaking the membrane with clusters *in vacuo* or using electrophoresis. A drawback of the vacuum technique consists in evaporation of the solution containing clusters, which produces voids in the membrane channels. In the case of electrophoresis one side of the membrane contacts a metal, *e.g.*, gold or aluminium, thus acting as a cathode to which clusters move. This allows the whole channel to be filled, but breaks are also possible due to large membrane thickness. For instance, a membrane 10 μm thick with channels 10 μm long should contain at most ~ 4000 clusters of diameter 2.5 nm per channel, but this is difficult to reach. At the same time a membrane a few micrometres thick is too brittle. Exposure of a thick membrane to ion irradiation makes it thinner (up to 100 nm) and enables fabrication of continuous nanowires.⁸⁵

b. Optical properties

Metallic nanoclusters and nanostructures. The optical properties of metal nanoclusters are due to plasmon vibrations of electrons in metals. The absorption spectra of small clusters exhibit an intense broad band that is absent in the spectra of bulk metals. This band is due to co-operative excitation of conduction electrons. Absorption in the visible region is responsible for, *e.g.*, unique colour grade of dilute colloidal sols of noble, alkali and rare-earth metals.

The nature of the plasmon peak is as follows. The electric field of incident radiation displaces the conduction electrons in the cluster relative to the charged core. The displacement is co-operative in character and all electrons move with the same phase. As a result of electron displacement, a force arises, which tends to return electrons to the equilibrium positions. As for typical oscillator, this force is proportional to the displacement; therefore, one can consider the eigenfrequency of collective electronic vibrations in the cluster. When the eigenfrequency of electrons becomes equal to the frequency of the external field, a resonance effect should be observed. Quantum mechanics treats

the collective motion of electrons in terms of excitation quanta called plasmons characterised by the energy $\hbar\omega$ and the resonance frequency ω_0 corresponding to the eigenfrequency of collective electronic vibrations (usually, 10^{14} s^{-1}).

The optical properties of colloid clusters are correctly described in the framework of the classical Mie theory,^{86,87} which considers the optical properties of spherical metallic particles in a dielectric matrix. Using this theory, one can describe the optical resonance due to collective excitation of electron plasma. If the cluster size is much less than the emission wavelength (λ), the absorption line in the vicinity of resonance has a Lorentzian shape and is characterised by the position of the resonance maximum, $\hbar\omega_0$, the width Γ and the absorption section

$$\sigma = \frac{n e^2}{m c \Gamma \epsilon_0} \left[\frac{\omega^2}{\omega^2 - \omega_0^2} + (\omega \Gamma)^2 \right], \quad (52)$$

where n is the electron distribution density, ϵ_0 is the dielectric constant, m_e is the effective mass of the conduction electron and c is the speed of light.

In case of spherical monovalent metal particles the equation for the resonance frequency has the form

$$\omega_0^2 = \frac{e^2}{4\pi\epsilon_0 r_s^3}, \quad (53)$$

where r_s is the Wigner–Seitz radius.

The corresponding plasmon frequency for bulk metal is given by

$$\omega_p^2 = \frac{e^2}{4\pi\epsilon_0 v}, \quad (54)$$

where $v = (4/3)\pi r_s^3$. Then the resonance frequency of a metallic sphere should be

$$\omega_0^2 = \frac{\omega_p^2}{\sqrt{3}}. \quad (55)$$

The resonance linewidth is

$$\Gamma_{r0} = 2\epsilon_2(\omega) \left[\left(\frac{\partial \epsilon_1}{\partial \omega} \right)^2 + \left(\frac{\partial \epsilon_2}{\partial \omega} \right)^2 \right]^{-1/2}, \quad (56)$$

where $\epsilon_1(\omega)$ and $\epsilon_2(\omega)$ are the real and imaginary parts of the dielectric permittivity of the cluster, respectively.

It should be noted that the Mie theory predicts no size effect. Nevertheless, the results of numerous measurements show that ω_0 and Γ depend on the cluster size. For small clusters, an important role should be played by collisions between electrons and the cluster surface (mean free path of electrons is $\sim 20 \text{ nm}$). In this case one has

$$\Gamma_r = \Gamma_{r0} + \frac{2\omega_0^2}{\omega^3} v_F \left[\left(\frac{\partial \epsilon_1}{\partial \omega} \right)^2 + \left(\frac{\partial \epsilon_2}{\partial \omega} \right)^2 \right]^{-1/2} \frac{A}{r}, \quad (57)$$

where v_F is the velocity of an electron on the Fermi surface and A is a constant. Clearly, this relation is invalid for small cluster sizes, *i.e.*, at $r \rightarrow 0$. Indeed, the metallic state typical of bulk metal and large clusters will disappear upon localisation of electrons on particular atomic levels and upon transition from the conduction and valence bands to individual localised energy levels. In this case the concept of plasmon resonance should be replaced by the resonant electron absorption between certain electron energy levels. Following this (classical) treatment procedure, it is impossible to obtain a critical cluster size, but this parameter can be determined from experimental data.

Good agreement between the calculated and experimental resonance frequencies and spectral linewidths was reported.⁸⁸ A relatively narrow line of silver clusters is due to a simpler structure of the Ag conduction band compared to the Au and Cu conduction bands characterised by a broad interband transition above 2 eV for bulk metal. Narrow plasmon resonance lines of

silver clusters suggest that they can be used in optical materials for characterisation of the interaction between the clusters and the environment and for studying the surface chemistry effects. Note that narrow spectral lines similar to the silver cluster lines were observed for the plasmon resonances of alkali metals, which was associated with the shell-type cluster structure ('jellium model') and with the fact that only s-electrons are involved in resonance (as in case of silver). However, the alkali metal clusters are extremely reactive and seem to be inappropriate for fabricating optical nanomaterials.

Figure 30 illustrates the size effects for silver clusters in argon matrix. Here, it is possible to determine the critical size for the onset of plasmon vibrations.

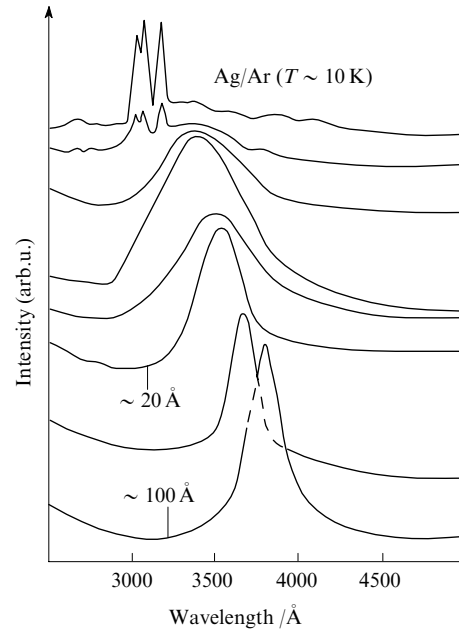


Figure 30. Absorption spectra of surface plasmons in silver clusters in argon matrix. The cluster size decreases upward.⁸⁸

As the cluster size decreases, the resonance frequency experiences a clearly seen shift towards the short-wavelength region ('blue' shift) up to the appearance of lines corresponding to individual monomers, dimers, trimers, *etc.* and the spectral lines are broadened. The following empirical dependences for the resonance energy and the line half-width were obtained based on the analysis of experimental data:

$$\hbar\omega = 3.21 + 0.58 \frac{1}{d}, \quad (58)$$

$$\Gamma = 0.04 + 0.59 \frac{1}{d}, \quad (59)$$

where d is the average cluster diameter (in nanometres); here $\hbar\omega$ and Γ are given in electronvolts.

Comparison of experimental spectra showed that if the cluster size is about 1 nm and the number of silver atoms in the cluster is at most ten, a number of resonance lines is observed. The critical size of silver clusters for plasmon resonance was estimated from the characteristics of these lines at $\sim 1 \text{ nm}$.

Semiconductor nanostructures and nanodevices. Semiconductor clusters also exhibit noticeable size effects, namely, a shift of the absorption frequency of optical photons and an increase in the oscillator strength, which are already used in various nanomaterials and nanodevices, *e.g.*, light-emitting diodes or tunable lasers. As the cluster size decreases, the electron excitation bands are shifted to the high-energy region and the oscillator strength (absorption intensity) is concentrated on a few transitions. These

changes associated with the change in the character of transitions between the valence band and the conduction band for bulk material give rise to a line spectrum of the cluster. The transition energy is given by

$$E \approx \frac{1}{r^2},$$

where r is the cluster radius. According to this expression, the transition energy increases as the cluster size decreases. This expression can be derived from the uncertainty relation

$$\Delta p \Delta x \geq \hbar$$

(p is the momentum and x is the coordinate) assuming $\Delta x = r_{\text{cr}}$.

For semiconductors, the absorption and emission of energy are related to the excitation of an electron and to the formation and decomposition of an exciton (hydrogen-like bound state of a conduction electron and a positively charged hole). The equation for the energy of exciton excitation has the form

$$E_n = \frac{\hbar^2 n^2}{3r^2 m_{\text{ef}}}, \quad (60)$$

where n is an integer and m_{ef} is the effective mass of the exciton.

The dependence of the absorption coefficient of CdS colloid clusters of size from 6.4 to 48 nm on the wavelength of incident radiation is shown in Fig. 31. The change in the absorption or luminescence wavelength can be due to the change in the inter-cluster interactions,⁸⁹ photochromic and electrochromic effects. The dependence of the emission wavelength on the cluster size can be employed in, *e.g.*, light-emitting diodes or tunable lasers.

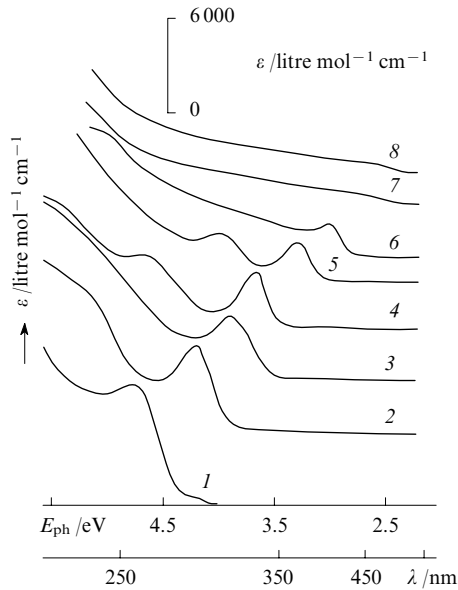


Figure 31. Optical absorption coefficients of CdS clusters of different size plotted vs. photon energy.⁸⁹ Cluster size/nm: 6.4 (1), 7.2 (2), 8.0 (3), 9.3 (4), 11.6 (5), 19.4 (6), 28.0 (7) and 48.0 (8).

As an example, we will consider CdSe-based light-emitting diodes with tunable colour of the emission.⁹⁰ The light-emitting cell has the following structure. CdSe nanoclusters were distributed within a thin surface layer of a luminescent polymer (poly-*p*-phenylenevinylene), the polymer was synthesised on ITO substrate (hole conductor). CdSe nanoclusters were coated with a magnesium/aluminium film for injection of electrons into the CdSe nanoclusters. Applying a voltage to this system causes electroluminescence. The wavelength of emission can be varied by changing the cluster size.

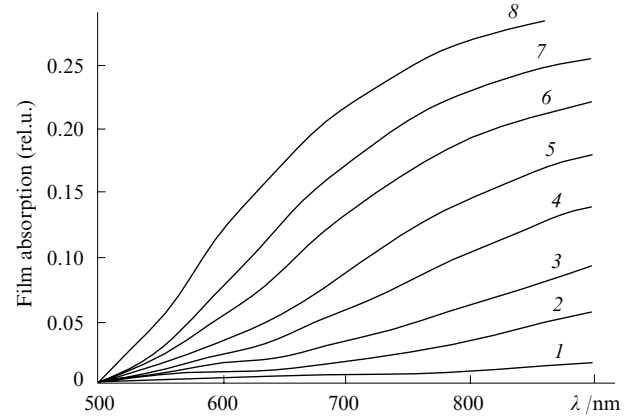


Figure 32. Electrochromic effect in nanostructured WO₃ at different voltage applied: 0 (1), -0.2 (2), -0.3 (3), -0.4 (4), -0.5 (5), -0.6 (6), -0.7 (7) and -0.8 V (8).⁹¹

Nanostructured tungsten oxide WO₃ as well as TiO₂/WO₃, WO₃/V₂O₅ and WO₃/MoO₃ compositions also possess electrochromic properties.⁹¹ The light absorption in tungsten oxide films at different voltages is shown in Fig. 32. At positive potentials (0 V or higher), no absorption occurs, but an increase in the negative potential causes an increase in the IR absorption. At positive potentials, the films are blue, whereas at negative potentials (starting with -1.2 V) they turn brown.⁹¹

Yet another example is as follows. Using nanoclusters (quantum dots), it is possible to fabricate tunable lasers in which the wavelength of emission is varied by changing the nanocluster size. This requires fabrication of ordered nanostructures from clusters with narrow size distribution, dispersed in semiconductor solid solutions. Semiconductors can initiate population of higher electron energy states by injecting electrons and holes into nanoclusters. Transition of nanoclusters to the lowest energy state as a result of relaxation should cause emission of photons with the same wavelength, which can be focussed to produce a coherent laser beam. A scheme of a laser based on this principle is shown in Fig. 33.

The use of nanoclusters in optical devices requires meeting certain conditions related to the cluster size. The minimum critical size of a nanocluster is determined by the condition for the presence of at least one electron energy level and is characterised

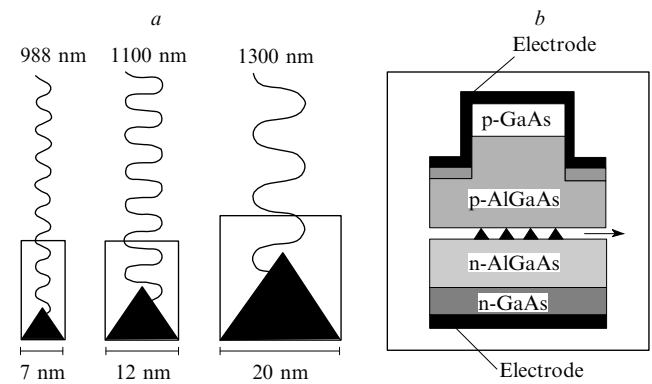


Figure 33. Scheme of laser based on InAs nanoclusters.

Change in photon wavelength with a change in the nanocluster size (a) and scheme of a device including InAs nanoclusters (triangles), a medium consisting of an electron injector n-AlGaAs/n-GaAs (-), hole injector p-AlGaAs/p-GaAs (+) and electrodes (b); an arrow shows the output of light emission.

by an energy difference ΔE_c in the conduction band, corresponding to emission in the visible region. For a rectangular potential well, the electron level exists if ΔE_c exceeds the following value

$$\Delta E_c^0 = \frac{\hbar^2}{2m_c^*} \left(\frac{\pi}{D_{\min}} \right)^2 \equiv \Delta E_1, \quad (61)$$

where m_c^* is the effective mass of electron and ΔE_1 is the energy of the first level in the rectangular potential well of width D . Assuming $\Delta E_c = 0.3$ eV for related semiconductors, the nanocluster diameter should be at least 4 nm.

The maximum critical size of a nanocluster is determined taking into account the fact that the energy difference between the cluster levels becomes comparable with the thermal energy, which causes an increase in the population of higher levels

$$kT \leq E_2 - E_1, \quad (62)$$

where E_2 and E_1 are the energies of the first and second energy levels related to the size quantisation of the nanocluster. In practice, it is sufficient that

$$kT \leq E_1. \quad (63)$$

The maximum cluster sizes determined from this condition for various GaAs and InAs compositions lie between 12 and 20 nm.

Porous silicon. The properties of porous silicon differ from those of crystalline silicon. These are, *e.g.*, unusual chemical properties of the surface, biocompatibility and optical properties related to the quantum confinement effects.⁹²

Porous silicon is obtained by etching the surface of crystalline silicon. The material consists of bent silicon wires of nanometre sizes. Formally, radiative transitions between the valence band and the conduction band of crystalline silicon are symmetry forbidden. Nevertheless, transitions do occur, but they are photon assisted and therefore the rate of radiative transitions is low. Because of this, silicon is not used for generation of optical signals. Porous silicon exhibits intense photoluminescence, which was initially associated with possible violation of selection rules in the nanosystem without translational symmetry. The quantum confinement effects do play the key role in the mechanism of onset of photoluminescence upon a change in the intensity ratio of radiative and nonradiative transitions. The intensity of radiative transitions somewhat increases, but the intensity of nonradiative transitions mainly decreases; in particular, the probability of three-body Auger processes associated with electron emission after absorption of light dramatically decreases compared to crystalline silicon.

Specific optical properties of porous silicon can be used for fabrication of optical sensors for, *e.g.*, detecting changes in the reflection coefficients upon adsorption of various molecules. For instance, by measuring the changes in the wavelength with a Fabry–Perot interferometer it is possible to detect small amounts of substances in air at the porous silicon–bulk silicon interface after diffusion of gas through a membrane (Fig. 34). The radiation reflected from the surface of porous silicon and the porous silicon–bulk silicon interface forms an interference spectrum. Adsorption of various molecules on the silicon membrane causes the interference fringes to shift. The magnitude of the shift can be measured in some way. The results of a sorption study of air containing 1.7% of ethanol at different thickness of porous silicon layer are shown in Fig. 35.⁹³

The lowest ethanol concentration that can be determined by this sensor was 250 ppm. It is important that such devices demonstrate good reproducibility of results and can be efficiently reused and that the parameters of porous silicon can be varied over a broad range by etching, thus allowing various gas components to be detected and studied. Additionally, the interference sensor permits temporal separation of binary mixtures (*e.g.*, ethanol and acetone) in air, because the mixture components have different reflection coefficients, which depend on the diffusion and adsorption rates. This is to some extent similar to gas

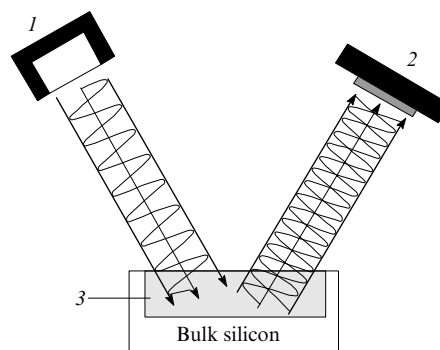


Figure 34. Scheme of a sensor involving an interferometer based porous silicon.⁹³

Incident radiation (1), detector (2) and porous silicon (2).

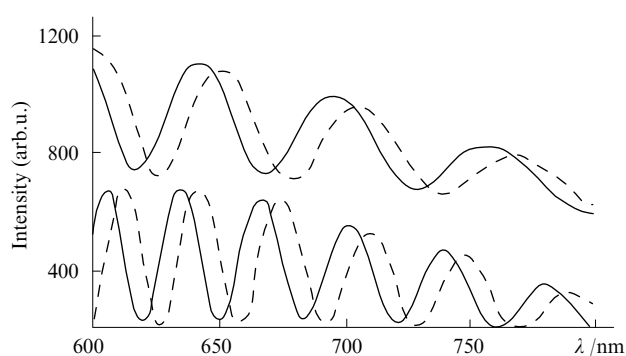


Figure 35. Reflectance spectra of porous silicon samples of different thickness before (solid line) and after (dashed line) sorption of ethanol (1.7%)–air mixture.⁹³

chromatography, however the interference sensor offers the advantage consisting in combining separation and detection.

Yet another original field of application of porous silicon consists in initiation of a local explosion in a pore.⁹⁴ The effect is probably due to the hydrogenated surface of porous silicon and to the fact that the reaction was carried out in a nanoreactor, which accelerates the process. For instance, detonation of freshly prepared porous silicon soaked with aqueous $Gd(NO_3)_3$ solution can be achieved by using a mechanical or chemical ignition system. The colour temperature of the microexplosion was estimated at 2000 K, which makes it possible to carry out a microscopic analysis of metals based on their emission spectra. It is possible to initiate microexplosions of porous silicon after condensation of oxygen in a pore. This is achieved by exposure to UV light or by simply scratching.⁹⁵ The power of a microexplosion is 12 kJ g^{-1} and the energy released is 4.2 kJ g^{-1} . In addition to atomic emission spectroscopy and elemental analysis the microexplosions can be used in microelectromechanical systems, as energy sources for electronic systems and in self-destroying computer security networks.

Photonic crystals. Photonic crystals are formed from dielectric or semiconductor particles of size comparable with the wavelength of a photon (hundreds of nanometres for the visible region). Therefore, in this case one deals with the diffraction processes and conditions similar to those for scattering of X-rays by the atomic crystal lattice. This in turn causes manifestation of coherent effects in the scattering and absorption of emitted radiation. These effects are rather sensitive to the energy and direction of propagation of photons. For instance, photonic crystals have a periodically varied reflection coefficient, which makes it possible to change the optical properties of materials. One-dimensional structures are used as interference filters; how-

ever, two- and three-dimensional crystals are of greater interest. The dispersion curves obtained for photon scattering by two-dimensional phononic crystals assembled from nanocylinders are similar to the electron dispersion curves. By analogy with such notions as electron valence, forbidden and band conductivity, the dielectric band, photonic gap and air gap were introduced.⁹⁶ Removal of a row of cylinders in the photon crystal causes the appearance of an energy level in the photonic gap similar to a p- or n-level in the electron energy gap. By removing a cylinder and thus creating a void or by changing the cylinder size one can vary the photon frequency *via* a change in the nanocluster size (Fig. 36).

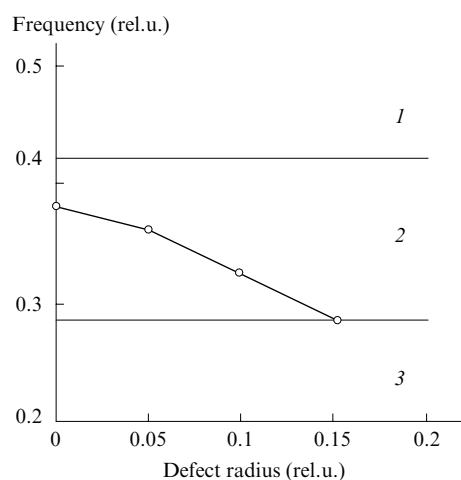


Figure 36. Frequency dependence of localised states within the photonic band gap.

Air band (1), photonic band gap (2) and dielectric band (3).

The energy and dispersion spectra of three-dimensional photonic crystals are also characterised by the presence of photonic gaps similar to the forbidden bands in the electron energy and dispersion spectra in atomic crystals. Taking into account this fact, one can suggest the existence of a photonic gap with the frequencies at which the propagation of a photon inside the crystal is impossible and the photon experiences elastic reflection from the nanocrystalline layer. This offers prospects for the synthesis of nanomaterials with variable optical properties for the use in light guides and tunable lasers and for the design of devices for integrated electronic networks based on optical integrated systems. Photons propagate in dielectrics at higher frequencies compared to electrons moving in conductors and can be much more informative. Fibre optical systems operate at THz frequencies (*cf.*, GHz frequency range for conventional electric current systems).

Photonic crystals with the photonic gap are fabricated by various methods. One of them involves self-organisation of spherical particles of a critical submicron size (hundreds of nanometres) in a colloid solution to give a face-centred lattice obeying the closest packing principle, which limits further growth of particles. This procedure was used to obtain an artificial opal with inclusions of monodisperse silica spheres. However, this crystal is characterised by unstable photonic gap, which is easily destroyed in the presence of various defects and imperfections. The artificial opal is used as a template for the preparation of semiconductor material. Namely, infiltration of the nanocrystalline opal with silicon followed by removal of the template results in nanocrystalline inverted opal (*cf.* nanosized reverse micelle structure) with an ordered void structure (Fig. 37).

According to calculations, a semiconductor with rather high reflection coefficient (> 2.85) should have a photonic gap. This was experimentally found in a silicon photonic crystal.⁹⁸ In this connection it is of great interest to fabricate GaS-, InS- or GaP-

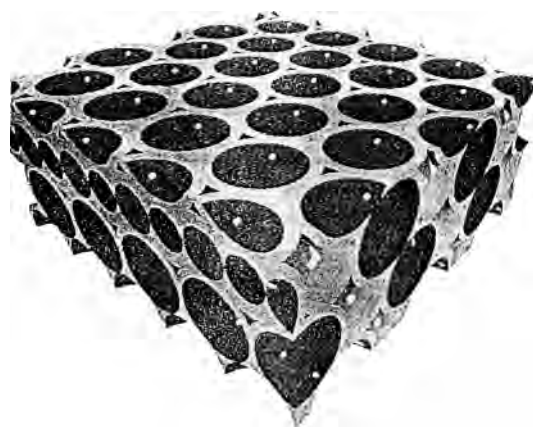


Figure 37. Cross-sectional view through an incompletely infiltrated opal nanocrystal. After etching out the SiO₂ spheres, the incomplete infiltration of silicon (shown in gray) results in additional triangular (or diamond-shaped) pores.⁹⁷

based photonic crystals capable of emitting intense light or to create ordered voids in a diamond structure that, according to calculations, can have a wider photonic gap and be less dependent on the defects and disorder.

5. Magnetoelectric and magnetic properties

a. Giant magnetoresistance effect

The giant magnetoresistance (GMR) effect represents a great decrease (to 1000%) in the resistance of the nanocluster material in a magnetic field. For comparison, the magnetoresistance of bulk samples changes only slightly under identical conditions (*e.g.*, the resistance of permalloy, 80% Ni–20% Fe, increases only by 3%). The GMR effects were observed in studies of the magnetic properties of various metallic and oxide nanosystems. The mechanisms of GMR origination for nanocrystalline metals and metal oxides are different.

Nanocluster metallic materials exhibiting the GMR effect (magnetic clusters) are prepared by dissolving nanoclusters of one metal (*e.g.*, iron or cobalt) in the matrix of another metal possessing high conductivity (*e.g.*, copper or silver); the two components should be poorly soluble in each other. In a nano-system comprising a conducting metallic matrix and magnetic clusters, the conduction electrons of the matrix are scattered by the magnetic moments of the clusters. The clusters are sufficiently small and can possess superparamagnetic properties. However, for the conduction electrons moving at the Fermi velocity, the magnetic moments of the clusters are blocked, because the magnetisation measuring times (~ 100 s) are much longer than the characteristic time taken by an electron to pass through the sample ($\sim 10^{-9}$ s). The electronic structure of the metallic matrix has marked effect on the magnetic properties of clusters.⁹⁹

If electrons in metals are scattered prior to changing the directions of the spins, the relative orientation of the magnetic moments of the clusters affects the rate of scattering and conductivity. Once a magnetic field is applied to the sample, the direction of the magnetic moments changes, this causes their interaction with the conduction electron and, hence, a change in the conductivity. The magnitude of the GMR effect (and the GMR effect itself) is determined by the ratio of the electron free path to the distance between the neighbouring magnetic clusters, which depends on the concentration of the metal nanoclusters in the matrix. When the concentration is low and, correspondingly, the free path is long, an electron experiences numerous scattering events before it enters into interaction with the magnetic cluster. In this case the direction of the magnetic moment of the cluster has no effect on the electron scattering and no GMR effect is observed. At high concentration of the metal clusters, the mag-

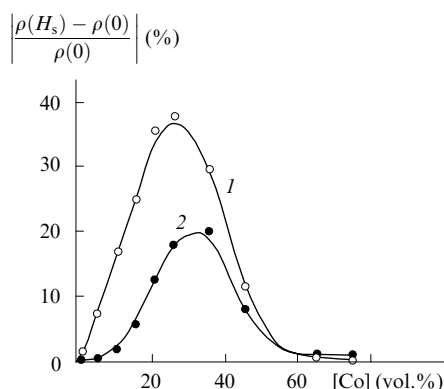


Figure 38. Change in magnetoresistance $[\rho(H_s) - \rho(0)]/\rho(0)$ of Co–Ag nanosystems with different cobalt concentrations at 5 (1) and 300 K (2).⁹⁹

netic clusters interact with one another and are involved in the percolation processes, which eliminates the GMR effect.

An optimum situation is observed for the Co–Ag nanosystem.⁹⁹ As the cobalt concentration changes from 15% to 40%, the GMR effect is observed. The change in the relative GMR effect vs. the cobalt concentration in the sample at different temperatures are shown in Fig. 38. The maximum GMR effect was observed at a cobalt concentration of about 20%, which was associated with the critical size of cobalt clusters in the silver matrix.

The GMR effect increases as the temperature decreases. The mechanism of the effect can be explained using the two-current model, according to which electron scattering on the cluster magnetic moment in a disordered nanosystem is possible in two directions, (e.g., up or down). In a nanosystem ordered by an external magnetic field, one direction, namely, that along the field, has a lower resistance than the other direction; this results in an overall decrease in the resistance by a value of $\Delta\rho$. The $\Delta\rho$ value correlates with the cluster size: $\Delta\rho \sim 1/d$. This indicates that the GMR effect is determined by the ratio of the surface area of the magnetic clusters to the volume of the clusters and that it is the cluster–matrix interface where the spin-dependent electron scattering occurs.

Small cobalt clusters possess the properties of superparamagnetic materials and the direction of the magnetic moment of a cluster can easily be changed in an external magnetic field or by the interaction with conduction electrons. However, this interaction can occur if the time of magnetic moment fluctuations exceeds the travel time of the conduction electrons. The minimum cluster size corresponding to the onset of the GMR effect can be evaluated from Eqn (29) for the superparamagnetic relaxation time. The cluster size estimates obtained assuming $\tau_{cr} \geq \tau_0$ and substituting $K = 10^6 \text{ J mol}^{-3}$ for cobalt are $\sim 4\text{--}8 \text{ nm}$ at room temperature and $\sim 1 \text{ nm}$ at 4.2 K.

In ceramic materials, the GMR effect is observed in a narrower temperature range.¹⁰⁰ The temperature dependences of changes in the magnetoresistance $[\rho(H_s) - \rho(0)]/\rho(0)$ (%), resistance (ρ) and magnetisation (M) for $\text{La}_{0.67}\text{Ca}_{0.33}\text{MnO}_x$ are shown in Fig. 39.

The maximum value of the GMR effect is $\sim 1300\%$ at $T = 200 \text{ K}$. In the region 100–200 K, a metal–semiconductor transition occurs and the magnetisation increases. The appearance of the GMR effect can also be explained by the influence of superparamagnetism in this temperature range. In the temperature interval where the GMR is observed, the Mössbauer spectra exhibit a superparamagnetic doublet which is due to the appearance of nanosized regions of iron-doping induced fluctuations of the magnetic moment of ceramics.¹⁰¹ The characteristic time of thermal fluctuations of the magnetic moment is also determined using expression (29); the estimate of the critical nanocluster size corresponding to the onset of the GMR effect in ceramics is

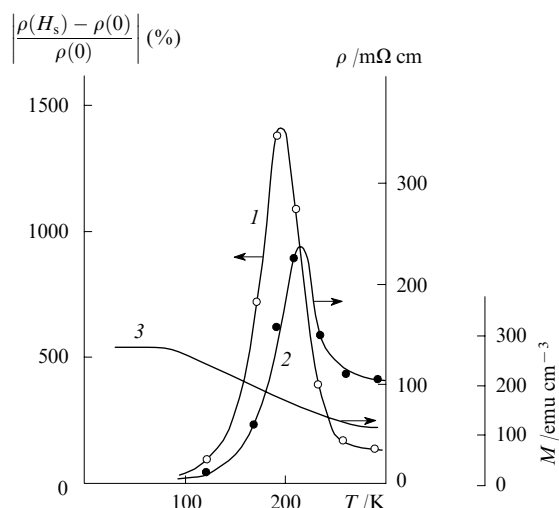


Figure 39. Parameters $[\rho(H_s) - \rho(0)]/\rho(0)$ (1), ρ (2) and M (3) of $\text{La}_{0.67}\text{Ca}_{0.33}\text{MnO}_x$ ceramics plotted vs. temperature.¹⁰⁰

$\sim 2\text{--}4 \text{ nm}$ at $K = 10^5 \text{ J m}^{-3}$. A decrease in temperature leads to reduction of the GMR effect, extension of the fluctuation regions and disappearance of superparamagnetism. This effect can be treated as the percolation effect for metallic matrix. The existence of superparamagnetic fluctuations of the ceramic matrix was also confirmed by inelastic neutron scattering data.¹⁰²

Based on this, one can assume that the GMR effect in the region of the semiconductor–metal transition of the ceramic material is due to the appearance of fluctuating magnetically ordered nanodomains. The nanodomain size increases as the temperature decreases; this is accompanied by an increase in the superparamagnetic relaxation time and in the time taken to attain the magnetically ordered ferromagnetic state. The temperature interval of the magnetic transition spans tens of degrees; the GMR effect observed in the same temperature range is due to the change in the scattering of conduction electrons caused by the change in the relaxation time of the magnetic moment, in the distance between fluctuating clusters and in the cluster size (no ferromagnetic nanoblocks at temperatures below the phase transition temperature and no metallic conductivity at high temperatures).

b. Quantum magnetic tunnelling

Quantum tunnelling transitions in cluster molecular crystals are accompanied by discrete changes in the magnetisation of nanoclusters and of the whole nanocrystal. This was observed for a cluster single crystal $[\text{Mn}_{12}(\text{AcO})_{16}(\text{H}_2\text{O})_4\text{O}_{12}] \cdot \text{AcOH} \cdot 4\text{H}_2\text{O}$ built of identical Mn_{12} clusters with acetate ligands.¹⁰³ This nanostructure is characterised by a stepwise character of the magnetisation curve (Fig. 40).

The hysteresis loop consists mainly of vertical and horizontal portions. In horizontal portions, the relaxation time of the magnetic moment exceeds the measurement time ($t_m \sim 600 \text{ s}$); in the slope portions, the relaxation time is similar to the measurement time. This leads to a number of minima in the plot of the superparamagnetic relaxation time τ on external magnetic field, which are associated with the steps in the hysteresis loop. Experimentally found critical H_0 values corresponding to the steps in the hysteresis loop change from 0 to 2.64 T with an increment of

$$\Delta H = H_{n+1} - H_n = 0.44 \text{ T}.$$

Here, the relaxation time of the magnetic moment of the cluster changes in a stepwise manner. These effects can be explained with allowance for the electronic structure and tunnelling transitions between the electron energy levels of molecular cluster Mn_{12} . The cluster core has a tetragonal two-layer structure in which the

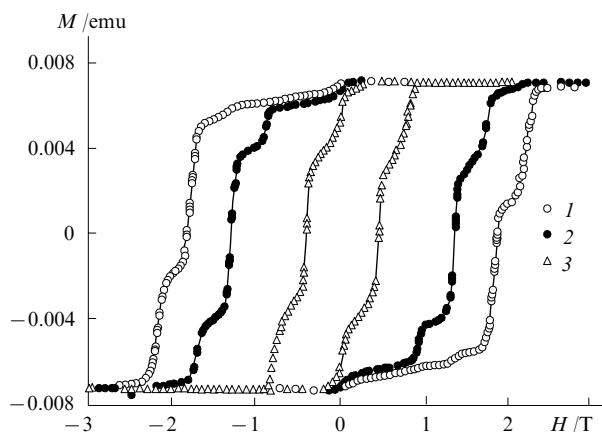


Figure 40. Magnetisation curves of Mn_{12} acetate cluster single crystal at different temperatures.¹⁰³ Temperature /K: 1.77 (1), 2.10 (2), 2.64 (3).

Mn^{4+} atoms form the inner cubane cage Mn_4O_4 with the spin $S = 3/2$, and eight external Mn^{3+} atoms with the spin $S = 2$ form the outer layer. The ground ferrimagnetic state of the cluster with the collective spin $S = 10$ is stabilised by internal exchange interactions. The energy of axially symmetric crystallographic anisotropy

$$\Delta E = DS^2$$

causes the ground spin state to split into two levels with $S_z = \pm 10$ and a crystal field constant $D = 0.61$ T. For a thermally activated process at $kT \gg \Delta E$, off-resonance spin transitions occur with the probability and transition times characteristic of larger clusters. At low temperatures, quantum tunnelling of the projection of the magnetic moment is possible if the energy levels of the clusters with $M = S_n$ and $M = -S_n$ in an external magnetic field coincide. Calculations using the relation

$$\Delta H = \frac{D}{g\mu_B} = 0.44 \text{ T},$$

where g is the gyromagnetic ratio and μ_B is Bohr magneton give $D = 0.6$ T.

Thus, the relaxation of the magnetic moment of the cluster accelerates when tuning by the magnetic field results in coincidence of the energy levels of all clusters in the nanostructure. This effect corresponds to quantum tunneling in the whole nanostructure. Such clusters are treated as molecular magnets with a colossal writing density, which can be used for information storage and retrieval. Owing to multilevel tunneling, such nanodevices can be used in quantum computers in order to achieve a considerable increase in the storage capacity and performance.

c. Magnetic phase transitions

The magnetic phase transitions are classified depending on the type of changes in the magnetisation or in the character of magnetic ordering near the critical temperatures (Curie point for ferromagnetics or the Néel points for anti- and ferrimagnetics). Sharp (stepwise) and gradual changes in these characteristics correspond to the first- and second-order transitions, respectively. Changes in the unit cell volume or the thermal effect in the case of a first-order phase transition can be either significant or not. Most bulk magnets undergo second-order phase transitions, but a number of substances undergo a first-order phase transition on going from the magnetically ordered to the paramagnetic state and upon change in the type of magnetic ordering. Examples are provided by MnAs (ferromagnet $\rightarrow$ paramagnet), MnO , UO_2 , Eu (antiferromagnet $\rightarrow$ paramagnet) and $\alpha\text{-Fe}_2\text{O}_3$ (antiferromagnet $\rightarrow$ weak ferromagnet).¹⁰⁴

When studying nanoclusters and nanostructures, the magnetic phase transitions become of particular importance due to manifestation of versatile new (compared to the case of bulk materials) factors affecting the character and mechanism of transitions (size effects, surface effect, intercluster and nanoclusters–matrix interactions, effect of magnetic fields, *etc.*). Specific features of magnetisation transitions can be used as a new tool of studying the structure of nanosystems and design of novel nanomaterials and nanodevices.

Nanoclusters and nanomaterials also undergo the first- and second-order magnetic phase transitions. Similarly to most bulk magnets, the second-order magnetic phase transitions of metal and metal oxide clusters are characterised by the Langevin dependences of the magnetisation and by gradual disappearance of the magnetic order and spontaneous magnetisation near T_C or T_N . Nanoclusters of size less than 10 nm possess the properties of superparamagnets, which leads to efficient reduction of T_C or T_N .

Unlike bulk metal oxides characterised by second-order magnetic phase transitions, the corresponding oxide nanoclusters undergo the first-order transitions accompanied by abrupt loss of spontaneous magnetisation at a particular temperature or by transition to the paramagnetic rather than superparamagnetic state as the cluster size becomes less than a critical size.³⁶

When observing and studying the first-order magnetic phase transitions of nanoclusters, the problem is first of all to distinguish them from the superparamagnetic behaviour. In most cases, a scatter of cluster size occurs. Additionally, nanosystems that do not form cluster crystals are characterised by scatter of intercluster interactions. These factors hamper the detection of the first-order magnetic phase transitions of nanoclusters and nanostructures by the magnetisation measurements that provide some averaged magnetic characteristics. In this connection, one should expect a high efficiency of spectroscopic methods (in particular, Mössbauer spectroscopy with characteristic times of $10^{-7} - 10^{-10}$ s) that permit separate characterisation of the magnetic and non-magnetic fractions in the same sample.

Magnetic phase transitions manifest themselves differently in systems including isolated clusters (or clusters with weak intercluster interactions) and in nanostructures comprising clusters of size at most 100 nm with strong intercluster interactions. The reasons and mechanisms of the magnetic phase transitions in these cases are different. In this connection, it is appropriate to consider the first-order magnetic phase transitions in (i) nanosystems including isolated small nanoclusters of size less than 10 nm and (ii) nanostructures composed of larger clusters (up to 100 nm in size) characterised by strong intercluster interactions, in which magnetic transitions associated with co-operative change in the nanostructure can occur.

Nanosystems with isolated clusters. The magnetic ordering of a cluster is a co-operative phenomenon. For instance, iron atoms have a magnetic moment and possess paramagnetic properties at all temperatures. This holds for low concentrations of iron atoms present in non-magnetic (*e.g.*, polymer) matrices. A cluster comprising a few (at most ten) iron atoms is characterised by exchange interaction; however, no spontaneous magnetisation appears in this case owing to thermal fluctuations and fast spin–spin relaxation. The number of magnetic moments and, correspondingly, the cluster size should be large enough that the total exchange energy be higher than the energy of thermal fluctuations, which is of the order of kT . Using quantum-statistical methods, one can specify the energy level scheme for a cluster, calculate the total exchange energy and compare it with the energy of thermal fluctuations. This makes it possible to determine the critical cluster size corresponding to the onset of spontaneous magnetisation and magnetic ordering.

However, the character of exchange interactions and, hence, the critical cluster size will be affected by various factors, *e.g.*, the state of the cluster surface, intercluster interactions, cluster shape, *etc.* Therefore, carrying out accurate critical-size calculations is a rather complicated task. Meanwhile, the estimates of the quantum

confinement effects made in considering the electrical, optical, thermal and other properties can also be applied for the determination of the critical size of a magnetic cluster. Indeed, assuming that

$$\Delta p \Delta x = \Delta p d_{cr} \approx \hbar,$$

where p is the momentum, x is the coordinate and d_{cr} is the critical size (diameter) of the cluster, one has

$$\Delta p = \frac{\hbar}{d_{cr}},$$

and the uncertainty of the electron energy, exchange interaction or magnon due to quantum confinement effects is given by

$$\Delta \varepsilon \approx \frac{(\Delta p)^2}{2m} \approx \frac{\hbar}{2m} (d_{cr})^{-2}.$$

Assume now that this value equals the energy of exchange interaction, which is mainly responsible for the onset of magnetic ordering, *i.e.*, $\Delta \varepsilon \approx kT_C$, where T_C is the Curie temperature of bulk material. Then, the critical size (in metres) can be determined from a simple relation

$$d_{cr} \sim 2 \times 10^{-8} T_C^{-1/2}. \quad (64)$$

For $T_C \sim 500 - 1000$ K, one gets $d_{cr} \approx 1$ nm. This is the critical size of a magnetic cluster. Smaller clusters lose the magnetic ordering and undergo a transition to a magnetically disordered (*e.g.*, paramagnetic) state at any temperature. This is also the minimum size of a superparamagnetic cluster (the upper bound is ~ 10 nm and depends on many parameters, *e.g.*, the energy of magnetic anisotropy, temperature, measurement time, *etc.*). Thus, all clusters of size $d < d_{cr}$ should be in the magnetically disordered state.

The critical cluster size can also be determined using the thermodynamic theory of magnetic phase transitions in nanoclusters.^{105, 106} This theory predicts the first-order magnetic phase transitions of nanoclusters and the change in the character of the phase transition depending on the cluster size.

The first-order magnetic phase transitions can occur in bulk samples characterised by a change in the unit cell volume on transition from the magnetically ordered to a non-magnetic state, *i.e.*, in the materials, possessing magnetostriction and exhibiting hysteresis-type temperature dependences of the specific volume and magnetisation.¹⁰⁷

The Curie (Néel) temperature depends on the change in the volume as follows:

$$T_C = T_0 \left(1 + \beta \frac{V - V_0}{V_0} \right). \quad (65)$$

Here T_0 is the Curie temperature of the substance with uncompressed crystal lattice, β is the magnetostriction constant of the substance, V and V_0 are the molar volumes of the substance in the magnetically ordered (compressed) and in the non-magnetic (paramagnetic) states, respectively.

The first-order magnetic transitions of nanoclusters are realised using a dependence similar to expression (65).

The equation for the change in the Gibbs free energy density upon transition of the cluster from the magnetically ordered to the non-magnetic state is written with allowance for the change in the cluster volume as a result of magnetostriction, compressibility under pressure

$$P = \frac{2\alpha}{r}$$

due to the surface tension of the cluster of radius r

$$\Delta G = -\frac{1}{2} NkTm^2 + \frac{1}{2} \eta \left(\frac{V - V_0}{V_0} \right)^2 + \frac{2\alpha}{r} \frac{V - V_0}{V_0} + \frac{1}{2} NkT \left[\ln \left(1 - \frac{m^2}{4} \right) + m \ln \frac{1+m}{1-m} \right]. \quad (66)$$

Here N is the number of atoms with the spin $1/2$, $m = M/M_S$ is the relative magnetisation, η is volume compressibility and α is the surface tension. The equation includes four terms. The first term corresponds to the exchange energy density, the second term reflects the energy of cluster deformation, the third term corresponds to the surface energy and the fourth one is the entropy term responsible for the Langevin type of the temperature dependence of magnetisation.

To obtain the parameters of a stable magnetic state of the cluster, one should minimise the Gibbs free energy with respect to the change in the volume and magnetisation on the magnetic phase transition. Having solved the system of equations

$$\begin{aligned} \frac{\partial \Delta G}{\partial V} &= 0, \\ \frac{\partial \Delta G}{\partial m} &= 0, \end{aligned} \quad (67)$$

which determine the equilibrium state of the system, one gets

$$\frac{T}{T_{C0}} = m \left(\frac{1}{3} \gamma m^2 + 1 \right) \left(\frac{1}{2} \ln \frac{1+m}{1-m} \right)^{-1} \quad (68)$$

where $\gamma = (3/2) NkT_0 \eta \beta^2 / (1 - \eta \beta P)$ and the Curie temperature, *viz.*, $T_{C0} = T_0(1 - \eta \beta P)$, is lower than T_0 due to the pressure produced by the surface tension of the cluster.

The calculated changes in the relative magnetisation at different γ values are plotted *vs.* temperature in Fig. 41. The parameter γ determines the character of the magnetic phase transition. The case $\gamma < 1$ corresponds to the second-order magnetic phase transitions, whereas the case $\gamma \geq 1$ corresponds to the first-order magnetic phase transitions of clusters accompanied by abrupt loss of magnetic ordering. The Z-shaped portion of the magnetisation curve corresponds to an increase in the Gibbs free energy, *i.e.*, to unstable magnetic structures. The abrupt change in the magnetisation for an actually observed first-order magnetic phase transition is shown by dashed line.

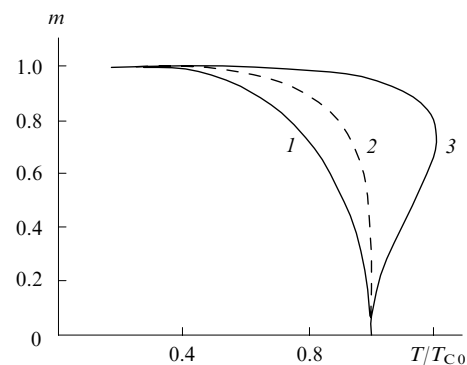


Figure 41. Relative cluster magnetisation plotted *vs.* temperature at different γ values. $\gamma < 1$ (1), $\gamma = 1$ (2) and $\gamma > 1$ (3).

The critical cluster size corresponding to stepwise transition from the magnetically ordered to paramagnetic state can also be estimated from the γ value. For convenience, we will re-write the expression for γ as follows:

$$\gamma = \frac{T_{Cc}}{T_{C0}}, \quad (69)$$

where

$$T_{Cc} = \frac{3}{2} NkT_0^2 \eta \beta^2.$$

At $\gamma \geq 1$, clusters pass to the paramagnetic state upon a first-order magnetic phase transition if

$$r \leq r_{cr} = \frac{2\alpha\beta\eta}{1 - T_{Cc}/T_0}. \quad (70)$$

Large clusters ($r > r_{cr}$) will lose their magnetisation with an increase in temperature upon the second-order magnetic phase transitions.

To realise the first-order magnetic phase transitions, one should obtain clusters of substances that have a sufficiently high compressibility η . (Clusters with zero compressibility correspond to $r_{cr} = 0$ and second-order magnetic phase transitions.) The surface tension α is the key parameter that governs the occurrence or lack of the first-order magnetic phase transitions and variation of the critical cluster size [see Eqn (66)]. This model for phase transitions treats an isolated cluster characterised by the surface tension α at the cluster–vacuum interface. Any interaction between the cluster and the stabilising matrix or the neighbouring clusters leads to a decrease in α and r_{cr} and to disappearance of the first-order magnetic phase transitions. Therefore, studies of this type of phase transitions can serve as a tool for characterisation of intercluster and cluster–interface interactions.

In order to observe the first-order magnetic phase transitions, a nanosystem comprising ferrihydrite $\text{Fe}_3\text{HO}_8 \cdot 4\text{H}_2\text{O}$ nanoclusters formed in polysorb pores 13 to 75 nm in diameter was synthesised.^{36,105} This matrix-type nanosystem permits formation of isolated metal oxide clusters or accumulation of several clusters in the same pore. Polysorbs used were styrene and divinylbenzene copolymers without surface functional groups. The pore walls in such polysorbs have hydrophobic properties, which significantly weakens the interaction of ferrihydrite clusters with the matrix and leads to an increase in r_{cr} . Intercluster interactions and the number of clusters in the pore were changed by varying the concentration of iron atoms. To increase the sensitivity of Mössbauer spectrometers, experiments were carried out using ^{57}Fe -enriched iron-containing clusters synthesised in pores by soaking polysorbs with alcoholic solutions of $^{57}\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ with the iron concentrations of 1.2×10^{-2} and 1.2×10^{-3} mol litre $^{-1}$ and subsequent treatment with air/gaseous ammonia mixture. An increase in the polysorb pore size from 13 to 75 nm was followed by an increase in the size of the clusters formed in the pores.

The Mössbauer spectra of ferrihydrite clusters in polysorb pores ($c = 1.2 \times 10^{-3}$ mol litre $^{-1}$) at different temperatures are shown in Fig. 42. At all temperatures, the spectra consist of a narrow-line magnetic HFS and a central doublet. As the temperature increases, the HFS is partially converted to the paramagnetic doublet without passing through the forms corresponding to superparamagnetic broadening and to line shift leading to a considerable decrease in the magnetic field at the core. The results obtained suggest that the first-order magnetic phase transitions occur in ferrihydrite clusters in the temperature range 4.2–6 K.

Analysis of the Mössbauer spectra¹⁰⁵ allows one to reveal the effects of the interactions between clusters and the pore wall and the intercluster interactions on the character of magnetic phase transitions. First of all it should be noted that the Mössbauer spectra of (i) synthetic and natural ferrihydrites of cluster size 2–5 nm (this corresponds to magnetically ordered structures) and (ii) ferrihydrite clusters formed in polysorb pores are different. The former group of spectra exhibits a magnetic HFS at 4.2 K and broad HFS components (~ 1.5 – 2 mm s $^{-1}$, see Ref. 108), while the latter group of spectra is characterised by much narrower lines

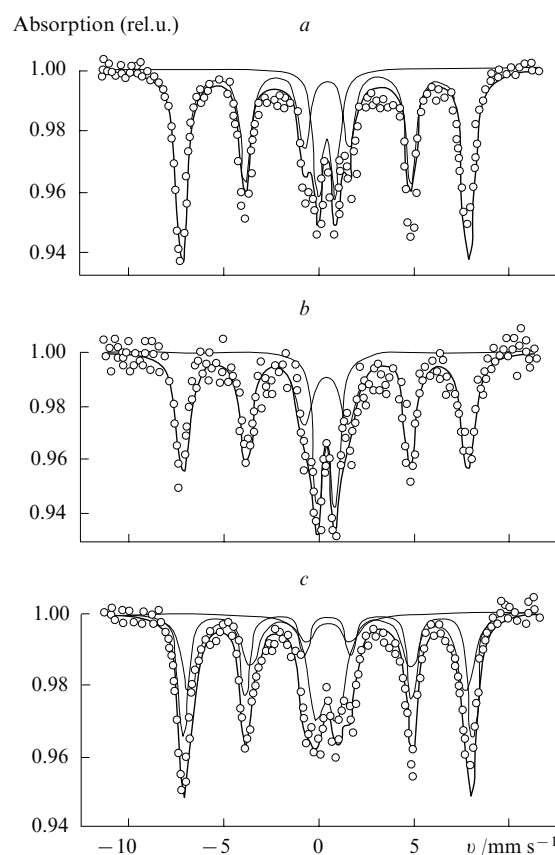


Figure 42. Mössbauer spectra of ferrihydrite clusters in polysorbs with pore sizes of 13 (a, b) and 20 nm (c).¹⁰⁵ $c = 1.2 \times 10^{-3}$ mol litre $^{-1}$ at 4.2 (a, c) and 10 K (b).

(~ 0.6 mm s $^{-1}$). This difference is due to isolation of ferrihydrite clusters in copolymer pores and indicates weak intercluster and cluster–pore walls interactions compared to similar interactions in polycrystalline ferrihydrite. Indeed, the iron concentration of 1.2×10^{-3} mol litre $^{-1}$ corresponds to nearly one 1–2-nm ferrihydrite cluster per pore of volume 10^{-22} – 10^{-23} m ^{3} and here the magnetic properties of the cluster depend on the interaction between the cluster and the matrix surface. Thus, a first-order magnetic phase transition occurs at 4.2–6.0 K; clusters that are smaller than the critical cluster abruptly lose spontaneous magnetisation and go to the paramagnetic state.

As the temperature increases to 10 K, the relative proportion of the HFS in the Mössbauer spectrum decreases due to superparamagnetic relaxation. At a constant concentration of iron atoms ($c = 1.2 \times 10^{-2}$ mol litre $^{-1}$), an increase in the pore size to 20 nm is accompanied by an increase in the cluster size, which causes an increase in the proportion of the HFS (see Fig. 42 c), a decrease in the probability of the first-order magnetic phase transitions and strengthening of the interaction between clusters and the pore surface. A tenfold increase in the ^{57}Fe concentration at the same pore size is followed by nucleation of several clusters in the same pore (up to 5–8 clusters of size ~ 2 nm), strengthening of intercluster interactions and, as a consequence, by the overall decrease in r_{cr} values corresponding to the first-order magnetic phase transitions.¹⁰⁵ Here, this makes it possible to estimate the size of ferrihydrite clusters involved in superparamagnetic relaxation. Using relation (29) and $\tau_0 = 1 \times 10^{-9}$ s, $\tau_{cr} \sim 189 \times 10^{-9}$ s, $T = 10$ K and $K = 1.7 \times 10^5$ J m $^{-3}$, the upper limit for clusters with iron concentration of 1.2×10^{-2} mol litre $^{-1}$ was estimated at ~ 2.2 nm.

Thus, these nanosystems permit observation of the first- and second-order (superparamagnetism) magnetic phase transitions

for clusters of size ~ 2 nm. The magnetic phase transitions were detected in the temperature range 4.2–6 K.

An increase in the pore size to 75 nm at an iron concentration of 1.2×10^{-2} mol litre $^{-1}$ causes fundamental changes in the spectral pattern. This nanosystem shows the second-order magnetic phase transitions and clusters behave as superparamagnets. Calculations of superparamagnetic relaxation give an estimate $r \sim 2.5$ nm for both iron concentrations, because the average cluster size in the pore is determined by the average pore size. An increase in the iron concentration in a pore leads to multiple cluster formation, strengthening of intercluster interactions, a decrease in the critical cluster size and suppression of the first-order magnetic phase transitions.

It is interesting to compare the experimental estimates of r_{cr} obtained using the Mössbauer spectra, concentrations of the iron atoms in pores and relationships (68)–(70). Calculations for small clusters carried out assuming the critical first-order magnetic phase transition temperatures of ~ 4.2 –6 K, the second-order magnetic phase transition temperature of ~ 20 –30 K, the molar volume of 14.4×10^{-29} m ^{3} , the inverse compressibility of $\sim 1.5 \times 10^{11}$ Pa, and the cluster surface tension of ~ 1 J m $^{-2}$ led to $r_{cr} \sim 1$ nm, which is in agreement with the experimental estimates $r_{cr} \sim 1.5$ –2 nm. Indications of the first-order magnetic phase transitions were observed for small clusters of other iron oxides (see, *e.g.*, Ref. 36), but this was not observed for metal clusters (Fe, Co, Ni), probably due to lower compressibility of these particles.

The pressure is an important factor determining the appearance or disappearance of the first-order magnetic phase transitions. According to the thermodynamic model for magnetic phase transitions of nanoclusters [see Eqns (68)–(70)], the critical transition temperature reduces as the external pressure increases:

$$T_{C0} = T_0(1 - \beta\eta P). \quad (71)$$

A simple method of producing an excess pressure in a confined volume is to freeze water. The volume of ice is 8% larger than the volume of water and can produce a pressure of up to a few GPa in pores of nanometre size. Investigations of the effects of hydration, freezing of nanostructures and the action of pressure on clusters upon freezing of water in nanopores involved two series of experiments with the systems including iron oxyhydroxide nanoclusters in pores of an ion-exchange resin (sulfo cation exchange resin) and in iron-accumulating protein (ferritin) in the dry and hydrated states.¹⁰⁹

The major difference in the Mössbauer spectra of iron hydroxide clusters in the hydrated and dry samples manifests itself in the temperature range of 8.5–15 K. Comparison of the spectra of the dry samples of sulfo cation exchange resin containing iron oxyhydroxide clusters at 13 K and the spectra of the hydrated samples at 10 K showed that these spectra are identical, which suggests the temperature shift of the magnetic phase transition upon hydration. The transition is completely reversible. The spectrum of hydrated ferritin containing iron oxide core (similar to sulfo cation exchange resin) exhibits an increase in the proportion of the paramagnetic doublet compared to the spectrum of the dry sample. By comparing the spectra, it is possible to determine the magnitude of the temperature shift of the magnetic phase transition under pressure $\Delta T = 3$ –4 K.

Nanostructures. The first-order magnetic phase transitions induced by intercluster stresses and defects can occur in nanosystems containing nanoclusters of size 20–50 nm. Such nanostructures are formed in solid-phase chemical reactions, *e.g.*, cluster sintering; they are characterised by rather strong intercluster interactions. A nanostructure including α -Fe $_2$ O $_3$ and γ -Fe $_2$ O $_3$ clusters exhibits not only the first- and second-order magnetic phase transitions, but also a weak ferromagnetic–antiferromagnetic phase transition and a novel type of magnetic phase transition, accompanied by the formation of twin nanostructures.¹¹⁰

The first-order magnetic phase transitions similar to the transitions in the 1–3-nm ferrihydrite clusters (see Ref. 105) were observed in the α -Fe $_2$ O $_3$ – γ -Fe $_2$ O $_3$ nanostructure formed in the initial stage of cluster sintering by the solid-phase chemical reaction.¹¹⁰ The AFM images of this nanostructure are shown in Fig. 22.

First-order magnetic phase transitions. As mentioned above, Mössbauer spectroscopy is the most efficient method of investigation of the first-order magnetic phase transitions in clusters. The Mössbauer spectra of the α -Fe $_2$ O $_3$ – γ -Fe $_2$ O $_3$ nanostructure at different temperatures are shown in Fig. 23. As the temperature increases, the magnetic phase transitions from the ordered magnetic state to the paramagnetic (superparamagnetic) state of the nanostructure are observed, the former state being characterised by a magnetic HFS. At 77 K, the spectra exhibit two magnetic HFSs corresponding to α -Fe $_2$ O $_3$ ($\Delta E_Q = -0.29$ mm s $^{-1}$) and γ -Fe $_2$ O $_3$ ($\Delta E_Q = 0$ mm s $^{-1}$). Raising the temperature up to $T = 120$ K causes the appearance of a quadrupole doublet with $\Delta E_Q = 0.78$ mm s $^{-1}$ and the isomer shift $\delta = 0.42$ mm s $^{-1}$ relative to the metallic iron HFS, but the overall spectral pattern remains unchanged. Starting with $T = 120$ K, these spectra are transformed into spectra with one magnetic HFS ($\Delta E_Q = 0$ mm s $^{-1}$).

The Mössbauer spectra in the temperature range 120–300 K are characterised by reversible transformations of the magnetic HFS into a paramagnetic doublet without noticeable shift or broadening of the lines characteristic of the second-order magnetic phase transitions (or superparamagnetism). This is an indication of the first-order magnetic phase transitions (magnetisation of the nanomaterial disappears abruptly). These transitions occur at the critical temperatures $T_{C0} = 120$ –300 K, which are lower than T_0 temperatures for bulk samples of α -Fe $_2$ O $_3$ and γ -Fe $_2$ O $_3$ (856 and 965 K, respectively). The lack of superparamagnetism for such large clusters becomes clear from the estimate using relation (29). Taking the magnetic anisotropy constant to be $K \approx 10^5$ J m $^{-3}$ and $\tau_0 = 10^{-9}$ – 10^{-10} s, the relaxation time τ is several orders of magnitude longer than the measurement time (period of Larmor precession for ^{57}Fe nucleus is $\sim 10^{-8}$ s). Therefore, superparamagnetism has no effect on the magnetic properties of these nanostructures and cannot cause a reduction of T_{C0} .

In the nanostructures of α -Fe $_2$ O $_3$ and γ -Fe $_2$ O $_3$ the magnetisation and magnetic ordering disappear due to the first-order magnetic phase transition (abruptly), namely, the magnetic induction decreases from ~ 50 T to 0. It should be noted that the critical size, r_{cr} , of isolated ferrihydrite clusters is about 1.5 nm; smaller clusters undergo a stepwise transition to the paramagnetic state. There is also a narrow temperature range (4.2–10 K) characteristic of the first-order phase transitions. These effects were associated with the effect of surface tension.

For clusters of size 20–50 nm the pressure due to the surface tension should be an order of magnitude lower; additionally, a strong intercluster interaction causes α to decrease. Therefore, there also should be some other reasons for the first-order magnetic phase transitions and reduction of T_{C0} in this nanostructure (corresponding to $\gamma \geq 1$, see Ref. 105). Clearly, these reasons are associated with the influence of defects on the properties of the nanostructure [see Eqn (28)]. It is assumed that iron oxide clusters of size 20–50 nm provide a maximum defect density. For larger clusters, the effect of the surface as a source of defects is insignificant, whereas for smaller clusters the surface pressure is large enough to displace defects from the cluster. So, small clusters are defect-free.¹¹¹

Following this model, there should exist a maximum defect density at which clusters of critical size (tens of nanometres) are formed in the nanosystem. If the cluster sizes are less than the critical size, first-order magnetic phase transitions occur in the nanosystem; otherwise, the second-order magnetic phase transitions characteristic of bulk materials occur.

The extremal character of the dependence of defect concentration on the cluster size [see Eqn (47)] also affects the temperature dependences of the magnetisation of a nanocluster structure comprising clusters of different size. One can assume a linear dependence of the critical temperature on the defect concentration in the cluster

$$T_C = T_{C0}(1 + \beta c_v), \quad (72)$$

where $\beta < 0$, c_v is the defect concentration in the cluster.

Taking into account the magnetic intercluster interaction, the thermodynamic potential of the nanosystem 'magnetic clusters – medium – defects' can be represented by the sum including the surface energy and the change in the chemical potential upon the change in the cluster size and in the defect density in the cluster,

$$G = \Delta\mu n_v + \alpha s n_v - 0.5 N_v k T_{C0}(1 + \beta c_v) m^2 + N k T \left(\frac{1}{2} \ln \frac{1 - m^2}{4} + m \ln \frac{1 + m}{1 - m} \right), \quad (73)$$

where $\Delta\mu = \mu_0 + kT \ln(N_s n_v / N_v n_s)$ is the chemical potential difference between the defects inside the cluster and on the cluster surface; N_v is number of atoms in the cluster; N_s is number of atoms in the intercluster medium per cluster; n_v is number of defects in the cluster; n_s is number of defects in the intercluster medium per cluster; α is the surface tension of the cluster in the intercluster medium; s is cluster surface area; $m = M/M_0$ is the relative magnetisation of the cluster and N is the number of spins in the cluster. The temperature dependences of the relative magnetisation calculated for iron oxide nanoclusters of different size with energy minimisation are shown in Fig. 43.¹¹¹

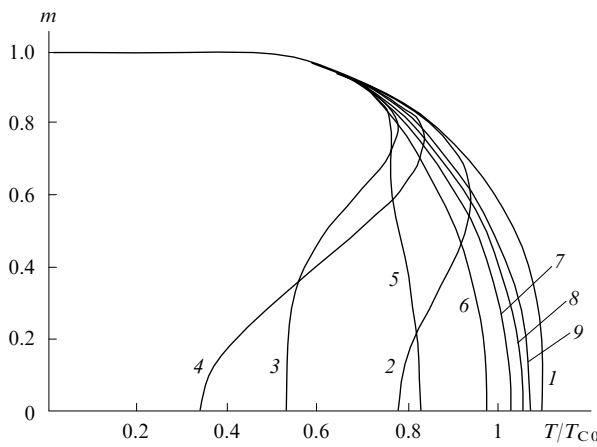


Figure 43. Relative magnetisation (m) of iron oxide plotted vs. T/T_{C0} at different r/a : 6 (1), 12 (2), 25 (3), 50 (4), 100 (5), 200 (6), 300 (7), 400 (8) and 500 (9).¹¹¹

The temperature dependence of the magnetisation is consistent with the published data.¹¹¹ For the oxide clusters, it predicts the existence of a critical size of 30–40 nm, which corresponds to the maximum defect density in the cluster. If a cluster size is larger (smaller) than the critical size range indicated, the character of the magnetic phase transitions changes from the first-order to the second-order magnetic transitions.

Collective magnetic phase transitions with the formation of twin nanostructures. Now we will consider Fig. 23 in more detail. At low temperatures ($T < 120$ K), both phases, α -Fe₂O₃ and γ -Fe₂O₃ exist in the nanostructure. At temperatures above 120 K, in addition to a Morin transition (transition from antiferromagnetic to a weakly ferromagnetic structure; in bulk iron oxides occurs at 256 K, see Refs 104, 112) the α -Fe₂O₃ and γ -Fe₂O₃ phases undergo transformation into a common phase similar to the

α -Fe₂O₃ phase in ΔE_Q , the structural symmetry of the α -Fe₂O₃ and γ -Fe₂O₃ phases being retained (according to X-ray analysis data). The temperature dependences of the isomer shift show an abrupt change δ at 120 K. As a result, δ for the α -phase decreases while that for the γ -phase increases jumpwise to an average value of 0.45 mm s⁻¹. These data also indicate collective transformations of the γ - and α -phases into an α -like phase with retention of cubic spinel symmetry. This transition can be explained by the formation of a twin structure. Twinning is known to occur upon crystallisation, mechanical deformation, seed sintering, fast thermal expansion or compression, and heating of deformed crystals.^{113, 114}

Nanostructures formed under shear stress and high pressure. Exposure of bulk materials to shear stress under high pressure leads to nanostructuring and a decrease in the nanocrystallite size to 5–10 nm. Simultaneously, plastic deformation leads to generation of numerous defects that affect the magnetic properties of nanostructures, in particular, the character and critical parameters of magnetic phase transitions. When unloaded, nanocomposites comprising α -Fe₂O₃ and γ -Fe₂O₃ nanoclusters retain the stresses and defects; they are characterised by the first-order magnetic phase transitions and a decrease in T_{C0} due to an increase in the defect density. Nanostructuring of bulk samples should also induce shifts of the critical points and change the character of magnetic phase transitions from the first-order to the second order ones or *vice versa*.

Here we will consider magnetic phase transitions in two nanosystems based on the α -Fe₂O₃ and γ -Fe₂O₃ (I) and metallic europium (II) nanoclusters. The first nanosystem included α -Fe₂O₃ and γ -Fe₂O₃ nanoclusters of size 20–50 nm (I.1) and identical α -Fe₂O₃ and γ -Fe₂O₃ nanoclusters with addition of 50% monomeric acrylamide (I.2). The second nanosystem included metallic europium nanoparticles (II.1), metallic europium with addition of 1% of α -Fe₂O₃ and γ -Fe₂O₃ nanoclusters of size 20–50 nm (II.2) and metallic europium with addition of 10% of adamantane (II.3).^{111, 115}

A high-pressure apparatus of Bridgman anvil type allowed one to produce pressures of up to 5 GPa with the simultaneous accumulation of the total shear stress with an increment of 10° during 5 s. A pressure of 2 GPa was applied and the turn angles of the anvil varied from 120 to 240°.

Exposure of system (I.2) to shear stress under a pressure of up to 2 GPa causes polymerisation of acrylamide. The shear deformations in the unloaded polymer remain unchanged, which precludes recrystallisation of α -Fe₂O₃ and γ -Fe₂O₃ and recovery of the initial phase equilibrium. The action of shear stress under high pressure led to an increase in the proportion of the non-magnetic component in this system, but the most remarkable result was obtained for the nanosystem (II.2). The ⁵⁷Fe Mössbauer spectrum of nanostructure (II.2) at 300 K after shear stress under pressure (Fig. 44) exhibits almost complete loss of magnetic ordering in the α -Fe₂O₃ and γ -Fe₂O₃ clusters, which indicates a decrease in the average nanocrystallite size and reduction of the Curie or Néel temperatures below room temperature.

Mössbauer spectroscopy data for the nanosystems based on metallic europium show the reverse, namely, an increase in the transition temperature for europium.

The ¹⁵¹Eu Mössbauer spectra of nanostructures (II.1), (II.2) and (II.3) at 90 K measured after exposure to shear stress under high pressure are shown in Fig. 45.

The spectrum of nanostructure (II.1) includes not only the metallic component corresponding to four lines in the HFS, but also the europium dioxide and europium oxide lines (Fig. 45a). The spectrum of nanostructure (II.2) consists of three components, a broad line of metallic europium and the EuO and Eu₂O₃ lines (Fig. 45b). The spectrum of nanostructure (II.3) exhibits three components corresponding to lines of the magnetic HFS of metallic europium in the magnetically ordered state, a very broad line of metallic europium and a line of EuO (Fig. 45c).

Analysis of the experimental results suggests the following.

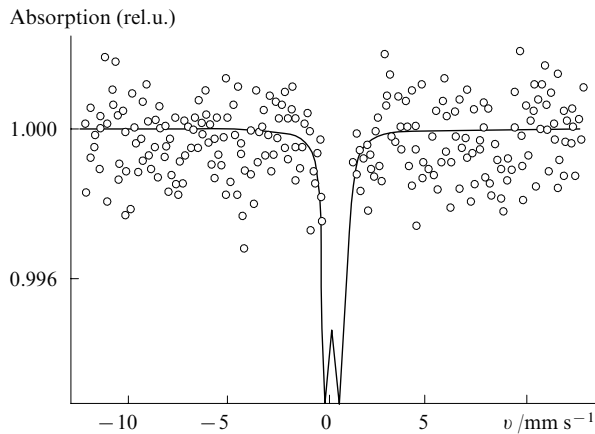


Figure 44. ^{57}Fe Mössbauer spectrum of nanostructure II.2 at room temperature upon a pressure with the turn of anvils.

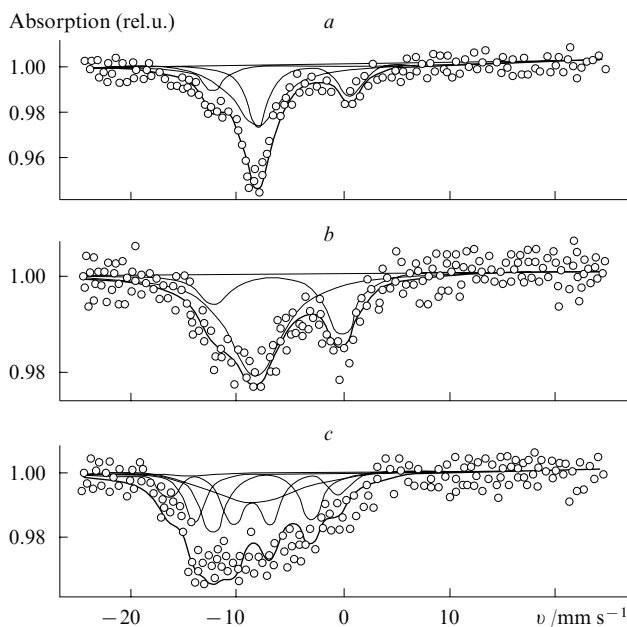


Figure 45. ^{151}Eu Mössbauer spectra of nanostructures II.1 (a), II.2 (b), and II.3 (c) at 90 K upon a pressure of 2 GPa with the turn angle of anvils of 120° .

1. The first-order magnetic phase transitions (jumpwise disappearance of the magnetisation of the nanostructure at certain critical temperature) are observed in nanostructures (I.1), (I.2), (II.2) subjected to shear stress under high pressure. As the measurement temperature increases from 77 to 300 K, the spectra of the nanosystems studied show a transition of iron oxide nanoclusters from the magnetic state characterised by a magnetic HFS to the paramagnetic state without line broadening and shift due to the existence of the critical cluster size.

2. The critical temperatures of magnetic phase transitions (T_C or T_N) in nanostructures (I.1), (I.2) and (II.2) are much lower than the magnetic phase transition temperatures of bulk samples. The critical temperatures decrease even more appreciably upon adding acrylamide or metallic europium.

3. In contrast to nanosystem (I.1), a characteristic feature of nanosystem (II.1) is the second-order magnetic phase transition. This follows from the fact that above the critical transition temperature (~ 80 K, see Ref. 116) the Mössbauer spectrum exhibits a superposition of the narrow line of non-magnetic europium and the broad line with unresolved magnetic HFS of

the magnetically ordered europium. Thus, the magnetic phase transition temperature T_N of nanostructured europium is about 100 K higher than T_N of bulk metal.

4. Adding 1% of $\alpha\text{-Fe}_2\text{O}_3$ and $\gamma\text{-Fe}_2\text{O}_3$ nanoclusters [nanosystem (II.2)] or 10% of adamantane [nanosystem (II.3)] to metallic europium causes further increase in T_N , especially pronounced for nanosystem (II.3).

These features are characteristic of the nanostructures comprised of relatively large nanoclusters in which the high density of defects formed upon exposure to shear stress under high pressure should retain. The results obtained make it possible to employ the defect density distribution in the nanostructure, which passes through a maximum at cluster sizes of 30–50 nm, for characterisation of the magnetic properties of these nanostructures. The critical defect densities should correspond to the critical cluster sizes upon the change in the character of the magnetic phase transition from the first-order to the second-order transition and *vice versa*.

A model for magnetic phase transitions in defect nanostructured systems¹¹⁵ provides an explanation for all the effects considered above for the oxide and metallic nanosystems.

First-order magnetic phase transitions (Z-shaped curves) should be observed for iron oxide clusters of size 20–50 nm. At temperatures above T_C , the magnetisation of such clusters disappears jumpwise. The T_C value also depends on the size of the clusters present in the system. If the cluster size exceeds the maximum critical value ($> r_{cr}^{max}$), the second-order magnetic phase transition characteristic of bulk samples occurs and T_C increases. Reduction of the cluster size ($< r_{cr}^{min}$) also causes the second-order magnetic phase transitions to occur due to the decrease in the defect concentration.

The character of magnetic phase transitions and the T_C value are affected by the intercluster magnetic interactions. However, the changes in the intercluster distance affect the temperature dependence of magnetisation to a lesser extent compared to the changes in the cluster size. For instance, a maximum increase in T_C with a decrease in the intercluster distance from R to the lattice constant a is $\sim 6\%$.¹¹⁵ This is accompanied by the change in the character of the magnetic phase transition from the first-order to the second-order one.

Nanostructuring of nanosystems (I.1) and (I.2) by exposure to shear stress under pressure leads to reduction of the average cluster size and the average intercluster distance. For nanosystem (I.1), the effect of the decrease in the cluster size on T_C is counterbalanced by the effect of compaction, which causes strengthening of the magnetic intercluster interaction. Nanosystems (I.2) or (II.2) are characterised by reduction of T_C and an increase in the contribution of the first-order magnetic phase transition. This is particularly pronounced for nanostructure (II.2) in which the magnetic ordering in all iron oxide nanoclusters is destroyed at room temperature. Therefore, an increase in the intercluster distances leads to weakening of magnetic interactions, extension of the jumpwise magnetic phase transitions and an increase in the probability of the first-order magnetic phase transitions.

Exposure of nanosystem (II.1) to shear stress under pressure leads to nanostructuring of the material. At temperatures below T_N , the starting metal has a domain structure with a domain size of up to tens of nanometres.¹⁰⁴ Above T_N (~ 80 K), bulk metallic europium undergoes a first-order magnetic phase transition accompanied by sharp loss of magnetic ordering. The structure of metallic europium in the magnetically ordered state can be considered as consisting of nanocluster ‘domains’ packed in the crystal lattice of metallic europium. The size of these magnetic nanocluster ‘domains’ close to 20–30 nm provides the maximum defect density and, hence, the maximum density of strain, which induces the first-order magnetic phase transitions in metallic europium.

The aforesaid can be substantiated by high magnetostriction coefficients of rare-earth metals. The shear stress under pressure

causes a decrease in the size of the cluster 'domains' and they become smaller than the critical value. This leads to a decrease in the defect concentration and elimination of strain in the nano-system. As a result, the first-order magnetic phase transition is destroyed and, as a consequence, the magnetically ordered state is extended to the region of higher temperatures. This leads to an increase in T_N of metallic europium. The addition of 1% of iron oxide clusters makes this effect more pronounced due to higher strain in the iron oxides (compared to metallic europium) responsible for the decrease in the size of the nanoclusters composing the nanostructure. The effect is more pronounced upon filling the europium matrix with adamantane molecular clusters, which retain the strain in the nanostructure after the pressure is removed. Additionally, it seems likely that the introduction of iron oxide clusters and adamantane molecules as additives favours uniform nanostructuring on exposure to shear stress under pressure. Thus, nanostructuring of substances can either decrease or increase the T_C (T_N) temperatures of nanomaterials.

* * *

Summing up, nanoclusters and nanostructures exhibit specific features related to their stability and structure, which can be treated as the onset of discreteness of matter on the nanolevel. This manifests itself in the formation of nanoclusters and nanostructures and in consideration of the mechanical, thermal, electrical, optical and magnetic properties. The discreteness is characterised by the 'magic' numbers of atoms and the critical sizes of nanoclusters, which are related to the stability and preferred formation of nanoparticles of particular sizes and to manifestation of certain specific properties of nanomaterials, e.g., changes in the melting temperature, heat capacity, one-electron conductivity, onset of laser emission, appearance of the first-order magnetic phase transitions, etc.

This work has been written with the financial support from the Russian Foundation for Basic Research (Project No. 06-03-32006).

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^a — *Kinet. Catal. (Engl. Transl.)*

^b — *Dokl. Chem. (Engl. Transl.)*

^c — *J. Exp. Theor. Phys. (Engl. Transl.)*

^d — *Chem. Phys. Rep. (Engl. Transl.)*

^e — *Bull. Russ. Acad. Sci., Phys. (Engl. Transl.)*

^f — *Phys. Met. Metallogr. (Engl. Transl.)*

^g — *Russ. Chem. Bull., Int. Ed. (Engl. Transl.)*

Methods of synthesis of Group 4–9 transition metal imido complexes

D N Zarubin, N A Ustynyuk

Contents

I. Introduction	671
II. Intermolecular imidation methods	672
III. Intramolecular imidation methods	696
IV. Conclusion	701

Abstract. The synthetic routes to Group 4–9 transition metal imido complexes are considered. Both common and less common approaches are analysed. The classification of the methods for the synthesis of imido complexes is based on the way of formation of the imido ligand, the change in the metal oxidation state during imidation and the type of imidation reagent. The bibliography includes 415 references.

I. Introduction

The chemistry of transition metal imido complexes is currently a priority avenue of research in coordination chemistry which arouses an ever increasing interest. The intensive development of this field is caused by a number of reasons, first of all, successful use of imido complexes in organic synthesis and in metal complex catalysis and also as promising materials for various purposes.

It is expedient to distinguish two groups of stoichiometric and catalytic reactions involving imido complexes. The first group includes various nitrogen group transfer reactions (redox reactions and metathesis) with direct participation of the imido ligand of the complex. Examples are amination of alkenes to give *vic*-amino alcohols and *vic*-diamines,^{1–3} allylamines⁴ and aziridines;^{4–6} hydroamination of carbodiimides,⁷ alkenes,⁸ alkynes and allenes;^{9–12} transfer of the imido groups onto tertiary phosphines and isocyanides yielding iminophosphoranes^{13–21} and carbodiimides, respectively;^{22, 23} condensation of organic isocyanates to give carbodiimides;²⁴ and metathesis of carbodiimides^{25, 26} and imines.^{27–31}

The second group comprises reactions involving transition metal imido complexes in which the imido ligand does not undergo chemical transformation but acts as a 'spectator ligand' stabilising the complex. These reactions are exemplified by alkene dimerisation³² and polymerisation;^{33–43} C–H bond activation;^{44–47} and alkene cyclopropanation.⁴⁸ Special mention should be made of the metathesis of unsaturated hydrocarbons catalysed by Schrock imidocarbene complexes.^{49, 50} These reactions include ring-opening metathesis polymerisation (ROMP) of cyclic

alkenes;^{51–58} ring-closing metathesis (RCM) of dienes^{59–69} and diynes;⁷⁰ asymmetric ring-opening metathesis/cross metathesis (AROM/CM) of acyclic and cyclic alkenes;^{64, 69–73} and a tandem of asymmetric ring-opening and ring-closing metathesis reactions (AROM/RCM).^{64, 69, 74–76} R Schrock was awarded the Nobel Prize in 2005 for the invaluable contribution to the development of organic synthesis.

In recent years, the use of imido complexes of some metals as promising starting compounds for the chemical vapour deposition (MOCVD) of nitrides has been reported.^{77–82}

The chemistry, spectroscopic characteristics and structures of transition metal imido complexes have been considered comprehensively in reviews.^{83–86} The present review is devoted to comparative analysis of the methods of synthesis of Group 4–9[†] transition metal complexes with terminal imido RN groups containing alkyl, aryl and trialkylsilyl organic groups. Due to the limited size of the publication, we leave aside the complexes containing bridging imido ligands; they are mentioned only in the cases where a complex contains both bridging and terminal imido ligands. The review is focused on the imido derivatives of d elements; examples of imido compounds formed by f elements reported in the literature are few in number and represented in the review by only uranium complexes.[‡] This review covers publications up to the end of 2004.

Imidation methods are usually classified according to the types of imidating agents.^{83–86} The classification used in this review takes into account consecutively the way of formation of the imido ligand, the change in the metal oxidation state during imidation, the type of the imidating agents and the nature of the starting compounds. All the methods of synthesis of imido complexes known to date can be divided into two large groups. The first one includes intermolecular imidation methods in which the imido complex is formed using an external imidating agent. In the case of intermolecular imidation, the formal oxidation state of the metal in the complex can either change or remain unchanged depending on the nature of the agent and the starting metal-containing compound.

The second group comprises intramolecular imidation methods in which the imido group is formed from another nitrogen-containing ligand present in the metal complex. Nitride and amide complexes are used most often as the starting compounds; examples of the transformation of other nitrogen-containing

D N Zarubin, N A Ustynyuk A N Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, ul. Vavilova 28, 119991 Moscow, Russian Federation. Fax (7-495) 135 50 85, tel. (7-495) 135 88 61, e-mail: zarubine@ineos.ac.ru (D N Zarubin), tel. (7-495) 135 50 64, e-mail: ustynyuk@ineos.ac.ru (N A Ustynyuk)

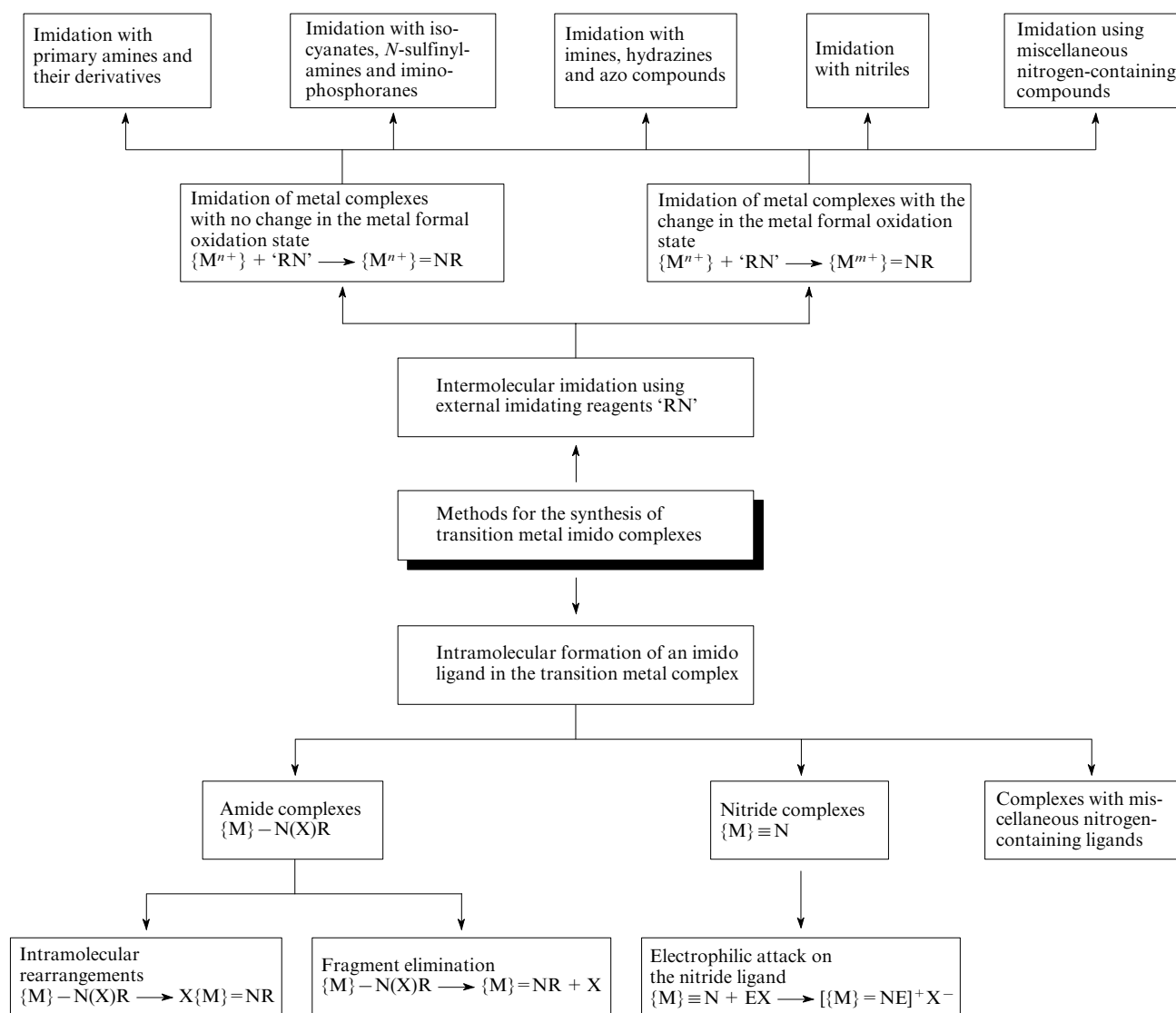
Received 19 January 2006

Uspekhi Khimii 75 (8) 753–790 (2006); translated by Z P Bobkova

[†] Group 10 and 11 transition metals are beyond the scope of the review, as they form complexes with bridging imido ligands.^{87, 88}

[‡] Data on the imido derivatives of p elements can be found in recent reviews.^{89, 90}

Scheme 1



ligands are scarce. In the intramolecular imidation, the formal oxidation state of the metal usually remains unchanged.

Scheme 1 shows the classification of the methods of synthesis of transition metal imido complexes used in this review.

II. Intermolecular imidation methods

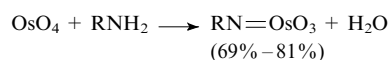
1. Imidation of metal complexes with no change in the metal oxidation state

a. Imidation with primary amines

Primary amines were historically the first compounds proposed as external imidation agents. Nevertheless, methods using these reagents have still not lost their practical value, which is determined first of all by wide choice, ready availability and relatively low cost of aliphatic and aromatic amines. Amines are suitable for imidation of metal-containing compounds of various types, among which metal oxides and halides are used most often.

The imidation of oxides (imido-deoxygenation) with primary amines is accompanied by elimination of water and can be carried out for transition metals of Groups 7 and 8, such as Tc, Re, and Os. For example, the first known imido complex, $\text{Bu}^t\text{N}=\text{OsO}_3$, was prepared by treatment of osmium tetroxide with *tert*-butyl-

amine.^{2, 91} Subsequently, this approach has been used to prepare other osmium monoimido complexes.^{2, 3, 92}



R = Bu^t , CMe_2Et , $\text{CMe}_2\text{CH}_2\text{Bu}^t$, Ad.

Table 1 presents examples of rhenium and technetium imido complexes obtained by imido-deoxygenation with amines. For this type of complexes, this is the main method of synthesis, which is usually more convenient than imido-deoxygenation using isocyanates, *N*-sulfinylamines, iminophosphoranes, hydrazines, formamides and hydrazides.

In bi- and polynuclear oxo complexes [for example, $\text{Re}_2\text{O}_3(\text{S}_2\text{CNEt}_2)_4$]¹⁰⁶ containing both bridging and terminal oxo groups, only the latter undergo the oxo–imido exchange.

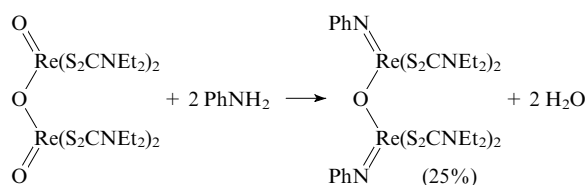


Table 1. Synthesis of rhenium and technetium imido complexes by imido-deoxygenation with primary amines.

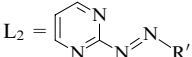
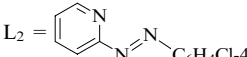
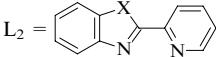
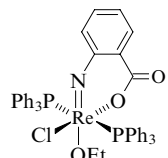
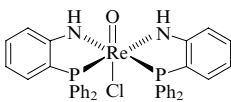
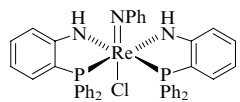
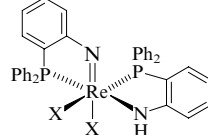
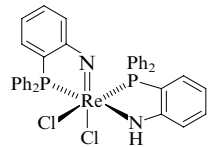
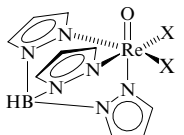
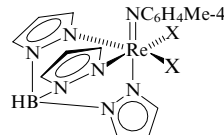
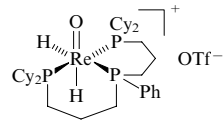
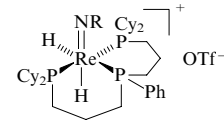
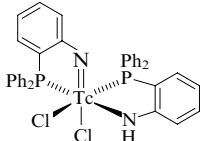
Starting compound	Amine (RNH ₂)	Product	Yield (%)	Ref.
ReOCl ₃ L ₂ L = PPhEt ₂ L = PPh ₃	PhNH ₂ 4-FcC ₆ H ₄ NH ₂ 2-XC ₆ H ₄ NH ₂ (X = NH ₂ , 2-NH ₂ -3-HOC ₆ H ₃ , 2-NH ₂ -3-MeC ₆ H ₃)	RN=ReCl ₃ L ₂ R = Ph R = 4-FcC ₆ H ₄ R = 2-XC ₆ H ₄	— 44 61–77	93 94 95
L ₂ =  R' = Ph R' = C ₆ H ₄ Cl-4	PhNH ₂ 4-ClC ₆ H ₄ NH ₂	R = Ph R = 4-ClC ₆ H ₄	65 70	96 96
L ₂ = 	4-XC ₆ H ₄ NH ₂ (X = H, Cl, Me)	R = 4-XC ₆ H ₄	75–80	97
L ₂ = bipy	PhNH ₂	R = Ph	65	98
L ₂ =  X = O X = S	PhNH ₂ PhNH ₂	R = Ph R = Ph	81 79	99 99
ReOCl ₃ (PPh ₃) ₂	2-HO ₂ CC ₆ H ₄ NH ₂ –EtOH (see ^a)		59	100
	PhNH ₂		60	101
ReOX ₂ (OEt)(PPh ₃) ₂ X = Cl, Br, I	2-Ph ₂ PC ₆ H ₄ NH ₂		69–83	102
(Bu ₄ N)[ReOCl ₄]	2-Ph ₂ PC ₆ H ₄ NH ₂		81	102
 X = Cl X = I	4-MeC ₆ H ₄ NH ₂		50 84	103 103
 (Cy is cyclohexyl, OTf is triflate)	PhNH ₂ , 4-MeC ₆ H ₄ NH ₂ , CyNH ₂		56–92	104
(Bu ₄ N)[TcOCl ₄]	4-MeC ₆ H ₄ NH ₂ –PPh ₃ (see ^a)	4-MeC ₆ H ₄ N=TcCl ₃ (PPh ₃) ₂	—	105

Table 1 (continued).

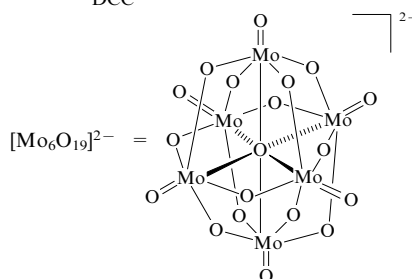
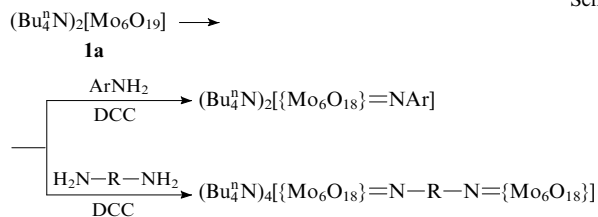
Starting compound	Amine (RNH ₂)	Product	Yield (%)	Ref.
(Bu ₄ N)[TcOCl ₄]	2-Ph ₂ PC ₆ H ₄ NH ₂		73	102

^a Additional reagents present in the reaction mixture and in the final products are indicated.

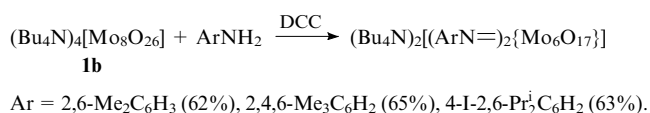
For Group 4–6 metals, imido-deoxygenation with primary amines is inapplicable with rare exceptions, because of high oxophilicity of the metal. In this case, imidation requires additional promoting reagents, for example, a Me₃SiCl–Et₃N mixture, which chemically binds water (see Section II.1.c). Imido-deoxygenation of polymolybdates (Bu₄N)₂[Mo₆O₁₉] (**1a**) and (Bu₄N)₄[Mo₈O₂₆] (**1b**) with aromatic amines occurs efficiently in the presence of dicyclohexylcarbodiimide (DCC) (Scheme 2).^{107–109} The reaction of polymolybdate **1a** with *p*-phenylenediamine in the presence of triethylamine has been reported.¹¹⁰ Depending on the reactant ratio, this gave imido complexes with different compositions, in particular (Bu₄N)₂[H₂NC₆H₄N={Mo₆O₁₇}=NC₆H₄NH₂], (Bu₄N)₄·[{Mo₆O₁₈}=NC₆H₄N={Mo₆O₁₈}], etc.

For successful imidation of the oxo complex MoOCl₂·(S₂CNEt₂)₂ (**2**) with various amines, adjustment of the reaction conditions for each particular case is required. For example, when sterically unhindered *ortho*-substituted anilines, *o*-NH₂C₆H₄NH₂ and *o*-HSC₆H₄NH₂ are used, the reaction is carried out in the presence of triethylamine (Scheme 3, paths *a* and *b*).^{111,112} In the case of sterically hindered anilines, the reaction yields the target oxo–imido metathesis products only in the presence of the strong base BuⁿLi (Scheme 3, path *c*).¹¹³ Meanwhile, imido-deoxygenation of complex **2** under the action of various *p*-phenylenediamines, 1,5-bis(dimethylamino)naphthalene and *para*-substituted anilines can proceed without any auxiliary reagents (Scheme 3, paths *d–f*).¹¹⁴

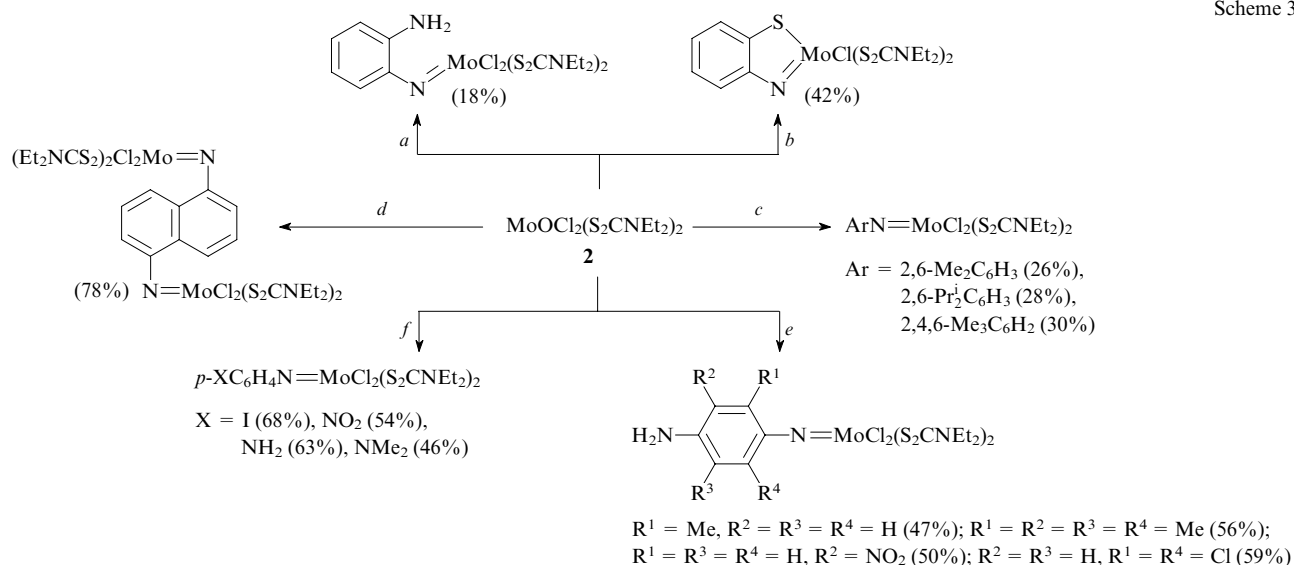
Scheme 2



Ar = 2,6-Me₂C₆H₃ (95%), 2,6-Et₂C₆H₃ (95%), 2,6-Prⁱ₂C₆H₃ (91%), 4-I-2,6-Me₂C₆H₂ (72%), 4-(HC≡C)-2,6-Me₂C₆H₂ (91%);
R = 4-C₆H₄O(CH₂)_nOC₆H₄-4 (*n* = 3, 4, 8; 49%–76%).



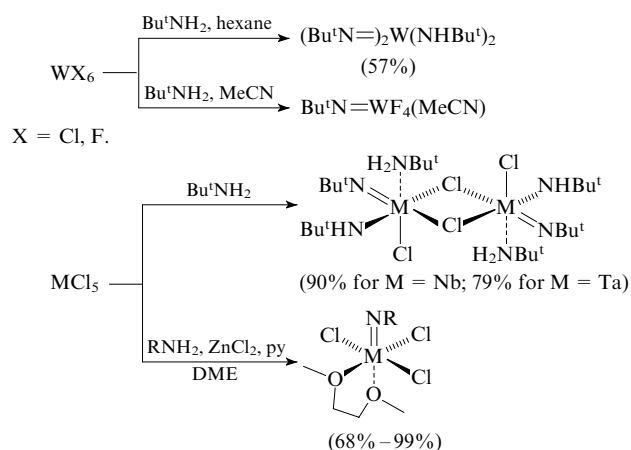
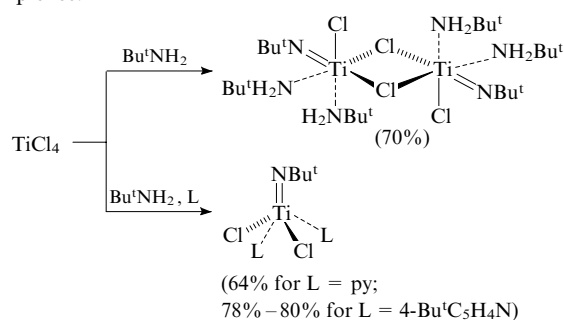
Scheme 3



(a) *o*-H₂NC₆H₄NH₂·2 HCl–Et₃N; (b) *o*-H₂NC₆H₄SH–Et₃N; (c) ArNH₂–BuⁿLi; (d) 1,5-(H₂N)₂C₁₀H₆; (e) *p*-(H₂N)₂C₆H₃R¹R²R³R⁴; (f) *p*-XC₆H₄NH₂.

The complex $\text{Tp}'\text{W}(=\text{NPh})(\text{CO})\text{I}$ [Tp' is tris(3,5-dimethylpyrazol-1-yl) borate] was prepared by imido-deoxygenation of $\text{Tp}'\text{W}(\text{O})(\text{CO})\text{I}$ with aniline in the absence of other reagents.¹¹⁵ No such reactions are known for metals of titanium and vanadium groups, which is due to higher oxophilicity of these elements.

The imido-dehalogenation (replacement of halogen atoms by the imido function) of transition metal halides with primary amines is widely used in the synthesis of imido complexes. The reaction of amines with homoleptic halides of Group 4–6 transition metals, for example, with TiCl_4 ,^{116–118} NbCl_5 ,^{77, 119–121} TaCl_5 ,^{77, 120} WX_6 ($\text{X} = \text{F}, \text{Cl}$),^{122, 123} usually afford dimeric imido complexes; however, the reaction carried out in the presence of n -donor compounds [py, 4- $\text{Bu}^t\text{C}_5\text{H}_4\text{N}$, MeCN, 1,2-dimethoxyethane (DME), *etc.*] results in mononuclear complexes.



$\text{M} = \text{Nb}, \text{Ta}$; $\text{R} = \text{Bu}^t, \text{Ph}, 2,6\text{-Me}_2\text{C}_6\text{H}_3, 2,6\text{-Pr}_2\text{C}_6\text{H}_3, \text{anthracen-2-yl}, \text{Ad}, 2\text{-naphthyl}, 4\text{-NCC}_6\text{H}_4, 4\text{-MeC}_6\text{H}_4, 4\text{-MeOC}_6\text{H}_4$.

Various heteroleptic transition metal chlorides are also successfully used for the preparative synthesis of imido complexes. Examples of imido complexes prepared by imido-dechlorination of heteroleptic metal chlorides with primary amines are summarised in Table 2. It is noteworthy that some of these can be prepared with equal success by imido-dehalogenation with trimethylsilylamines (see Section II.1.c, Table 5).

Table 2. Synthesis of Group 4–8 transition metal imido complexes by imido-dechlorination with primary amines.

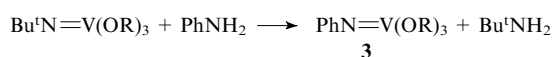
Starting compound	M	Ar or X	R in RNH ₂	Product	Yield (%)	Ref.
	Mo	H, Me, Pr ⁱ	Bu ^t , Pr ⁱ , Pr ⁿ , Ph, 2,6-Me ₂ C ₆ H ₃		36–83	124–126
	W	CH ₂ Cl	2,6-Me ₂ C ₆ H ₃		65	127
		H	Bu ^t		35	124
		Me	Bu ^t		70	125
		CH ₂ Cl	Bu ^t		70	127
	Mo		Bu ^t , Pr ⁱ , C ₆ F ₅ , 2,6-Pr ₂ C ₆ H ₃		39–75	128, 129
	W		Bu ^t , Pr ⁱ , C ₆ F ₅ , 2,6-Pr ₂ C ₆ H ₃		45–70	129, 130
	Re		Me		65	131
			Bu ^t		56	131
			Pr ⁱ		70	132
	V	4-MeC ₆ H ₄	Bu ^t , 4-XC ₆ H ₄ (X = H, Me, Cl, OMe)		54–69	133
	Ru	4-Bu ^t C ₅ H ₄	4-XC ₆ H ₄ (X = H, Me, Cl, I)		40–75	15
	Nb	2,4,6-Pr ₃ C ₆ H ₂	Bu ^t		59	134
	Ta	2,4,6-Pr ₃ C ₆ H ₂	Bu ^t		53	134
		2,6-Pr ₂ C ₆ H ₃ (Ar), 2,6-Me ₂ C ₆ H ₃ (Ar')	4-MeC ₆ H ₄ , 4-NO ₂ C ₆ H ₄ , 2-Bu ^t C ₆ H ₄		—	135

A convenient preparative-scale method for the synthesis of arylimido complexes of Group 4–6 transition metals is transimidation with various anilines. The method is based on equilibrium replacement of some imido ligands by other imido ligands.



tert-Butylimido complexes are the best starting compounds, because in this case, the shift of the equilibrium toward the substitution product is easily attained by removing volatile *tert*-butylamine from the reaction mixture. This method has opened the way to various arylimido titanium complexes (Table 3).

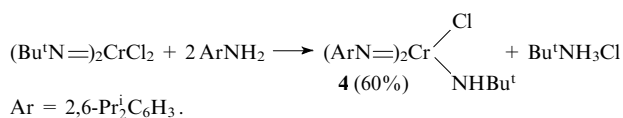
Transimidation with amines is successfully used to prepare arylimido complexes of other metals. This method was first used to prepare vanadium phenylimido complexes **3**.^{143, 144}



R = SiMe₃ (53%), Et (22%), Bu^t (69%).

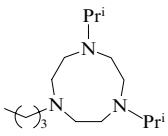
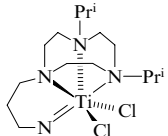
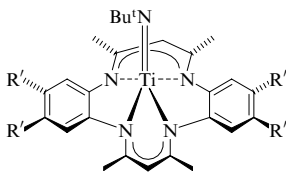
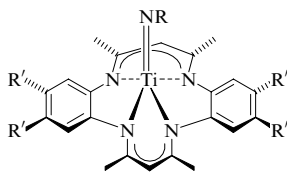
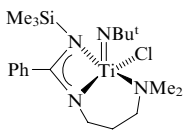
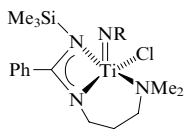
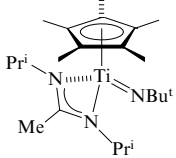
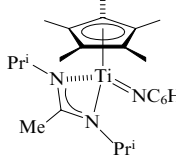
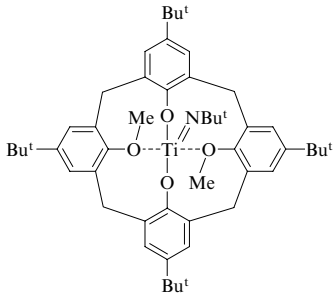
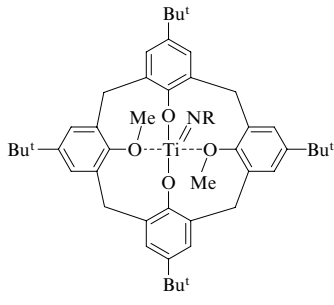
The method appeared to be especially convenient for the synthesis of asymmetric bisimido complexes. For example, treatment of the symmetric bisimido complex (Bu^tN=)₂MoCl₂(DME) with one equivalent of C₆F₅NH₂ or 2,6-Pr₂C₆H₃NH₂, gave the complexes (Bu^tN=)(RN=)MoCl₂(DME) (R = C₆F₅, 2,6-Pr₂C₆H₃) containing two different imido ligands in high yields (>90%).^{145, 146}

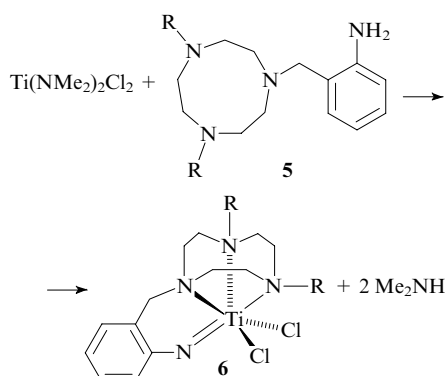
The reaction of (Bu^tN=)₂CrCl₂ with two equivalents of 2,6-diisopropylaniline gives bis(arylimido) complex **4**.¹⁴⁷



Other metal-containing compounds, for example dimethyl-amido, carbene and σ-alkyl complexes of transition metals, can also be used in the imidation with amines. The reaction of titanium diamide complex Ti(NMe₂)₂Cl₂ with amine **5** afforded imido chelate **6**.¹⁴⁸

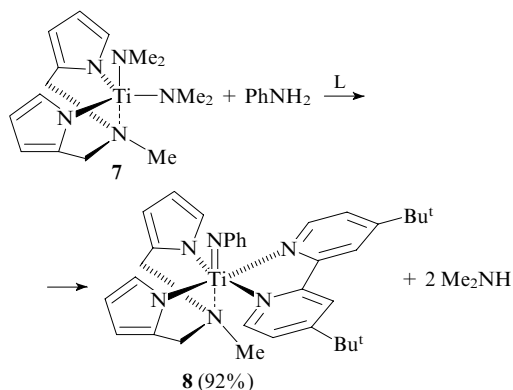
Table 3. Synthesis of titanium imido complexes by transimidation with amines.

Starting compound	R in RNH ₂	Product	Yield (%)	Ref.
Bu ^t N=TiCl ₂ (py) ₃	Ph, 4-MeC ₆ H ₄ , 2,6-Me ₂ C ₆ H ₃ , 2,6-Pr ₂ ⁱ C ₆ H ₃ 4-Me ₃ SiOC ₆ H ₄ 4-NH ₂ C ₆ Me ₄	RN=TiCl ₂ (py) ₃	36–86 77 91	118 136 137
Bu ^t N=TiCl ₂ (py) ₃			74	138
Bu ^t N=TiCl ₂ (TMEDA)	2-Bu ^t C ₆ H ₄	2-Bu ^t C ₆ H ₄ N=TiCl ₂ (TMEDA)	—	116
 (R' = H, Me)	4-XC ₆ H ₄ (X = H, Me, NO ₂ , NMe ₂)		75–95	139
	2,6-Me ₂ C ₆ H ₃ , C ₆ F ₅		90–93	140
	2,6-Me ₂ C ₆ H ₃		> 95	141
	4-MeC ₆ H ₄ , 2,6-Me ₂ C ₆ H ₃ , 2,6-Pr ₂ ⁱ C ₆ H ₃ , 4-FcC ₆ H ₄		84–100	142



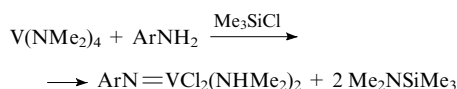
R = Me (58%), Prⁱ (64%).

A similar exchange of the NMe₂ ligands in titanium polyamide complex **7** yielded imido complex **8** containing simultaneously three types of metal–nitrogen bonds.¹⁴⁹



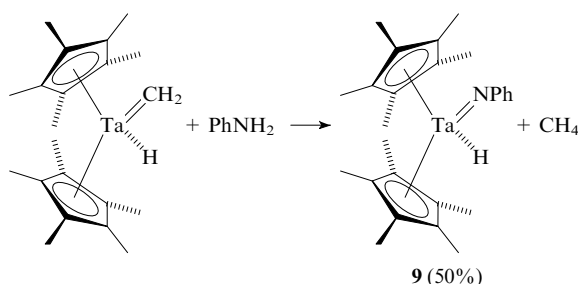
L is 4,4'-bis(*tert*-butyl)-2,2'-bipyridyl.

Imido-deamidation of homoleptic niobium and tantalum dimethylamide complexes M(NMe₂)₅ by amines is a convenient method for the synthesis of mixed imidoamide complexes of these metals (RN=M(NMe₂)₃ [R = Bu^t, 2,6-Prⁱ₂C₆H₃; M = Nb (79%), Ta (86%)].^{150, 151} By combining imido-deamidation and chloro-deamidation of the homoleptic complex V(NMe₂)₄ as a one-pot process, a series of d¹-vanadium complexes have been prepared.^{152, 153}



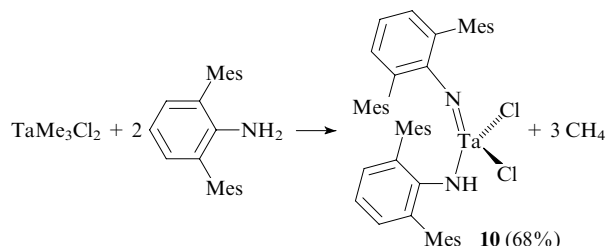
Ar = 2,6-Me₂C₆H₃ (79%), 2,6-Prⁱ₂C₆H₃ (88%), 2,6-Cl₂C₆H₃ (96%), Ph (80%), C₆F₅ (73%).

Examples of a methylene ligand displacement in carbene complexes by primary amines are known. In particular, this approach was used in the synthesis of tantalum imidohydride complex **9**.¹⁵⁴



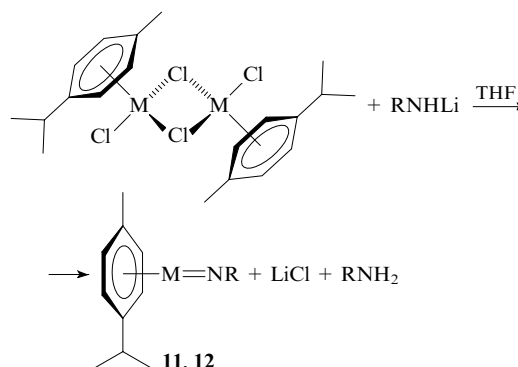
[Complex **9** is produced in higher yield in the redox imidation of (η⁵-Cp*)₂TaCl (see Section II.2.f, Table 12).]

Tantalum imidoamide complex **10** containing sterically hindered aryl groups has been prepared by imido-dealkylation of the trimethyl complex TaMe₃Cl₂ on treatment with 2,6-disubstituted aniline.¹⁵⁵

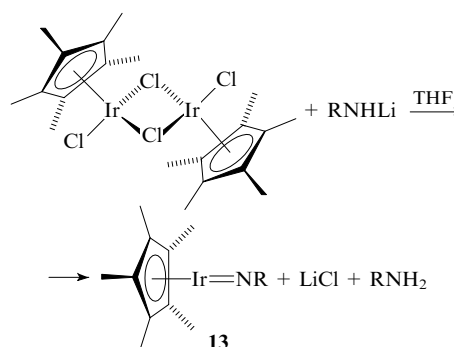


b. Imidation with lithium derivatives of primary amines

Lithium amides are widely used to prepare transition metal imido complexes. Examples of imidation of various homo- and heteroleptic Group 4 and 5 metal halides with lithium amides are given in Table 4. Lithium amides are, however, used much more rarely to prepare derivatives of transition metals of Group 6–9. Only a few examples of imidation of complexes containing Os, Ru and Ir in low oxidation states with lithium derivatives of a number of sterically hindered amines have been reported. In particular, imido-dechlorination of osmium^{168, 169} and ruthenium^{170, 171} arene chlorides or iridium pentamethylcyclopentadienyl chlorides^{172, 173} led to unusual mononuclear d⁶-complexes **11**–**13**.



11: M = Os; R = Bu^t (60%), 2,6-Prⁱ₂C₆H₃ (36%), 2,6-Me₂C₆H₃ (96%);
12: M = Ru; R = 2,4,6-Bu₃C₆H₂ (40%).



R = Bu^t (91%), 2,6-Me₂C₆H₃ (33%), Bu^tMe₂Si (90%), 2,6-Prⁱ₂C₆H₃ (77%).

c. Imidation with trimethylsilylamines

The use of trimethylsilyl derivatives of primary amines is among the most common methods for intermolecular imidation. Two versions of this process are known: one uses pre-synthesised mono- or bis(trimethylsilyl)amines, while in the other, trimethylsilyl derivatives of amines are prepared *in situ* by introducing the

Table 4. Synthesis of Group 4 and 5 transition metal imido complexes by imido-dechlorination with alkali metal amides.

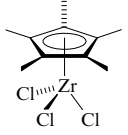
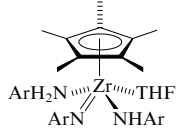
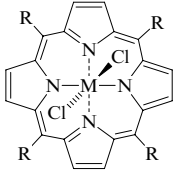
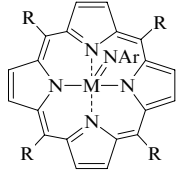
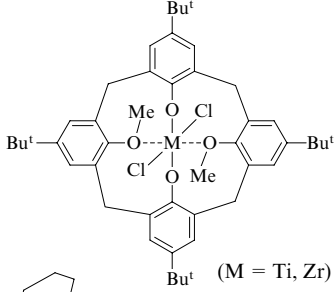
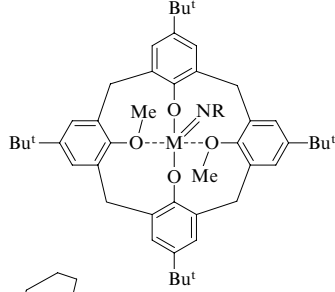
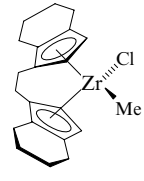
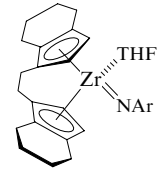
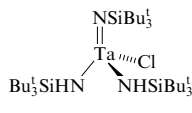
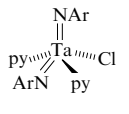
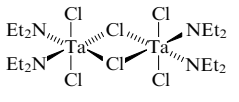
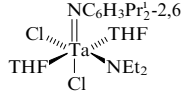
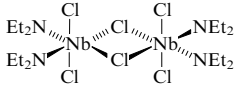
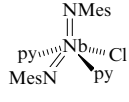
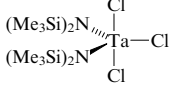
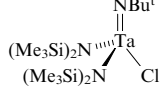
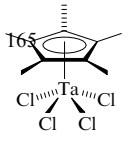
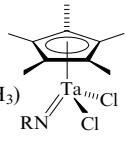
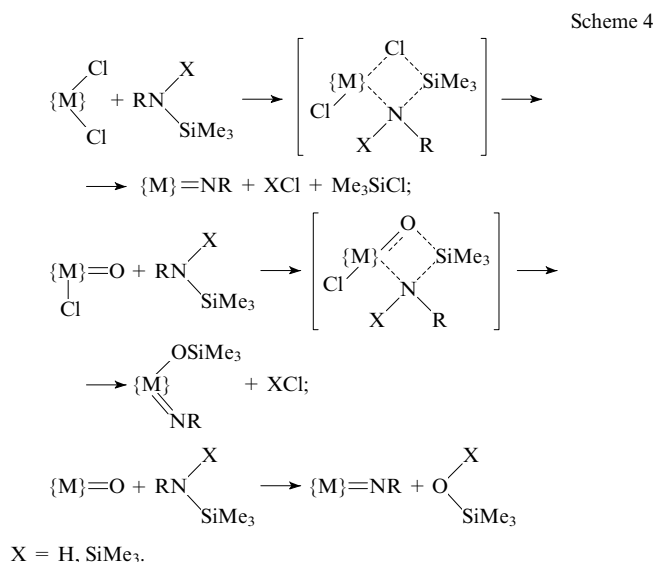
Starting compound	Reagents	Product	Yield (%)	Ref.
$\text{MCl}_4(\text{THF})_2$ (M = Zr, Hf)	ArNHLi (Ar = 2,6- $\text{Pr}_2\text{C}_6\text{H}_3$)	$\text{ArN}=\text{M}(\text{NHA}r)_2(\text{THF})_2$	85 (Zr), 49 (Hf)	156
	ArNHLi , THF (Ar = 2,6- $\text{Pr}_2\text{C}_6\text{H}_3$)		44	156
 (M = Zr, Hf, R = Ph; M = Ti, R = 4-Me C_6H_4)	ArNHLi [Ar = 2,6- $\text{Pr}_2\text{C}_6\text{H}_3$ (for Zr, Hf); Bu ^t , Ph, 4-Me C_6H_4 (for Ti)]		93 (Zr) 60 (Hf) 87–94 (Ti)	157 157 158
 (M = Ti, Zr)	RNHLi (R = Bu ^t , 2,6-Me $_2\text{C}_6\text{H}_3$, 2,6- $\text{Pr}_2\text{C}_6\text{H}_3$) or MesNHK (for Ti); 2,6- $\text{Pr}_2\text{C}_6\text{H}_3\text{NHLi}$ (for Zr)		75–100 (Ti); 61 (Zr)	142 142
	ArNHLi , THF (Ar = 2,6-Me $_2\text{C}_6\text{H}_3$, 4-Me C_6H_4)		65	159
MCl_5 (M = Nb, Ta)	Bu ^t NHLi + Me $_2\text{NLi}$	Bu ^t N=M(NMe $_2$) $_3$	20 (Nb) 40 (Ta)	150 160
TaCl $_5$	Bu $_3\text{SiNHLi}$		82	45
TaCl $_3(\text{NEt}_2)_2(\text{OEt}_2)$	ArNHLi , py (Ar = 2,6- $\text{Pr}_2\text{C}_6\text{H}_3$)		60	161
	2,6- $\text{Pr}_2\text{C}_6\text{H}_3\text{NHLi}$, THF		61	161
	MesNHLi, py		79	162
	Bu ^t NHLi		71	163
	RNHLi (R = Bu ^t , 2,6-Me $_2\text{C}_6\text{H}_3$, 2,6- $\text{Pr}_2\text{C}_6\text{H}_3$, 2,6-Me $_2\text{C}_6\text{H}_3$, 2,6-(2,4,6- $\text{Pr}_3\text{C}_6\text{H}_2)_2\text{C}_6\text{H}_3$)		64–85	46, 164,

Table 4 (continued).

Starting compound	Reagents	Product	Yield (%)	Ref.
	2,6-Pr ⁱ ₂ C ₆ H ₃ NHLi		31	166
	(Me ₃ Si) ₂ NLi		—	167
TaMe ₃ Cl ₂	2,6-Mes ₂ C ₆ H ₃ NHLi		71	155

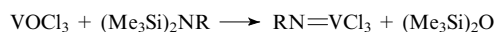
RNH₂–Me₃SiCl–B ternary system in the reaction (B is a base). Either the initial amine or another amine (most often, triethylamine or pyridine) is used as the base, and homo- and heteroleptic halides of Group 4–6 metals and oxo complexes of Group 5 and 6 metals, in particular, sodium or ammonium metallates, are used as the metal-containing compounds. The formation of imido complexes is due to thermodynamically favourable replacement of oxygen or chlorine atoms in the starting compounds by imido groups. In the former variant, Me₃SiCl, (Me₃Si)₂O or HCl (a base is added for binding of HCl) are formed together with target complexes (Scheme 4).



Imido-dechlorination of transition metal chlorides with trimethylsilylamines proceeds smoothly and, most often, gives products in high yields. Examples of imido complexes obtained by this method are presented in Table 5. Note that the use of primary amines (see Section II.1.a) and lithium amides (Section II.1.b) in imido-dechlorination gives most often comparable results.

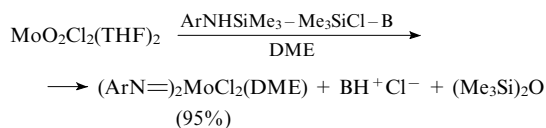
Another type of starting compounds frequently used for imidation with silylamines are oxohalides of Group 5 and 6 transition metals. The synthesis of imido complexes using these compounds is chronologically one of the earliest, because V, Cr, Mo and W oxohalides are easily available (either commercially or synthetically). Imidation can be accompanied by replacement of

either oxygen or chlorine atoms. The first vanadium imido complex MeN=VCl₃ was prepared by imido-deoxygenation of VOCl₃.¹⁸⁷ Later, the same method was used to prepare the phenylimide analogue, PhN=VCl₃.¹⁸⁸

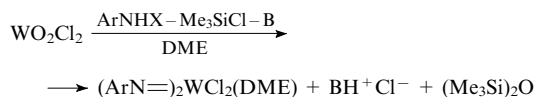


R = Me (80%), Ph.

Conversely, the reaction of WOCl₄ with 4-MeC₆H₄NHSiMe₃ in the presence of 2,2'-bipyridyl involves replacement of chlorine atoms to give the oxo–imido complex 4-MeC₆H₄N=W(O)Cl₂·(bipy).¹⁸⁵ The introduction of chlorotrimethylsilane directs the reaction along the imido-deoxygenation route. For example, on treatment with trimethylsilylamines, the chlorine atoms in chromium and molybdenum dioxodichlorides are replaced by the imido group, giving rise to silyloxyimido complexes (RN=)₂M(OSiMe₃)₂ [M = Cr: R = Bu^t (54%),^{123, 150} Ad (26%);¹⁸⁹ M = Mo: R = Bu^t (93%), 1-norbornyl (80%),^{123, 150} Me₃Si (60%)¹⁹⁰], whereas treatment with amines or their mono-silyl derivatives in combination with chlorotrimethylsilane leads to imido-deoxygenation.^{191–193}



Ar = 2,6-Prⁱ₂C₆H₃, B = 2,6-Me₂C₅H₃N.

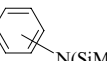
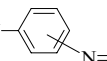
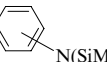
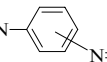
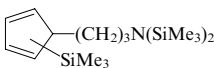
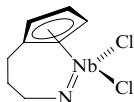
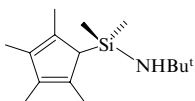
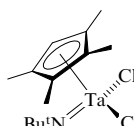
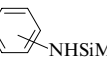
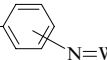
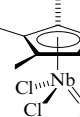
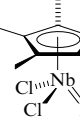
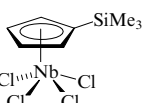
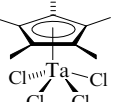


Ar	X	B	Yield (%)
2,6-Pr ⁱ ₂ C ₆ H ₃	H	2,6-Me ₂ C ₅ H ₃ N	70
	SiMe ₃	2,6-Me ₂ C ₅ H ₃ N	64
2,4,6-Me ₃ C ₆ H ₂	H	Et ₃ N	91

It is noteworthy that diimidomolybdenum dichlorides are prepared more conveniently directly from sodium or ammonium molybdate (see below).

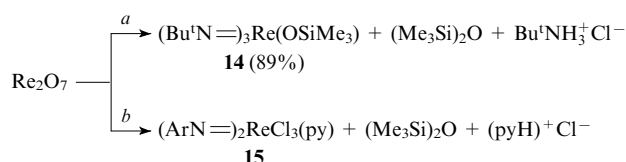
Examples of the synthesis of imido complexes by treatment of transition metal oxides with silylamines are known. The complex (Bu^tN=)₂Cr(OSiMe₃)₂, which is the key compound in the chemistry of d⁰-chromium imido complexes, can be obtained by imido-deoxygenation of chromium(VI) oxide with Bu^tNHSiMe₃

Table 5. Synthesis of Group 4–6 transition metal imido complexes by imido-dehalogenation with trimethylsilylamines.

Starting compound	Amine	Auxiliary reagent (L)	Product	Yield (%)	Ref.
TiCl ₄	(Me ₃ Si) ₂ N-  -N(SiMe ₃) ₂ (<i>meta</i> - and <i>para</i> -isomers)	4-Bu ^t C ₅ H ₄ N, TMEDA	L ₂ Cl ₂ Ti=N-  -N=TiCl ₂ L ₂	72–86	137
	Bu ^t NHSiMe ₃	py	Bu ^t N=TiCl ₂ (py) ₃	50	79
NbCl ₅	(Me ₃ Si) ₂ N-  -N(SiMe ₃) ₂ (<i>ortho</i> -, <i>meta</i> - and <i>para</i> -isomers)	4-Bu ^t C ₅ H ₄ N, MeCN	L ₂ Cl ₃ Nb=N-  -N=NbCl ₃ L ₂	88–90	137
		—		38	174
	Bu ^t NHSiMe ₃	PMe ₃	Bu ^t N=NbCl ₃ (PMe ₃) ₂	—	119
	4-Me ₃ SiC ₆ H ₄ N(SiMe ₃) ₂	MeCN	4-Me ₃ SiC ₆ H ₄ N=NbCl ₃ (MeCN) ₂	96	175
	4-Me ₃ SiOC ₆ H ₄ N(SiMe ₃) ₂	MeCN	4-Me ₃ SiOC ₆ H ₄ N=NbCl ₃ (MeCN) ₂	87	136
TaCl ₅	HN(SiMe ₃) ₂	py	Me ₃ SiN=TaCl ₃ (py) ₂	71	176
	2,6-Pr ⁱ ₂ C ₆ H ₃ NHSiMe ₃	THF	2,6-Pr ⁱ ₂ C ₆ H ₃ N=TaCl ₃ (THF) ₂	82	177
		—		45	39
TaX ₅ (X = Cl, Br)	2,6-Pr ⁱ ₂ C ₆ H ₃ NHSiMe ₃	TMEDA, DME, THF, py	2,6-Pr ⁱ ₂ C ₆ H ₃ N=TaX ₃ L ₂	29–82	178
MoCl ₅	2-NCC ₆ H ₄ N(SiMe ₃) ₂	MeCN	2-NCC ₆ H ₄ N=MoCl ₃ (MeCN) ₂	65	179
WCl ₆	2-NCC ₆ H ₄ N(SiMe ₃) ₂	—	[2-NCC ₆ H ₄ N=WCl ₄] ₂	91	179
	Me ₃ SiHN-  -NHSiMe ₃ (<i>ortho</i> - and <i>para</i> -isomers)	—	Cl ₄ W=N-  -N=WCl ₄	79, 90	180
	Bu ^t NHSiMe ₃	—	 R = Bu ^t	78	181
	MeN(SiMe ₃) ₂	—	 R = Me	60	181
	2,6-Me ₂ C ₆ H ₃ NHSiMe ₃	—	 R = 2,6-Me ₂ C ₆ H ₃	81	181
	2,6-Me ₂ C ₆ H ₃ NHSiMe ₃	Me ₂ C ₅ H ₃ N	 R = 2,6-Me ₂ C ₆ H ₃	46.5	182
	MeN(SiMe ₃) ₂	—	 R = Me	60	181
	2,6-Pr ⁱ ₂ C ₆ H ₃ NHSiMe ₃	—	 R = 2,6-Pr ⁱ ₂ C ₆ H ₃	77	181
	 R = SiMe ₃	—	 R = SiMe ₃	90	175
	RNHSiMe ₃ (R = SiMe ₃ , 2,6-Pr ⁱ ₂ C ₆ H ₃ , 2,6-Me ₂ C ₆ H ₃)	—	 R = SiMe ₃ , 2,6-Pr ⁱ ₂ C ₆ H ₃ , 2,6-Me ₂ C ₆ H ₃	89	183
	2,6-Pr ⁱ ₂ C ₆ H ₃ NHSiMe ₃	—	 R = 2,6-Pr ⁱ ₂ C ₆ H ₃	72	181
RN=WCl ₄ (THF) (R = 2,6-Pr ⁱ ₂ C ₆ H ₃)	2,6-Pr ⁱ ₂ C ₆ H ₃ NHSiMe ₃	THF	(2,6-Pr ⁱ ₂ C ₆ H ₃ N=) ₂ WCl ₂ (THF) ₂	87	184
(PhN=WCl ₄) ₂	4-MeC ₆ H ₄ NHSiMe ₃	bipy	(PhN=)(4-MeC ₆ H ₄ N=)WCl ₂ (bipy)	—	185
(PhN=W(OEt) ₂ Cl ₂) ₂	Bu ^t NHSiMe ₃	bipy	(PhN=)(Bu ^t N=)W(OEt) ₂ (bipy)	—	186

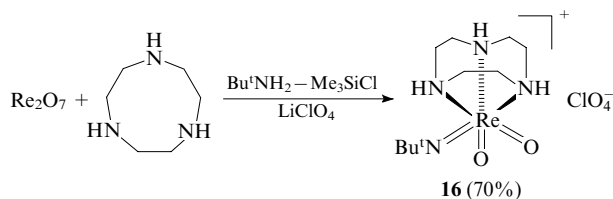
(yield < 30%).¹⁵⁰ Silyloxyrhenium trioxide ReO₃(OSiMe₃) reacts with three equivalents of Bu^tNHSiMe₃ to give the trisimido complex (Bu^tN=)₃Re(OSiMe₃) (**14**) in 64% yield.¹⁹⁴ Complex **14** is also formed in the reaction of rhenium(VII) oxide with

tert-butylamine in the presence of chlorotrimethylsilane.¹⁹⁵ The introduction of aromatic amines, together with Me₃SiCl and pyridine, allows one to synthesise complexes **15** of a different composition.



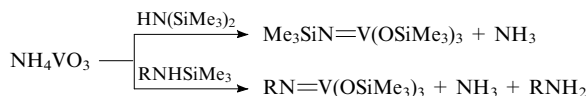
(a) $\text{Bu}^t\text{NH}_2 - \text{Me}_3\text{SiCl}$; (b) $\text{ArNH}_2 - \text{Me}_3\text{SiCl} - \text{py}$;
 Ar = 2,6- $\text{Me}_2\text{C}_6\text{H}_3$ (83%), 2,6- $\text{Pr}_2\text{C}_6\text{H}_3$ (76%).

The successive addition of *tert*-butylamine, chlorotrimethylsilane, 1,4,7-triazacyclononane and lithium perchlorate to rhenium(VII) oxide yielded cationic rhenium oxo–imido d⁰-complex **16**.¹⁹⁶



The reaction of osmium tetroxide with $\text{Bu}^t\text{NHSiMe}_3$ affords either osmium dioxo diimido ($\text{Bu}^t\text{N}=\text{OsO}_2$)¹⁹⁷ or osmium tetraimido ($\text{Bu}^t\text{N}=\text{Os}$) complexes depending on the amount of the amine.¹⁹⁸ It is worth noting that a similar reaction with trimethylsilylanilines proceeds as a redox process (see Section II.2.e).

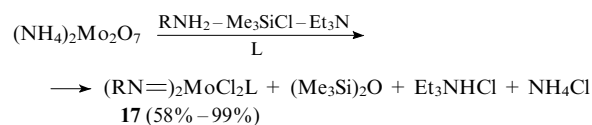
For the synthesis of V, Mo and Re imido complexes, it is rather convenient to use their metallates, in particular, NH_4VO_3 , Na_2MoO_4 , $(\text{NH}_4)_2\text{Mo}_2\text{O}_7$ and NH_4ReO_4 . The use of these compounds opened up the route to a broad range of imido derivatives. Thus ammonium vanadate reacts with silylamines giving imido-trimethylsilyl oxide complexes.^{143, 199}



R = Pr^n , Bu^t (72%).

Schrock^{200, 201} developed a general method for the synthesis of molybdenum bisimido complexes **17** [L = DME: R = Bu^t ,

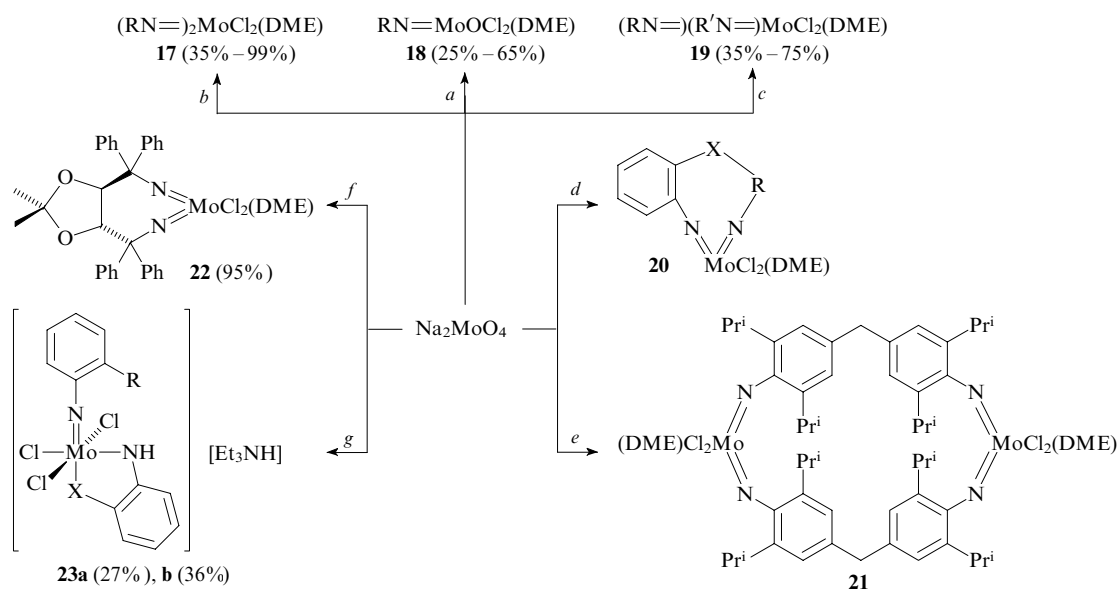
C_6F_5 , Ph, 2- $\text{Bu}^t\text{C}_6\text{H}_4$, 2,6- $\text{Pr}_2\text{C}_6\text{H}_3$, 2,6- $\text{Me}_2\text{C}_6\text{H}_3$, 4-Br-2,6- $\text{Pr}_2\text{C}_6\text{H}_2$, 4-CN-2,6- $\text{Pr}_2\text{C}_6\text{H}_2$, 3,5- $\text{Me}_2\text{C}_6\text{H}_3$, 2- $\text{Pr}^i\text{C}_6\text{H}_4$, 2- $\text{CF}_3\text{C}_6\text{H}_4$, Ad, 2-($\text{CH}_2=\text{CHCMe}_2\text{CH}_2\text{CH}_2$) C_6H_4 (see Ref. 202); L = py: R = 2- PhC_6H_4] based on the one-pot reaction between ammonium molybdate and two equivalents of a primary amine, which takes place in the presence of chlorotrimethylsilane and triethylamine in a coordinating solvent L (usually in 1,2-dimethoxyethane).



L = DME, py.

Gibson and co-workers,²⁰³ without changing the synthetic strategy as a whole, proposed to use sodium molybdate instead of ammonium molybdate. A number of publications^{204–213} demonstrate broad synthetic potential of this approach. Starting from Na_2MoO_4 , oxo–imido complexes (**18**) [R = Ad,²⁰⁴ 2,4,6- $\text{Ph}_3\text{C}_6\text{H}_2$,²⁰⁵ C_6F_5 (Ref. 206)] (Scheme 5, path *a*) and bisimido complexes (**17**) [R = 2,6- $\text{Et}_2\text{C}_6\text{H}_3$,²⁰⁷ 4-Fc-2,6- $\text{Pr}_2\text{C}_6\text{H}_2$, 4-(Fc $\equiv$ C)-2,6- $\text{Pr}_2\text{C}_6\text{H}_2$,²⁰⁸ 2- $\text{Bu}^t\text{C}_6\text{H}_4$, 2-Me-6- $\text{Pr}^i\text{C}_6\text{H}_3$,²⁰⁹ 2-NCC C_6H_4 ,²¹⁰ 2,5- $\text{Cl}_2\text{C}_6\text{H}_3$, 2,6- $\text{Cl}_2\text{C}_6\text{H}_3$ and 2,4,6- $\text{Cl}_3\text{C}_6\text{H}_2$ (Ref. 206)] were prepared (Scheme 5, path *b*), respectively. The ease of imido-deoxygenation is noticeably affected by the steric factor and by the electronic effects of substituents in the starting anilines. Thus the reaction of Na_2MoO_4 with sterically hindered 2,4,6-triphenylaniline precludes incorporation of more than one imido group into the molybdenum coordination sphere.²⁰⁵ The reaction with weakly nucleophilic perfluoroaniline results in a bisimido and oxo–imido products mixture with a substantial predominance of the latter. In the series of polychloroanilines, the yield of the target bisimido complexes decreases with a decrease in the nucleophilicity of the initial aniline, and 2,4,6-tribromoaniline does not enter into the reaction.²⁰⁶ The introduction of two different amines into the reaction allows one to prepare asymmetric diimidomolybdenum dichlorides **19** [R = Bu^t ; R' = C_6F_5 ,¹⁴⁵ 2,6- $\text{Pr}_2\text{C}_6\text{H}_3$,^{146, 204} R = Ad, R' = C_6F_5 ¹⁴⁵ (Scheme 5, path *c*). This procedure with Na_2MoO_4 was also used to prepare some molybdenum bisimido chelates **20** [R = *o*- C_6H_4 ; X = CH_2 , $(\text{CH}_2)_2$; R = CMe_2 , X = CH_2] (Scheme 5,

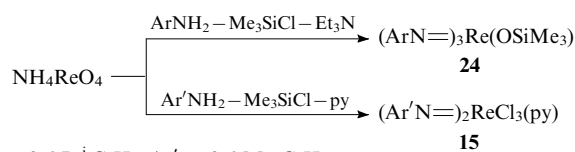
Scheme 5



(a) $\text{RNH}_2 - \text{Me}_3\text{SiCl} - \text{Et}_3\text{N}$; (b) RNH_2 (2 equiv.) – $\text{Me}_3\text{SiCl} - \text{Et}_3\text{N}$; (c) $(\text{RNH}_2 + \text{R}'\text{NH}_2) - \text{Me}_3\text{SiCl} - \text{Et}_3\text{N}$;
 (d) $o\text{-H}_2\text{NC}_6\text{H}_4\text{XRNH}_2 - o\text{-Me}_3\text{SiCl} - \text{Et}_3\text{N}$; (e) $(4\text{-H}_2\text{N}-3,5\text{-Pr}_2\text{C}_6\text{H}_2)_2\text{CH}_2 - \text{Me}_3\text{SiCl} - \text{Et}_3\text{N}$;
 (f) TADDAMIN – $\text{Me}_3\text{SiCl} - \text{Et}_3\text{N}$; (g) $o\text{-H}_2\text{NC}_6\text{H}_4\text{XH} - \text{Me}_3\text{SiCl} - \text{Et}_3\text{N}$;
 R, R', X — see text.

path *d*)^{211,212} and **21** (Scheme 5, path *e*)²¹¹ and the first molybdenum complex based on chiral (4*S*,5*S*)-4,5-di(aminodiphenyl)-methyl-2,2-dimethyl-1,3-dioxolane (TADDAMIN) (complex **22**, Scheme 5, path *f*)²¹³. The reactions of sodium molybdate with anthranilic acid and aniline-2-sulfonic acid are more complicated under similar conditions to give monoanionic (**23a**) [R = C(O).OSiMe₃, X = C(O)O] and dianionic (**23b**) (R = SO₃[Et₃NH]⁺, X = SO₃) complexes (Scheme 5, path *g*); their structure was confirmed by X-ray diffraction.²¹⁰

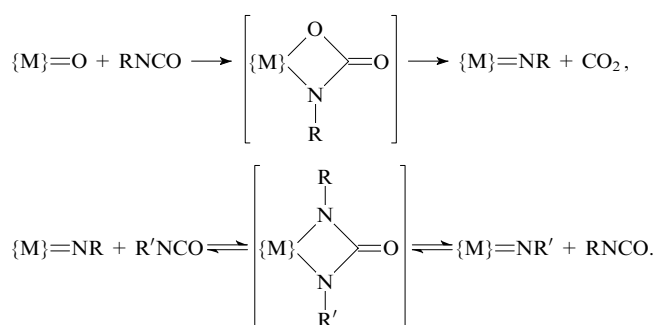
Ammonium perrhenate can be used to prepare rhenium d⁰-complexes of various compositions. For example, the reaction of NH₄ReO₄ with 2,6-diisopropylaniline in the presence of chlorotrimethylsilane and triethylamine gives trisimido complex **24**.²¹⁴ The use of excess pyridine instead of triethylamine results in bisimido complex **15**.¹⁹⁵



Ar = 2,6-Prⁱ₂C₆H₃, Ar' = 2,6-Me₂C₆H₃.

d. Imidation with organic isocyanates

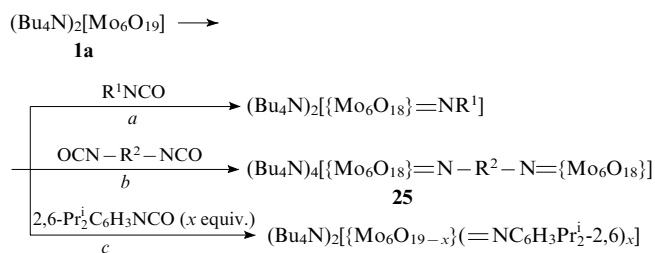
Metathesis imidation of transition metal complexes with alkyl and aryl isocyanates are widely used in synthetic practice. Isocyanates are mainly used for imidation of oxo complexes (for example, Group 5–7 transition metal oxohalides, Table 6); in some cases, imido complexes are used as the starting compounds. In the former case, metathesis imido-deoxygenation with carbon dioxide evolution takes place, while in the latter case, equilibrium transimidation occurs.



The reactions proceed *via* the formation of four-membered metallacycle intermediates, *viz.* *N,O*-carbamates and *N,N'*-ureates. *N,O*-Carbamates were not detected experimentally, while *N,N'*-ureates were in some cases isolated and characterised by spectral methods and X-ray diffraction.^{215–218} In both cases, to attain satisfactory yields of the products, long-term refluxing of the reactants in high-boiling solvents (xylene, toluene, octane,

etc.) is most often required; therefore, this method is inapplicable to thermally unstable complexes. Yet another drawback of the method is toxicity of organic isocyanates.

The imidation of polyoxo complexes by this method allows one to introduce varying numbers of imido groups in the complex. It was shown using polymolybdate **1a** as an example that by varying the amount of isocyanate used, one can incorporate one to five imido groups into the anion.^{233,234} The use of diisocyanates in the reaction with polymolybdate **1a** yields complexes **25** containing two polymolybdate moieties bridged by diimido ligands.²³⁵ Compounds of this type can also be prepared by imido-deoxygenation with amines, iminophosphoranes or by cross-coupling, the yields being comparable in all cases.



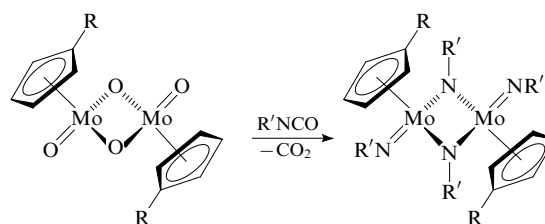
(a) R¹ = Buⁿ (56%), Cy (73%), Fc (19%);

(b) R² =  (80%),  (60%),  (60%);

(c) x = 1–5 (20%–86%).

By the use of three equivalents of 2,6-disubstituted aryl isocyanates in the reaction with silyloxytechnetium and -rhenium trioxides, all oxygen atoms were replaced by imido functions to give trisimido d⁰-complexes (RN=)₃M(OSiMe₃) [M = Tc: R = 2,6-Me₂C₆H₃ (61%), 2,6-Prⁱ₂C₆H₃ (60%);²³⁶ M = Re: R = 2,6-Me₂C₆H₃ (82%), 2,6-Prⁱ₂C₆H₃ (46%), 2,6-Cl₂C₆H₃ (79%)²³⁷].

Examples of successful use of isocyanates for the synthesis of imido derivatives of transition metal σ- and π-complexes are known. In particular, the reactions of binuclear cyclopentadienyl



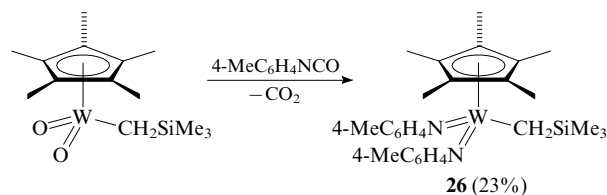
R = H: R' = Ph (41%); R = Me: R' = Ph (26%), 4-MeC₆H₄ (10%); R = Prⁱ, R' = Ph (12%).

Table 6. Synthesis of Group 5–7 transition metal imido complexes by imido-deoxygenation with organic isocyanates.

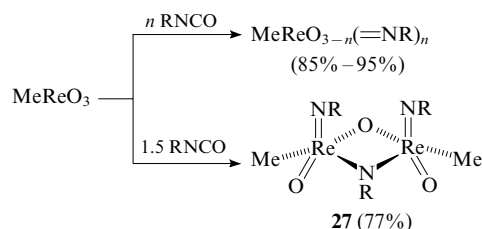
Starting compound	R in RNCO	Product	Yield (%)	Ref.
VOCl ₃	4-XC ₆ H ₄ (X = H, Me, CF ₃ , OMe, Cl, Br, F), 2,6-Pr ⁱ ₂ C ₆ H ₃	RN=VCl ₃	84 (X = Me) 99	219–222 221
VOCl ₃	4-OCNC ₆ H ₄	Cl ₃ V=NC ₆ H ₄ N=VCl ₃	84	223
WOCl ₄	Me, Et, Pr ⁱ , Bu ^t , Cy, Ph, 4-MeC ₆ H ₄ , 2-PhC ₆ H ₄ , 2-Bu ⁱ C ₆ H ₇ , 2-C ₁₀ H ₇ , 2,6-Pr ⁱ ₂ C ₆ H ₃	(RN=WCl ₄) ₂	70–98	25, 193, 209, 224–227
WOCl ₄	4-OCNC ₆ H ₄	Cl ₄ W=NC ₆ H ₄ N=WCl ₄	—	228
WO ₂ Cl ₂	2,6-Pr ⁱ ₂ C ₆ H ₃	(RN=) ₂ WCl ₂ (DME)	64	193
MoO ₂ Cl ₂	Bu ^t , 2,6-Pr ⁱ ₂ C ₆ H ₃	(RN=) ₂ MoCl ₂	95	229, 230
ReOCl ₃ L ₂ (L = PPh ₃ , PEt ₂ Ph)	Ph	RN=ReCl ₃ L ₂	—	231, 232
ReOCl ₄	Ph	(RN=ReCl ₄) ₂	88	185

complexes $[(\eta^5\text{-RC}_5\text{H}_4)\text{MoO}(\mu\text{-O})_2]$ with aryl isocyanates were reported. This reaction is a rare example of imido-deoxygenation occurring with replacement of both terminal and bridging oxygen atoms in the initial compound.^{238–240}

The synthesis of tungsten bisimido complex **26** has also been reported.²¹⁷

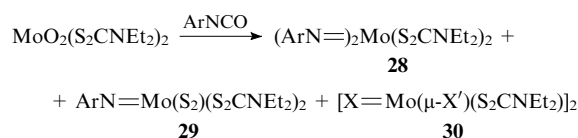


Study of the reaction of methyltrioxorhenium MeReO_3 with aryl isocyanates has shown that by varying the reactant ratio, one can obtain products with different imido-deoxygenation degrees. Upon the addition of one, two or three equivalents of aryl isocyanate to MeReO_3 , mono-, bis- or tris-imido complexes, respectively, are formed,^{131,241} while the addition of 1.5 equiv. RNCO results in the binuclear complex **27** containing terminal and bridging imido ligands.



$\text{R} = 2,6\text{-Me}_2\text{C}_6\text{H}_3, 2,6\text{-Pr}_2\text{C}_6\text{H}_3; n = 1\text{--}3$.

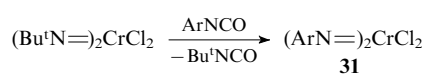
It has been noted above that this method is mainly used to imidate thermally stable compounds. The imido-deoxygenation of, for example, the complex $\text{MoO}_2(\text{S}_2\text{CNET}_2)_2$ with aryl isocyanates is accompanied by thermally induced destruction of the diethyldithiocarbamate group. As a result, the target bisimido complexes $(\text{ArN}=\text{Mo}(\text{S}_2\text{CNET}_2)_2)$ (**28**) are formed in low yields comparable with the yields of side products, *i.e.*, imido disulfide (**29**) and various binuclear (**30**) complexes.^{242–246}



$\text{Ar} = 2,6\text{-Me}_2\text{C}_6\text{H}_3, 2,6\text{-Pr}_2\text{C}_6\text{H}_3, 2,6\text{-Cl}_2\text{C}_6\text{H}_3; \text{X}, \text{X}' = \text{NAr}, \text{O}, \text{S}$.

The destruction products become predominant if aryl isocyanates without *ortho*-substituents, for example, phenyl and *p*-tolyl isocyanates, are used.

Transition metal imido complexes can also undergo transimidation with isocyanates; however, this method is seldom used in practice, unlike transimidation with primary amines. This is due to the very low rate of the process and the need to use high-boiling solvents. Nevertheless, this approach is one of the few known methods for the synthesis of bis(arylimido)chromium d⁰-complexes **31**.²⁴⁷



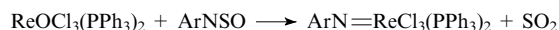
$\text{Ar} = \text{Mes}$ (75%), $2,6\text{-Me}_2\text{C}_6\text{H}_3$ (80%).

During thermolysis of the binuclear complex $[(\eta^5\text{-C}_5\text{Me}_5)\text{Mo}(=\text{NPh})(\mu\text{-NPh})_2]$ with excess $4\text{-MeC}_6\text{H}_4\text{NCO}$, successive replacement of two phenylimido groups by *p*-tolylimido groups was observed; transimidation involved only the

terminal imido groups, while bridging ligands remained intact even after long-term heating (8 weeks) with an excess of the starting isocyanate.²⁴⁸

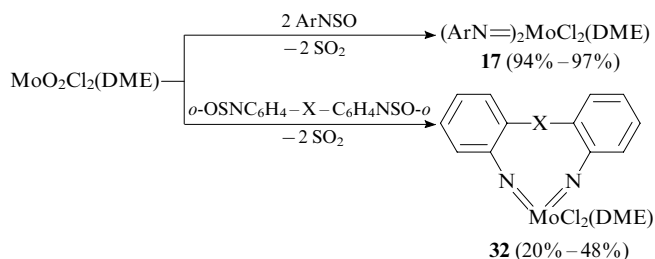
e. Imidation with *N*-sulfinylamines

The scope of using *N*-sulfinylamines for the synthesis of transition metal imido complexes has remained scarcely studied until recently. As regards the type of action, *N*-sulfinylamines are analogous to organic isocyanates, but they have advantages of being more readily available and more reactive toward imido-deoxygenation. It is essential that they are effective with both electron-donating and electron-withdrawing substituents. For example, sulfinyl derivatives of arylamines readily imidate the complex $\text{ReOCl}_3(\text{PPh}_3)_2$ (see Ref. 249).⁸



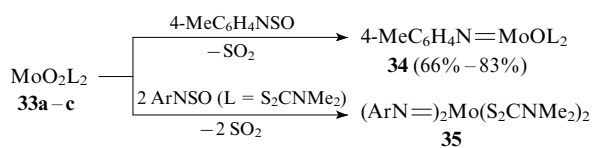
$\text{Ar} = \text{Ph}, 4\text{-MeC}_6\text{H}_4, 4\text{-MeOC}_6\text{H}_4$.

Molybdenum dioxodichloride easily undergoes imido-deoxygenation under the action of a number of halogen-substituted *N*-sulfinylanilines ArNSO to give corresponding bisimido complexes **17**.^{206,250} This approach was successfully used to prepare bisimido chelates **32**,^{250,251} the structure of which was confirmed by spectroscopic means.

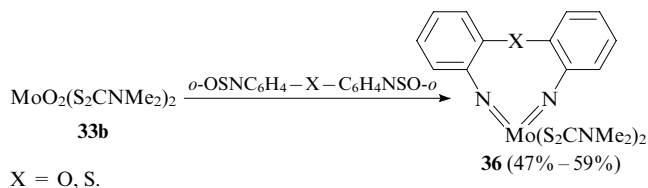


$\text{Ar} = \text{C}_6\text{F}_5, 2,6\text{-Cl}_2\text{C}_6\text{H}_3, 2,4,6\text{-Cl}_3\text{C}_6\text{H}_2, 2,4,6\text{-Br}_3\text{C}_6\text{H}_2; \text{X} = \text{O}, \text{S}$.

Owing to the high reactivity, *N*-sulfinylamines can be efficiently used for imidation of some thermally labile complexes, for example, molybdenum dioxobis(dialkylthiocarbamates) (**33a,b**). On treatment of complexes **33** with one equivalent of *N*-sulfinylanilines, monosubstitution takes place to give products **34**,²⁵² while the action of two equivalents of *N*-sulfinylanilines or one equivalent of *N*-sulfinyl derivatives of some diamines allows the preparation of full substitution products (compounds **35** or **36**, respectively),^{251,253} whose structure was confirmed by spectroscopic means.



$\text{L} = \text{S}_2\text{CNET}_2$ (**33a**), S_2CNMe_2 (**33b**), *acac* (**33c**); $\text{Ar} = 4\text{-MeC}_6\text{H}_4$ (64%), $2,4,6\text{-Cl}_3\text{C}_6\text{H}_2$ (86%), $2,4,6\text{-Br}_3\text{C}_6\text{H}_2$ (73%).



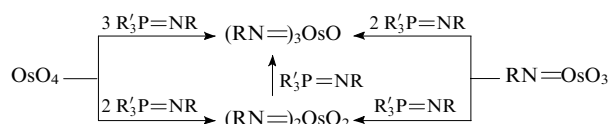
N-Sulfinylamines are able to transimide transition metal imido complexes; however, this reaction is of low practical value due to the low rate. Only prolonged heating (≥ 40 h) of 2,6-

[§] For the imidation of $\text{ReOCl}_3(\text{PPh}_3)_2$, amines, isocyanates, iminophosphoranes and hydrazines can be used with equal success.

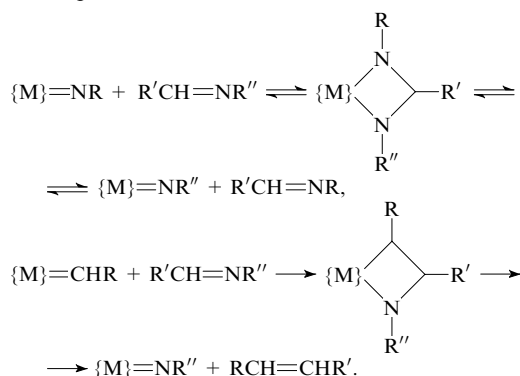
e. Imidation with iminophosphoranes

$$\{M\}=O + R'_3P=NR \longrightarrow \{M\}=NR + R'_3P=O.$$

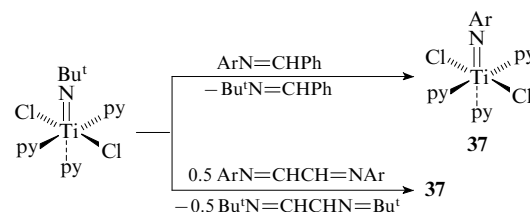
An essential advantage of iminophosphoranes is that they allow imidation of metal oxides that possess pronounced oxidative properties without reduction of the metal. For example, iminophosphoranes $R'_2P=NR$ enter into metathesis with osmium tetroxide or osmium oxoimides to yield bis- and tris-imido complexes $(RN=)_2OsO_2$, $(RN=)_3OsO$ with retention of the d^0 configuration of the metal.²


$$R = \text{Bu}^t, \text{Ad}, \text{CMe}_2\text{Et}; R' = \text{Bu}^n, \text{Ph}.$$

Examples of formation of transition metal imido complexes upon the action of the Schiff bases on other imido or carbene complexes of this metal are documented. In the former case, reversible metathesis transimidation takes place, while in the latter case, irreversible alkylidene-imine methathesis occurs giving rise to imido complexes and alkenes.

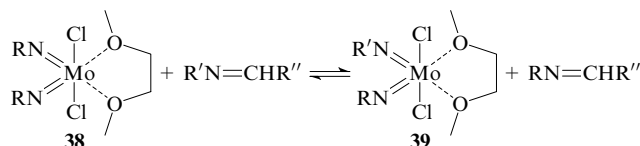


A study of the reaction of stoichiometric amounts of the complex $\text{Bu}^i\text{N}=\text{TiCl}_2(\text{py})_3$ and the Schiff bases $\text{ArN}=\text{CHPh}$ (NMR detection and a preparative experiment) has shown that the equilibrium is completely shifted towards the formation of the arylimido complex **37**,²⁶⁴ the imido–imine methathesis being slower for sterically more hindered 2,6-dimethylphenylimine (the process is over only after 96 h) than for *p*-tolylimine (4 h).



Ar = 4-MeC₆H₄, 2,6-Me₂C₆H₃.

During the imido–imine exchange between molybdenum bisimido complexes **38** and various Schiff bases, the equilibrium (a 1 : 1 ratio of the initial complex **38** and product **39**) can be attained relatively fast (after ~20 h) only for the imido ligand with alkyl groups (example *a*), whereas for aryl substituents (example *b*) this ratio is attained only in 18 days.²⁹

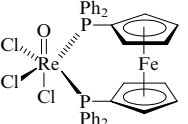
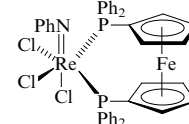


(a) $R = Bu^t$, $R' = Pr$, $R'' = Ph$; (b) $R = 2,6-Pr_2C_6H_3$, $R' = Ph$, $R'' = Bu^t$.

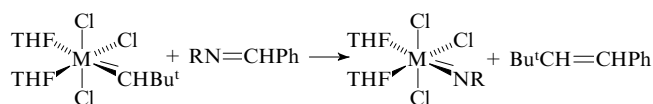
Thus, imido–imine metathesis reactions are seldom useful for the synthesis of transition metal imido complexes, because they are too slow. The best outcome of transimidation is attained when primary amines are employed (see Section II.1.a). Nevertheless, the imido–imine exchange underlies catalytic metathesis of azomethines, for which some molybdenum^{27–30} and zirconium³¹ imido complexes have been proposed as catalysts.

Niobium and tantalum carbene complexes $\text{Bu}^t\text{CH}=\text{MCl}_3(\text{THF})_2$ ($\text{M} = \text{Nb, Ta}$) undergo alkylidene-

Table 7. Synthesis of Group 6–8 transition metal imido complexes by imido-deoxygenation with iminophosphoranes.

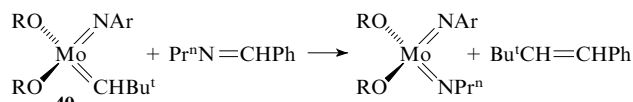
Starting compound	R in $\text{R}=\text{NP}'_3$	Product	Yield (%)	Ref.
$(\text{Bu}_4^{\text{n}}\text{N})_2[\text{Mo}_6\text{O}_{19}]$	4-MeC ₆ H ₄ , 4-(CH ₂ =CH)C ₆ H ₄	$(\text{Bu}_4^{\text{n}}\text{N})_2[\text{RN}=\{\text{Mo}_6\text{O}_{18}\}]$	90	254, 255
$\text{MoOCl}_2(\text{S}_2\text{CNEt}_2)_2$	Ph	$\text{PhN}=\text{MoCl}_2(\text{S}_2\text{CNEt}_2)_2$	60	256
$\text{ReOCl}_3(\text{PPh}_3)_2$	Ph, 4-MeC ₆ H ₄	$\text{RN}=\text{ReCl}_3(\text{PPh}_3)_2$	—	257, 258
$\text{ReOCl}_3(\text{PPh}_3)_2$	4-(Ph ₃ P=N)C ₆ H ₄	$(\text{Ph}_3\text{P})_2\text{Cl}_3\text{Re}=\text{N}-\text{C}_6\text{H}_4-\text{N}=\text{ReCl}_3(\text{PPh}_3)_2$	—	259
	Ph		—	260
$\text{Ru}_2\text{O}_2(\text{CH}_2\text{SiMe}_3)_6$	SiMe ₃	$\text{Ru}_2(=\text{NSiMe}_3)_2(\text{CH}_2\text{SiMe}_3)_6$	38	261

imine metathesis with some azomethines to give the corresponding imidochlorides and a *cis*- and *trans*-alkene mixture.^{266, 267}



M = Nb: R = Ph (40%); M = Ta: R = Ph, Me, Bu^t (80%–81%).

A study of the reactions of various molybdenum alkoxide imidocarbene complexes ($\text{ArN}=\text{C}(\text{Bu}^t\text{CH}=\text{CHPh})\text{Mo}(\text{OR})_2$ (**40**) with Schiff bases has demonstrated that the rate of alkylidene–imine metathesis depends substantially on the nature of the RO-ligands.²⁹

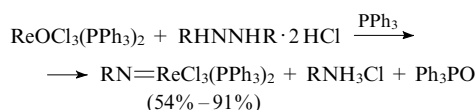


Ar = 2,6- $\text{Pr}_2\text{C}_6\text{H}_3$; R = $\text{C}(\text{CF}_3)_2\text{Me}$, $\text{C}(\text{CF}_3)_2\text{Me}_2$.

For example, when complex **40** containing ligands $\text{Me}(\text{CF}_3)_2\text{CO}$ is treated with $\text{Pr}^n\text{N}=\text{CHPh}$, complete exchange is attained after 20 h, while the exchange depth in complex **40** with less fluorinated $\text{Me}_2(\text{CF}_3)\text{CO}$ ligands is only 10% over the same period of time. The complex with ligands Bu^tO does not enter into this reaction.

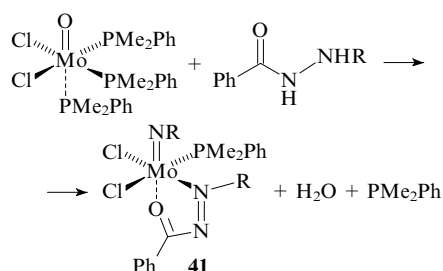
h. Imidation with hydrazine derivatives and azo compounds

Hydrazine derivatives and azo compounds are typical imidating oxidants (see Section II.2.b); however, there are some examples where a redox process involving these compounds does not result in a change in the formal oxidation state of the metal. This may be due to the presence of another reducing agent, and this role may be played, in particular, by hydrazine. For instance, treatment of the rhenium oxo complex $\text{ReOCl}_3(\text{PPh}_3)_2$ with a number of dialkylhydrazines in the presence of triphenylphosphine leads to imido-deoxygenation of the starting complex.²⁶⁸ This is obviously a redox reaction, nevertheless, rhenium retains its d²-configuration, because triphenylphosphine acts as a reducing agent.



R = Me, Et, Prⁿ, Cy.

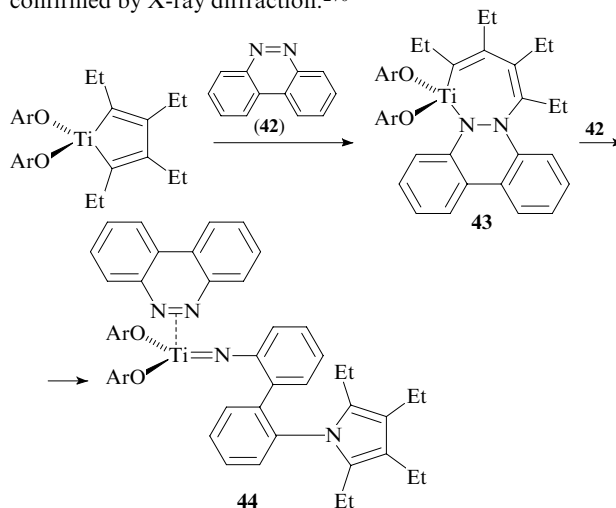
Substituted benzohydrazides can also function as imidating agents. On treatment with phenylhydrazides, the oxo complex $\text{ReOCl}_3(\text{PPh}_3)_2$ is converted into the imido complex $\text{RN}=\text{ReCl}_3(\text{PPh}_3)_2$.²⁶⁹ The reaction of $\text{MoOCl}_2(\text{PMe}_2\text{Ph})_3$ with *N*-arylbenzohydrazides results in imido complex **41**,^{257, 269} the formation of the imido ligand being accompanied by autooxidation of benzohydrazide.



R = 4-XC₆H₄ (X = H, Cl, Me, MeO), 1-C₁₀H₇.

An example of insertion of benzo[*c*]cinnoline **42** into the Ti–C bond in the complex $\text{Et}_4\text{C}_4\text{Ti}(\text{OAr})_2$ to give complex **43**

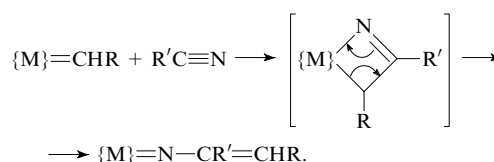
containing 2,3-diazatitanacyclohepta-4,6-diene fragment is reported (the conclusion about the structure of complex **43** was based on spectroscopic characteristics). Treatment of complex **43** with the second equivalent of benzo[*c*]cinnoline induces an intramolecular bond redistribution in the complex, which is thus converted into imido complex **44**, the structure of which was confirmed by X-ray diffraction.²⁷⁰



Ar = 2,6- $\text{Ph}_2\text{C}_6\text{H}_3$.

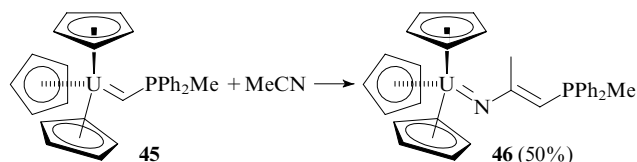
i. Imidation with nitriles

Nitriles have also found application as imidating reagents, but processes involving these compounds differ from those for all reagents described previously. Whereas reactions with isocyanates, *N*-sulfonfylamines, imines, iminophosphoranes, *etc.*, occur as metathesis, nitriles are formally inserted into the metal–carbon bond as a result of an electrocyclic rearrangement.



Typical examples of synthesis of imido complexes by this method are presented in Table 8.

The insertion of acetonitrile into the metal–carbon multiple bond in uranium complex **45** has been described.²⁷⁵ This reaction yields imido complex **46**.

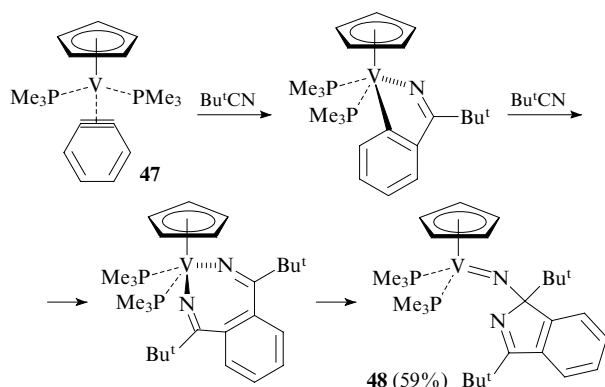


Examples of reactions involving two nitrile molecules are known. The high-spin vanadium d²-complex **47** reacts with two equivalents of pivalonitrile to give imido complex **48**,[¶] in which the imido ligand contains 1,3-di(*tert*-butyl)isoindol-1-yl as the organic group.²⁷⁶ It is believed that this compounds is formed upon two successive steps of nitrile insertion into the metal–carbon bonds with subsequent rearrangement of the intermediate into a more stable product.

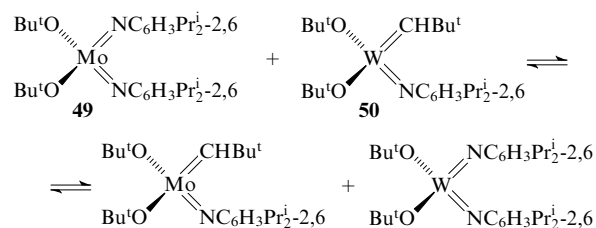
¶ The structure of complex **48** was confirmed by X-ray diffraction data.

Table 8. Synthesis of transition metal imido complexes using nitriles.

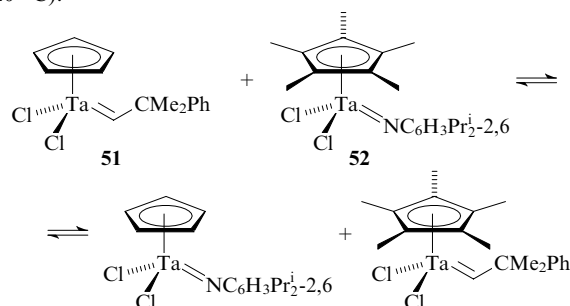
Starting compound	R in RCN	Product	Yield (%)	Ref.
	Bu ^t , Cy		—	271
	Me		—	272
	Ph, Me		60–61	273
	Bu ^t		48	274



reaction of tetrahedral molybdenum bisimido complex (**49**) with tungsten imidocarbene (**50**) complex showed that the equilibrium is attained only after several days at 60 °C.²⁸⁰

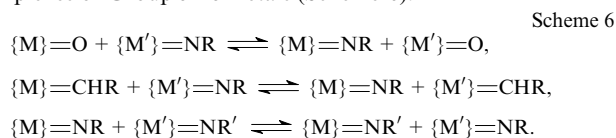


In the reaction of alkylidene–imido metathesis between half-sandwich tantalum complexes **51** and **52**, the equilibrium can be reached over the same time under more drastic conditions (120 °C).



j. Imidation with transition metal imides

In some studies, the possibility has been demonstrated to prepare transition metal imido complexes by the equilibrium metathesis transfer of the imido ligand from one metal complex to another. This intercomplex exchange can occur for oxo, carbene and imido complexes of Group 5–8 metals (Scheme 6).



In the reactions shown in Scheme 6, the equilibrium is shifted toward the formation of thermodynamically more favourable products.

Upon the oxo–imido exchange, the imido group is bound preferably to the more electron-deficient metal. Examples of imido complexes prepared by intercomplex oxo–imido exchange are presented in Table 9.

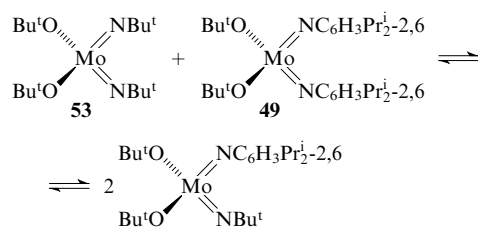
The Schrock carbenes can undergo metathesis with the imido complexes; however, unlike the oxo–imido metathesis, this approach is of low utility for preparative purposes due to the low reaction rate and the difficulty of isolation of the desired product from the equilibrium mixture. Thus NMR monitoring of the

The possibility of equilibrium imido–imido exchange between Group 5 and 6 metal complexes was demonstrated; however, in this case, too, a low reaction rate was noted. Thus symmetric molybdenum bisimido complexes with *tert*-butyl- (**53**) and 2,6-diisopropylphenylimido (**49**) ligands slowly exchange the imido ligands only at elevated temperature ($K_{60\text{ }^\circ\text{C}} = 25$), apparently, for steric reasons.²⁸⁰

The rate of intercomplex imide exchange can be considerably affected by Brønsted acids. Thus the addition of $(\text{Et}_2\text{O})_2\text{HB}[\text{C}_6\text{H}_3(\text{CF}_3)_2-3,5]_4$ into a mixture of complexes **49** and **53** substantially accelerates the exchange reaction ($K_{25\text{ }^\circ\text{C}} = 95$, $k = 5.0 \times 10^{-6} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$).²⁸³

Table 9. Synthesis of transition metal imido complexes by intercomplex ligand exchange.

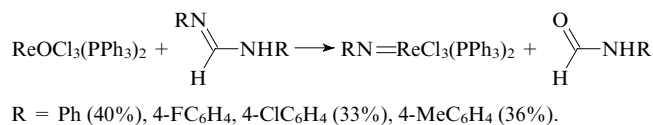
Starting compound	Imidating complex	Product	Yield (%)	Ref.
VOCl_3	$\text{RN}=\text{V}(\text{OSiMe}_3)_3$ R = Me_3Si R = Bu^t	$\text{RN}=\text{VCl}_3$	38 68	277 144
	R = 2,4,6- $\text{Me}_3\text{C}_6\text{H}_2$ R = Bu^t		59 100	278 279
	2,6- $\text{Pr}_2\text{C}_6\text{H}_3\text{N}=\text{Mo}(\text{OBu}^t)_2$ 2,6- $\text{Pr}_2\text{C}_6\text{H}_3\text{N}=\text{Mo}(\text{OBu}^t)_2$	2,6- $\text{Pr}_2\text{C}_6\text{H}_3\text{N}=\text{Mo}(\text{OBu}^t)_2$ 	—	280
OsO_4	2,6- $\text{Pr}_2\text{C}_6\text{H}_3\text{N}=\text{Mo}(\text{OBu}^t)_2$ 2,6- $\text{Pr}_2\text{C}_6\text{H}_3\text{N}=\text{Mo}(\text{OBu}^t)_2$	2,6- $\text{Pr}_2\text{C}_6\text{H}_3\text{N}=\text{Os}(\text{O})_2$ 2,6- $\text{Pr}_2\text{C}_6\text{H}_3\text{N}=\text{Os}(\text{O})_2$	83	281
	2,6- $\text{Pr}_2\text{C}_6\text{H}_3\text{N}=\text{Ta}(\text{OBu}^t)_3$	2,6- $\text{Pr}_2\text{C}_6\text{H}_3\text{N}=\text{Os}(\text{R})_2$ 2,6- $\text{Pr}_2\text{C}_6\text{H}_3\text{N}=\text{Os}(\text{R})_2$	50–70	282
(R = CH_2SiMe_3 , CH_2Bu^t , $\text{CH}_2\text{CMe}_2\text{Ph}$)				



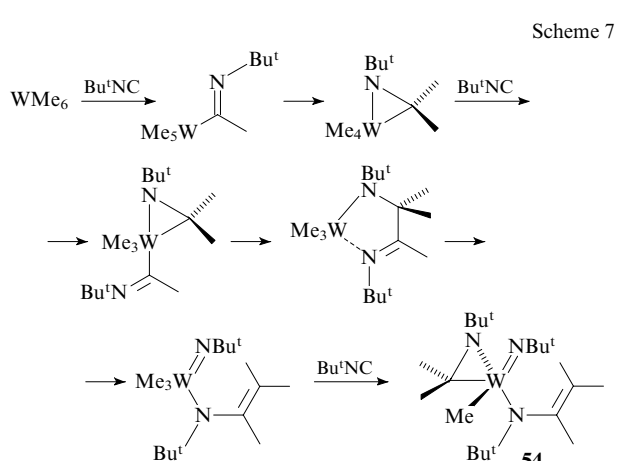
k. Imidation using miscellaneous nitrogen-containing compounds

Examples of the use of some other nitrogen-containing compounds as imidating reagents, in particular, formimidamides, isocyanides and iminoboranes have been documented.

Formimidamides imidate the oxo complex $\text{ReOCl}_3(\text{PPh}_3)_2$ to give the imido complexes $\text{RN}=\text{ReCl}_3(\text{PPh}_3)_2$.²⁸⁴ It is noteworthy that in this case, the yields of rhenium arylimido complexes are lower than those attained upon imidation with amines and hydrazines.

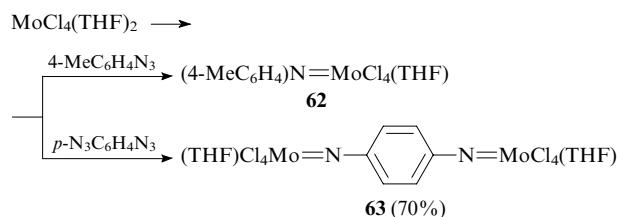


When Group 4–6 metal σ -alkyl complexes react with isocyanides, these are inserted into the metal–carbon bond to afford azavinyl intermediates, which undergo intramolecular rearrangement to yield imido products. (These reactions present no interest from the preparative standpoint, because they are not straightforward and their outcome is not always predictable.) The reaction may involve one to three isocyanide molecules. The homoleptic complex WMe_6 reacts with three equivalents of *tert*-butyl isocyanide to yield imido complex **54**, the structure of which was confirmed by X-ray diffraction. Presumably, this product is formed in a complicated sequence of insertion and rearrangement reactions (Scheme 7).^{285, 286}



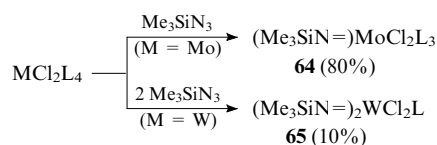
An example of formal substitution of an arylimido group for the alkyl groups in guanidinate complexes **55** on treatment with one equivalent of aryl isocyanide has been reported.^{287, 288} The formation of imido complexes **56** is attributed to redistribution of bonds in the intermediate resulting from isocyanide insertion into the metal – carbon bond (Scheme 8).

On treatment of the complex $(\eta^5\text{-C}_5\text{Me}_5)\text{TaMe}_2\text{Cl}_2$ with 2,6-Me₂C₆H₃NC, isocyanide is also inserted into the metal–carbon bond, which is followed by migration of the other methyl group to the electrophilic acetimidoyl carbon atom to give aza(tantalum)-cyclopropane complex **57**, which was isolated and characterised by spectroscopic means.²⁸⁹ This complex easily reacts with a second isocyanide molecule to give thermally unstable azatantalacyclobutane intermediate **58**, which eliminates arylketeneimine to give imido complex **59**, which is formally the substitution product of an imido ligand for two methyl groups in the starting complex.



Trimethylsilyl azide is rarely used for imidation of transition metal chlorides. This is due to the fact that the trimethylsilylimido chlorides formed are as a rule labile and readily eliminate chlorotrimethylsilane to give nitrido complexes. Thus it was found that vanadium tetrachloride reacts with Me_3SiN_3 yielding the unstable complex $\text{Me}_3\text{SiN}=\text{VCl}_3$,²⁹⁹ which, as has been specially shown,²⁷⁷ readily eliminates Me_3SiCl to afford vanadium chloronitride.

By varying the ratio of molybdenum (or tungsten) dichloride and trimethylsilyl azide used in the reaction, one can obtain labile complexes **64** and **65**, respectively.³⁰⁰



M = Mo, L = PMe_3 ; M = W, L = PPh_2Me .

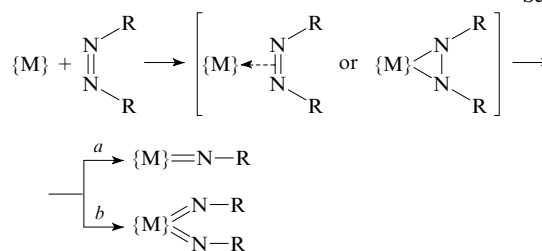
Organic azides are effective imidating agents for diverse metal complexes containing mono- and polydentate O-, S-, N- and P-ligands (Table 10). They are successfully used to prepare

imido derivatives of metallocenes and Group 4–9 transition metal carbene and σ -alkyl complexes (Table 11).

b. Imidation with azo compounds, hydrazines and their derivatives

Azo compounds are typical reagents imidation with which is accompanied by an increase in the formal oxidation state of the metal. They can be used in reactions with various mononuclear π -complexes and binuclear metal complexes. The mechanism of formation of imido derivatives from mononuclear complexes is not entirely clear; however, the process is considered to proceed *via* an η^2 -diazene or diazametallacyclopropane intermediate, in which activation of the $\text{N}=\text{N}$ bond and a decrease in its order take place and which is further converted into the mono- (path *a*) or bis-imido (path *b*) complex (Scheme 10).^{321, 325–327}

Scheme 10



However, examples are known where imidation follows a different mechanism. In a systematic study of the reaction of Cp_2TaMeL with azobenzene, the formation of diazametallacyclopropane product **66**, which is not converted into imido complex **67**, was confirmed by X-ray diffraction. Having studied

Table 10. Synthesis of transition metal imido complexes using organic azides.

Starting compound	R in RN_3	Product	Yield (%)	Ref.
$\text{Ti}(\eta^2\text{-EtC}\equiv\text{CEt})(\text{TTP})$ (see ^a)	Me_3Si	$\text{RN}=\text{Ti}(\text{TTP})$	38	158
$\text{Cr}(\text{TTP})$ (see ^a)	$4\text{-XC}_6\text{H}_4$ (X = Me, Cl, I, MeO)	$\text{RN}=\text{Cr}(\text{TTP})$	60–65	19, 301
$\text{Mo}(\text{CO})_2(\text{S}_2\text{CNEt}_2)_2$	Ph	$(\text{RN}=\text{Mo})(\text{S}_2\text{CNEt}_2)_2$	50	302
$\text{W}(\text{CO})_2(\text{PPh}_3)(\text{S}_2\text{CNEt}_2)_2$	$4\text{-MeC}_6\text{H}_4$	$\text{RN}=\text{W}(\text{CO})(\text{S}_2\text{CNEt}_2)_2$	—	303
	Me_3Si , $\text{Bu}^t\text{Me}_2\text{Si}$		—	304
$\text{W}(\text{OC}_6\text{H}_3\text{Me}_2\text{-2,6})_4$	Me_3Si	$\text{RN}=\text{W}(\text{OC}_6\text{H}_3\text{Me}_2\text{-2,6})_4$	—	305
	Me_3Si , Ph_3C		70 13	306 306
	Me_3Si		39	307

Table 10 (continued).

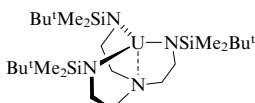
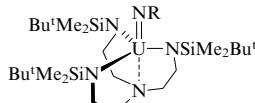
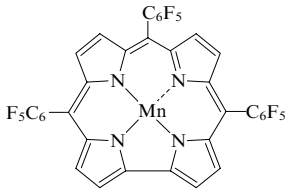
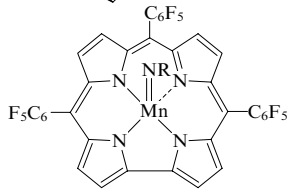
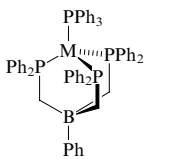
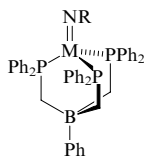
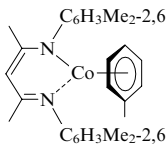
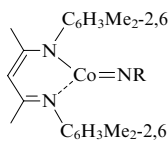
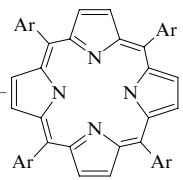
Starting compound	R in RN ₃	Product	Yield (%)	Ref.
	Me ₃ Si		90	308
	Mes, 2,4,6-Cl ₃ C ₆ H ₂		70–80	309
	4-MeC ₆ H ₄		97 50	310 311
	Ad		50	312
[Os(TPP)] ₂ (see ^a)	4-NO ₂ C ₆ H ₄	(RN=) ₂ Os(TTP)	42	313
[Os(4-Cl-TPP)] ₂ (see ^a)	4-NO ₂ C ₆ H ₄	(RN=) ₂ Os(4-Cl-TTP)	58	314
[Ru(TPP)] ₂ (see ^a)	4-NO ₂ C ₆ H ₄	(RN=) ₂ Ru(TTP)		314
^a TPP, TTP, 4-Cl-TTP —  [Ar = Ph (TPP), 4-MeC ₆ H ₄ (TTP), 4-ClC ₆ H ₄ (4-Cl-TTP)].				

Table 11. Synthesis of imido derivatives of organometallic compounds using organic azides.

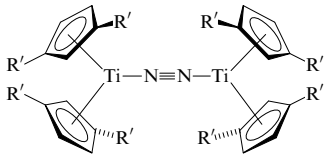
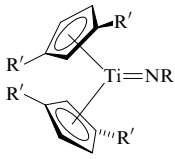
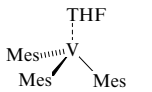
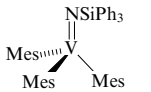
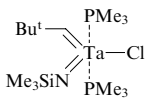
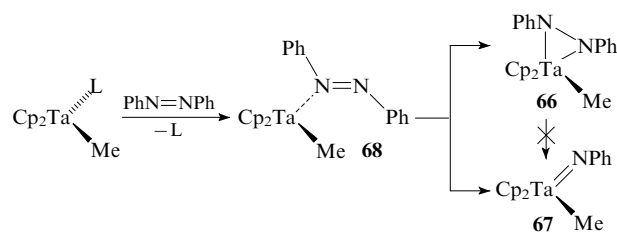
Starting compound	R in RN ₃	Product	Yield (%)	Ref.
	Me ₃ Si Mes		53 94	315 315
(R' = SiMe ₃)				
(η ⁵ -C ₅ Me ₅) ₂ V	Ph, C ₆ F ₅ , 2,6-Me ₂ C ₆ H ₃ , 2-PhC ₆ H ₄	(η ⁵ -C ₅ Me ₅) ₂ V=NR	39–70	292, 293, 316
(η ⁵ -C ₅ H ₅) ₂ V	SiPh ₃	(η ⁵ -C ₅ H ₅) ₂ V=NSiPh ₃	80	317
	Ph ₃ Si		—	304
(η ⁵ -C ₅ Me ₅) ₂ Ta 	Ph	(η ⁵ -C ₅ Me ₅) ₂ Ta 	76	318
Bu ^t CH=TaCl(PMe ₃) ₄	Me ₃ Si		—	267

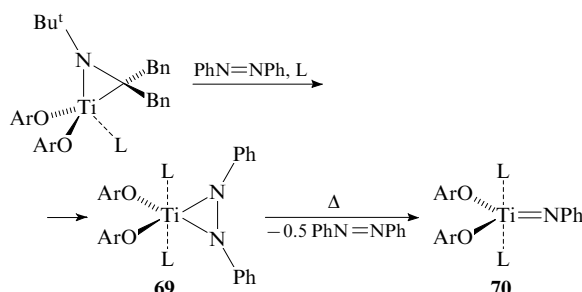
Table 11 (continued).

Starting compound	R in RN ₃	Product	Yield (%)	Ref.
	Ph Me ₃ Si		81–85 72	319, 320
	Ph Ad		84 71	321
(η ⁵ -MeC ₅ H ₄) ₃ U(THF)	Ph, Me ₃ Si	(η ⁵ -MeC ₅ H ₄) ₃ U=NR	50	322
(η ⁵ -MeC ₅ H ₄) ₃ U(THF)	3-C ₆ H ₄ N ₃ 4-C ₆ H ₄ N ₃		37 48	323 323
 (Ar = Mes, 2,6-Me ₂ C ₆ H ₄)	4-MeC ₆ H ₄ , 4-MeOC ₆ H ₄		100	324

the process kinetics, the researchers suggested that adduct **68** is the true intermediate on the route to imido product **67**.³²⁸



It was found that mononuclear bisimido complexes are formed along path *b* only starting from d⁴-complexes, while monoimido products (path *a*) are obtained by treating d²-complexes with azo compounds. Thus on treatment with azobenzene, the d²-complex (η²-Bu^tN=CBn₂)Ti(OC₆H₃Prⁱ-2,6)₂L is converted into η²-azo complex **69**. The latter is thermally unstable and is transformed on heating into imido d⁰-complex **70**.³²⁵



Ar = 2,6-Prⁱ₂C₆H₃, L is 4-pyrrolidinopyridine.

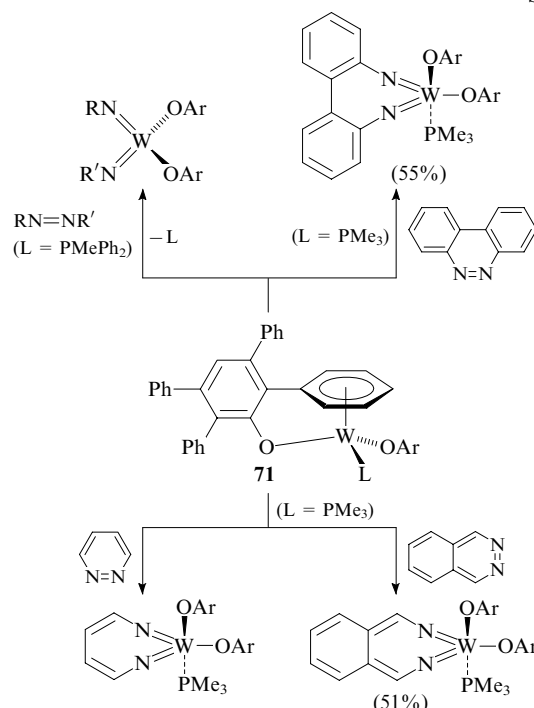
The d²-complex (TTP)Ti(η²-EtC≡CEt) and azobenzene taken in 2 : 1 ratio react in a similar way. The first step is replacement of the diethyacetylene molecule by the azo ligand to give the complex (TTP)Ti(η²-PhN=NPh), which was isolated and characterised. In the second step, the azo complex reacts with another

(TTP)Ti(η²-EtC≡CEt) molecule, being converted into mono-imido d⁰-complex (TTP)Ti=NR.^{158, 326}

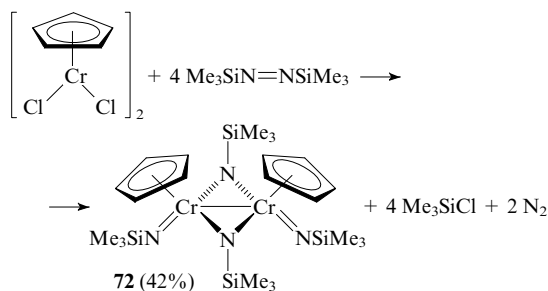
The oxidative addition of symmetric and non-symmetric (including cyclic) azo compounds to tungsten d⁴-complex **71** has been studied.^{329, 330} The structure of bisimido d⁰-complex formed (Scheme 11) was confirmed by X-ray diffraction.

The reaction of dimeric d³,d³-complex [CpCrCl₂]₂ with four equivalents of Me₃SiN=NSiMe₃ results in binuclear d¹,d¹-complex **72**, which contains, according to X-ray diffraction data, both terminal and bridging ligands.³³¹

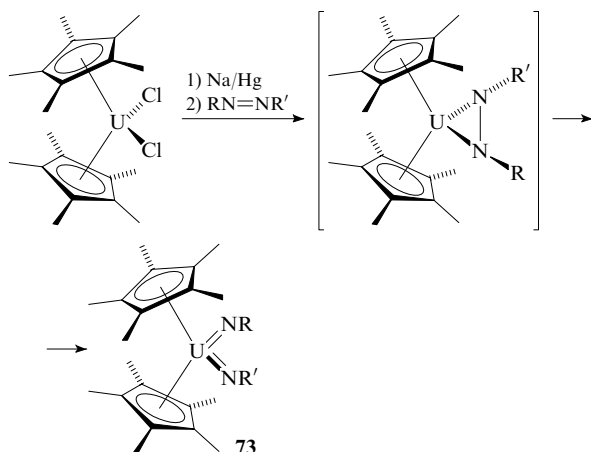
Scheme 11



Ar = 2,3,5,6-Ph₄C₆H; L = PMe₃, PMePh₂; R, R' = Ph, 4-MeC₆H₄, Mes.



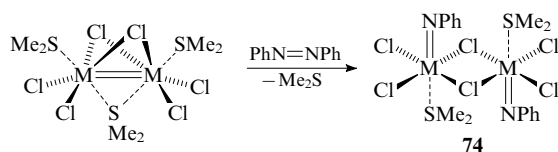
A two-stage method for the synthesis of symmetric and asymmetric bisimido uranium complexes **73** is based on the reaction of azo compounds with the complex $[(\eta^5\text{-C}_5\text{Me}_5)_2\text{UCl}_2 \cdot (\text{NaCl})]$, which is formed *in situ* upon the reduction of decamethyluranocene dichloride with sodium amalgam.³²¹



$\text{R} = \text{R}' = \text{Ph}$ (92%); $\text{R} = \text{Ph}$, $\text{R}' = \text{SiMe}_3$ (70%).

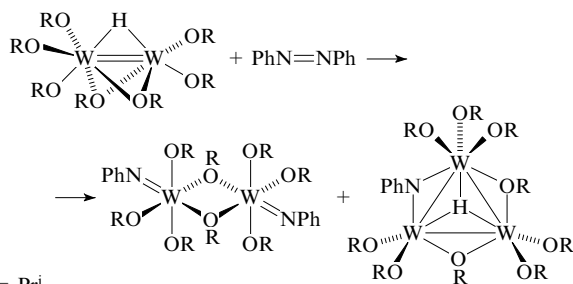
Complexes **73** can also be prepared by imidation of the complex $(\eta^5\text{-C}_5\text{Me}_5)_2\text{UCl}_2$ with azides or diphenylhydrazine.

Imidation of binuclear complexes containing multiply bonded metal atoms follows a different route as compared with the imidation of mononuclear complexes. The reaction of azobenzene with binuclear complexes $\text{M}_2\text{Cl}_6(\text{SMe}_2)_3$ proceeds as the metathesis of multiple bonds, $\text{M}=\text{M}$ and $\text{N}=\text{N}$, to give imido dimers **74**.^{332, 333}

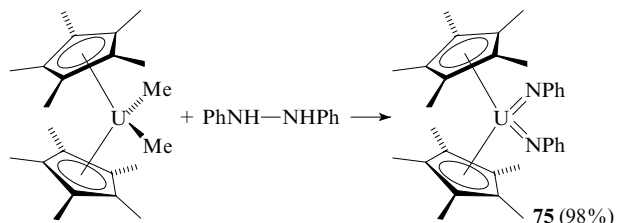


$\text{M} = \text{Nb}$ (55%), Ta (58%).

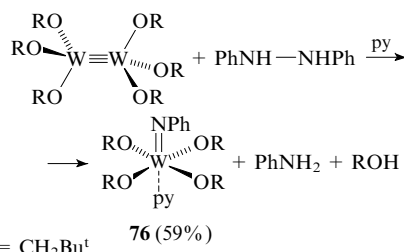
The reaction of azobenzene with the binuclear complexes $\text{W}_2(\mu\text{-H})(\text{OPr}^i)_7$ and $\text{W}_2(\text{OPr}^i)_6(\text{py})_2$,³³⁴ which also contain metal-metal multiple bonds, follows a more complex pattern, as indicated by the formation of a mixture of products, including clusters.



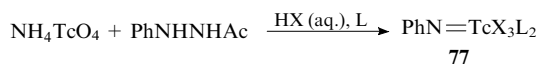
Imidation with hydrazine derivatives is usually a redox process. In those cases where other reducing agents are present or hydrazines undergo autooxidation, the initial electronic configuration of the metal can be retained (see Section II.1.h); however, more often, is oxidation state increases. The oxidative imidation of transition metal complexes with hydrazine derivatives can be exemplified by a one-stage synthesis of diimido complex **75**.³¹⁹



The imidation of the binuclear complex $\text{W}_2(\text{OCH}_2\text{Bu}^t)_6$ on treatment with 1,2-diphenylhydrazine is accompanied by oxidative cleavage of the metal-metal triple bond to give imido complex **76**.³³⁴



Conversely, the reaction of ammonium pertechnetate with phenylhydrazide in the presence of phosphines and small amount of a hydrohalic acid is accompanied by the reduction of technetium giving rise to d^2 -complexes **77**.^{335, 336}



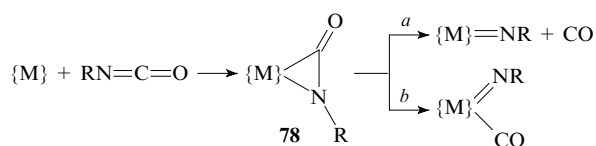
$\text{X} = \text{Cl}, \text{Br}$; $\text{L} = \text{PPh}_3$ (68%–75%), PMePh_2 (30%).

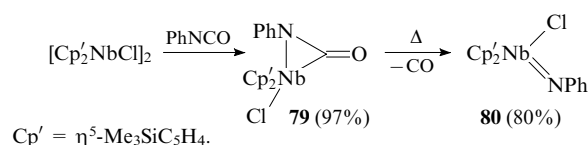
c. Imidation with organyl isocyanates

The imidation with isocyanates is usually a metathesis-type reaction occurring without a change in the formal oxidation state of the metal in the complex (see Section II.1.d). However, there are some examples where complexes of metals in low oxidation states are inserted into the $\text{N}=\text{C}$ bond of isocyanates to give azametallacyclopropane derivatives **78** (oxidative insertion, Scheme 12), which can subsequently be converted into imido complexes with elimination of carbon monoxide (path *a*) or form imido carbonyl complexes (path *b*).

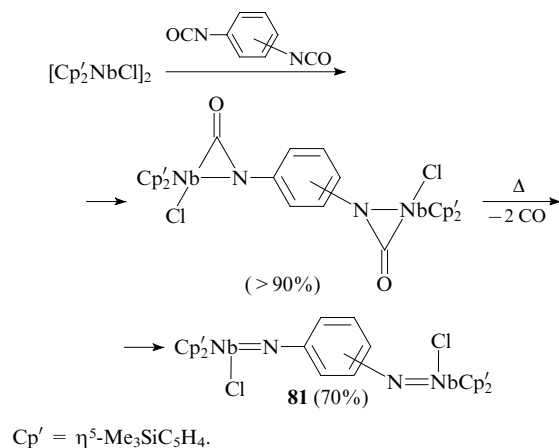
The d^2 -complex $[(\eta^5\text{-Me}_3\text{SiC}_5\text{H}_4)_2\text{NbCl}]_2$ coordinates phenyl isocyanate PhNCO to give stable compound **79** (characterised by X-ray diffraction). Thermolysis of complex **79** occurs with elimination of carbon monoxide to give imido complex **80**.^{337–339}

Scheme 12

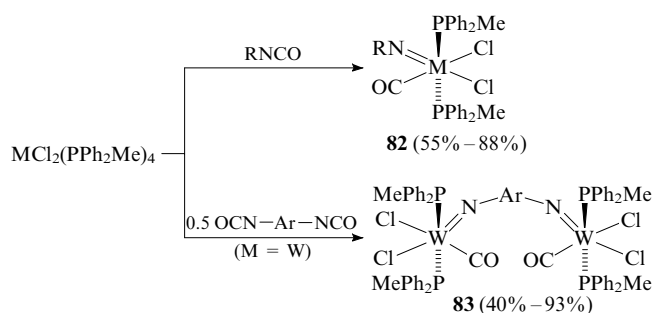




With diisocyanates [1,3- or 1,4-(OCN)₂C₆H₄], binuclear imido complexes **81** are formed.



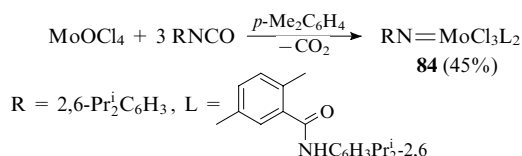
Molybdenum and tungsten d⁴-complexes MCl₂L₄ also react with various isocyanates RNCO; however, in this case, the insertion of the complex into the C=N bond is not accompanied by carbon monoxide evolution, but rather results in the formation of d²-imido carbonyl complexes **82**.^{340–342} A series of binuclear tungsten complexes **83** have been obtained in this way using various diisocyanates OCN–Ar–NCO.^{343, 344}



M = Mo, W; R = Bu^t, SiMe₃, Ph, 4-MeC₆H₄; Ar = 1,4-C₆H₄, 1,4-(2-MeC₆H₃), 1,4-(2,3-Me₂C₆H₂), 1,4-(2,5-Me₂C₆H₂), 1,4-C₆Me₄, 1,3-(4-MeC₆H₃), 1,3-C₆H₄, 1,5-C₁₀H₆, (4-C₆H₄)CH₂(C₆H₄-4), 1,1'-(2,6-Me₂C₆H₂-4)₂, 1,1'-(2-MeOC₆H₃-4)₂.

A few examples are known where imidation with isocyanates results in reduction of metal compounds having pronounced oxidative properties. For example, osmium tetroxide is reduced by three equivalents of 2,6-Pr₂C₆H₃NCO to give the imido d²-complex (2,6-Pr₂C₆H₃N=)₃Os in 50% yield.³⁴⁵ It should be noted that a similar reaction pattern is observed when OsO₄ is treated with trimethylsilylanilines (see Section II.2.e), whereas trimethylsilyl derivatives of aliphatic amines and iminophosphoranes imidate osmium tetroxide with retention of the oxidation state.

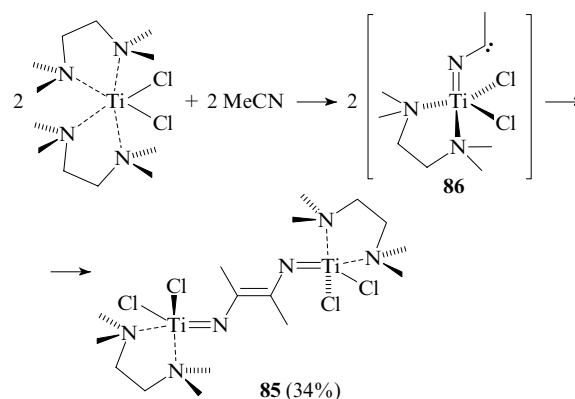
The imido-deoxygenation of molybdenum oxotetrachloride with excess 2,6-Pr₂C₆H₃NCO in *p*-xylene is also accompanied by the reduction of molybdenum and results in imido d¹-complex **84**.³⁴⁶



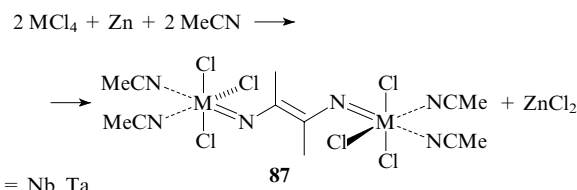
d. Imidation with nitriles

Group 4 and 5 transition metal halides in intermediate oxidation states can undergo redox reactions with nitriles to give binuclear imido complexes, the diimido fragment of which is formed by coupling of coordinated nitrile molecules. The mechanism of this multistep process has not been studied in detail so far.

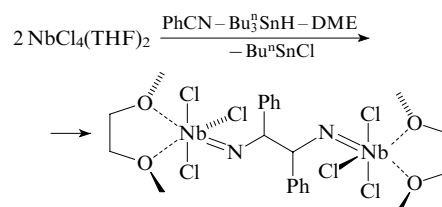
The reaction of the complex (TMEDA)₂TiCl₂ with acetonitrile is a typical example of this type of reactions. It was suggested that the formation of binuclear complex **85** is due to dimerisation of mononuclear carbene intermediates **86**;³⁴⁷ however, the possibility of stepwise (two-step) coupling to give, first, a single and then a double carbon–carbon bond cannot be ruled out either.



In the reduction of niobium or tantalum tetrachlorides with zinc in acetonitrile, a similar coupling of two nitrile molecules takes place to give binuclear diimido complexes **87**.³⁴⁸

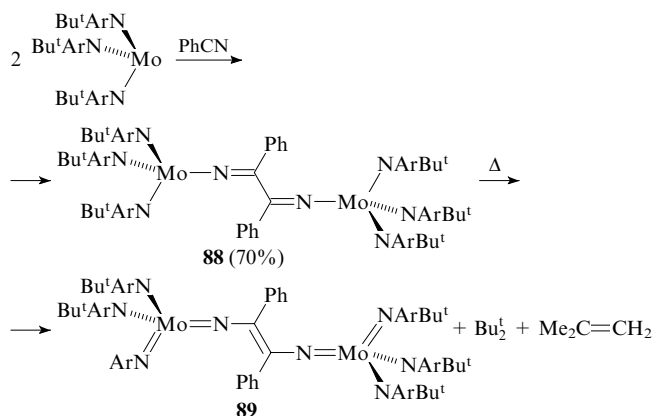


Under the action of an equimolar amount of tributyltin hydride in 1,2-dimethoxyethane, niobium tetrachloride induces hydrodimerisation of benzonitrile. Presumably, this reaction involves successively the formation of the hydride Cl₃NbH, insertion of benzonitrile into the Nb–H bond and recombination of the Cl₃Nb=N–C[•](Ph)H radicals thus formed.³⁴⁹



The reaction of trisamido complex Mo(NBu^tAr)₃ with benzonitrile gives diiminato complex **88**, the nitrile coupling product. Thermolysis of complex **88** is accompanied by homolytic cleavage of the Bu^t–N bond of the amido ligand followed by bond redistribution in the molecule, resulting in binuclear imidoamide

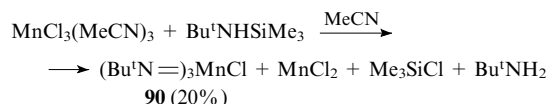
complex **89**.³⁵⁰ The formation of *tert*-butyl radicals is confirmed by the presence of their recombination and disproportionation products.



e. Imidation with amines, lithium amides and *N*-trimethylsilylamines

The imidation with amines and their lithium and trimethylsilyl derivatives usually proceeds with no change in the formal oxidation state of the metal (see Sections II.1.a–c). However, some reactions are accompanied by an increase in the metal oxidation state. This may be due to the action of some extraneous oxidant, disproportionation processes or other reasons. Examples of oxidative imidation of transition metal complexes involving amines or lithium amides are given in Table 12.

A unique compound **90**, which is the key derivative in the chemistry of manganese imido d⁰-complexes, was prepared by the reaction of manganese(III) chloride with Bu^tNHSiMe₃ in acetonitrile.

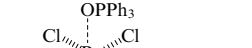
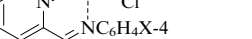
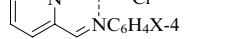


Presumably, complex **90** is formed in a multistep disproportionation of intermediate manganese compounds.^{358, 359}

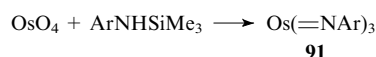
Table 12. Synthesis of transition metal imido complexes by oxidative imidation with amines and their lithium derivatives.

Starting compound	Imidating reagent	Product	Yield (%)	Ref.
(Ar = 2,6-Pr₂C₆H₃, L is 4-pyrrolidinopyridine)	RNH ₂ –L (R = Bu ^t , Ph)		—	325
(Cp' = η⁵-Me₃SiC₅H₄)	1,3- or 1,4-(H ₂ N) ₂ C ₆ H ₄	(<i>meta</i>- and <i>para</i>-isomers)	60–75	339
	RNHLi (R = Bu ^t , Ph)		83–90	318
	(PhS)NRLi (R = Bu ^t , 4-MeC ₆ H ₄ , 2,6-Pr ₂ C ₆ H ₃ , 2-Bu ^t C ₆ H ₄)		30–59	351, 352
	1,2-(2-NH ₂ C ₆ H ₄) ₂ C ₂ H ₄		46	353
	2-NH ₂ C ₆ H ₄ PPh ₂		30	353
Na(THF)₃⁺	Bu ^t ₃ SiNHLi		50–60	354

Table 12 (continued).

Starting compound	Imidating reagent	Product	Yield (%)	Ref.
 (X = Me, Cl)	ArNH ₂ (Ar = Ph, 4-ClC ₆ H ₄)		70–75	355
ReCl ₄ (OPPh ₃) ₂	2-MeNHC ₆ H ₄ NH ₂	2-MeNHC ₆ H ₄ N=ReCl ₄ (OPPh ₃)	22	356
	2,6-Pr ⁱ ₂ C ₆ H ₃ NHLi–O ₂		16	357

For metal compounds with pronounced oxidative properties, the imidation reactions can be accompanied by reduction of the metal. For example, on treatment with excess *N*-trimethylsilylalkylanilines, osmium tetroxide undergoes reductive imidation to give tris(imido) d²-complex **91** as the only osmium-containing reaction product.¹⁹⁸


$$\text{Ar} = 2,6\text{-Me}_2\text{C}_6\text{H}_3 \text{ (46\%)}, 2,6\text{-Pr}_2\text{C}_6\text{H}_3 \text{ (62\%)}. \quad \text{---}$$

It is of note that imidation of osmium tetroxide with aliphatic silylamines is not accompanied by its reduction (see Section II.1.c).

Ammonium pertechnetate is also reduced by a mixture of 2,6-diisopropylaniline and chlorotrimethylsilane in the presence of pyridine to give monoimido d²-complex **92** (see Ref. 85, p. 268).

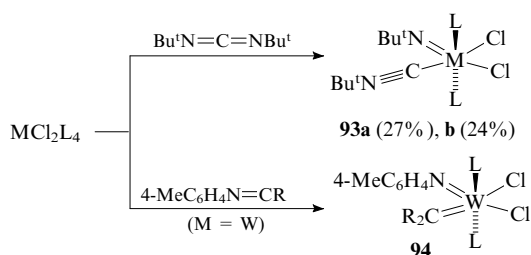

$$\text{Ar} = 2,6\text{-Pr}_2\text{C}_6\text{H}_3.$$

It should be noted that no reduction of rhenium takes place in the imidation of ammonium perrhenate under similar conditions (see Section II.1.c).

f. Imidation with miscellaneous nitrogen-containing compounds

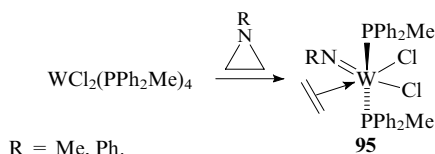
The use of other nitrogen-containing organic compounds as sources of imido groups is a specific case. A few examples of oxidative imidation of complexes of metals in low oxidation states with carbodiimides, aldimines, ketimines, sulfodiimines, aziridines, 2*H*-azirines and nitroso compounds have been reported.

Thus reactions of N,N' -di(*tert*-butyl)carbodiimide^{341, 342, 360} and ketimine 4-MeC₆H₄N=CR₂ (see Ref. 361) with molybdenum and tungsten dichlorides MCl₂L₄ occur as oxidative addition to give imidoisocyanide (**93a.b**) and imidocarbene (**94**) complexes.



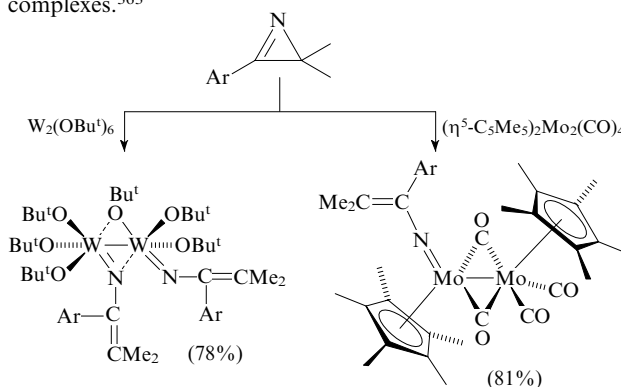
M = Mo (**a**), W (**b**); L = PPh₂Me; R₂ = Me₂, (CH₂)₄ (45%).

The reaction of tungsten dichloride with *N*-substituted aziridines is accompanied by ring opening and results in imidoethylene complexes **95**.³⁶²



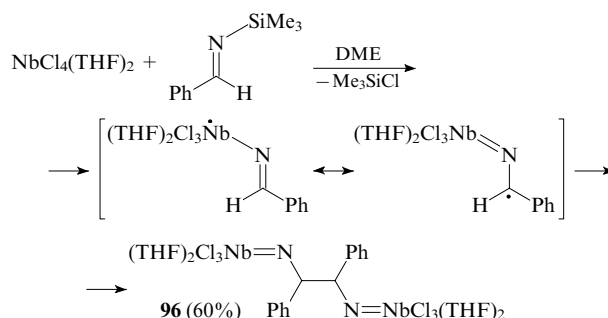
R = Me, Ph.

2*H*-Azirines can also be cleaved by treatment with some binuclear complexes of Group 6 metals to give various imido complexes.³⁶³



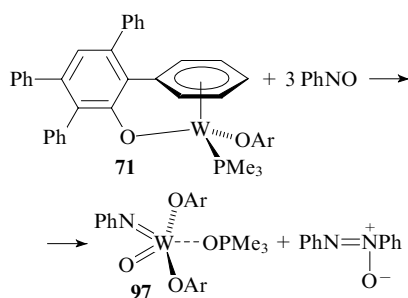
Ar = Ph, 4-Bu^tC₆H₄.

The reaction of niobium tetrachloride with an equimolar amount of *N*-benzylidene-*N*-trimethylsilylamine results in the formation of binuclear d⁰,d⁰-complex **96** with a diimido bridging ligand.³⁴⁹



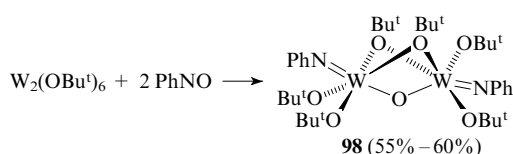
The formation of complex **96** is believed to be due to dimerisation of mononuclear radical intermediates.

The formation of imido complexes in the reactions with nitrosoarenes and sulfodiimines follows a complex route and is formally an oxidative addition of the metal to the nitrogen–heteroatom bond. For example, d⁴-complex **71** is oxidised with nitrosobenzene to give oxoimido d⁰-complex **97** and azoxybenzene.³³⁰

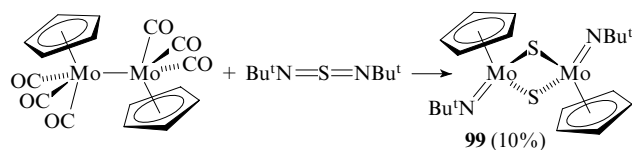


Ar = 2,3,5,6-Ph₄C₆H.

The reaction of two equivalents of nitrosobenzene with the d³,d³-complex W₂(OBu^t)₆, containing multiply bonded metal atoms, affords dimeric d⁰,d⁰-complex **98** with bridging *tert*-butoxide ligands and an oxygen atom.³⁶⁴ Thus, the outcome of the process is asymmetric oxidative addition of nitrosobenzene to metal sites accompanied by cleavage of the metal–metal bond.



Long-term refluxing of the binuclear complex [(η⁵-Cp)Mo(CO)₃]₂ with sulfodi(*tert*-butyl)imine in benzene induces oxidative imido-decarbonylation to give disulfido complex **99** in low yield.³⁶⁵



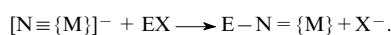
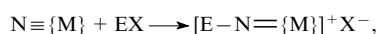
III. Intramolecular imidation methods

The other strategy of the synthesis of transition metal imido complexes is based on intramolecular formation of the imido group in the metal complex from nitrogen-containing ligands of a different type. Intramolecular imidation procedures are not so numerous as intermolecular imidation methods and are less often used in synthetic practice. The N-ligand precursors used to construct the imido group are nitrido, amido and some other ligands.

1. Transition metal nitrides

Complexes of transition metals of Group 6–8 with terminal nitrido ligands are convenient substrates for the synthesis of neutral and cationic imido complexes. The imido complexes are formed upon an electrophilic attack by alkylating reagents on the nitrogen atom of the nitride group of anionic or neutral transition metal complexes (Scheme 13). Trialkyloxonium tetrafluoroborate, methyl iodide, alkyl and trimethylsilyl triflates, tritylhexafluorophosphate, and so on are used as alkylating reagents.

Scheme 13



A kinetic study of the reaction of the nitrido complex (NBu₄⁺)[N≡Os(CH₂SiMe₃)₄] with methyl iodide has shown that the reaction is first order with respect to each reactant, which is indicative of the S_N2 mechanism.³⁶⁶ It is worth noting that only electron-enriched nitrido complexes, for example, osmium and ruthenium nitride s- and p-complexes and molybdenum, tungsten, rhenium and osmium complexes with S-, O- and N-ligands possess nucleophilicity sufficient for this electrophilic attack. Table 13 presents examples of the use of Group 6–8 transition metal nitrido complexes for the synthesis of the corresponding imido complexes.

Table 13. Synthesis of Group 6–8 transition metal imido complexes by alkylation of nitrides.

Starting compound	Alkylating agent	Product	Yield (%)	Ref.
N≡Mo(S ₂ CNR ₂) ₃ (R = Me, Et; R ₂ = (CH ₂) ₄)	[Me ₃ O]BF ₄ , MeI 2,4-(NO ₂) ₂ C ₆ H ₃ Cl, Ph ₃ CBF ₄	[R'N≡Mo(S ₂ CNR ₂) ₃] ⁺ X [−] (R' = Me, 2,4-(NO ₂) ₂ C ₆ H ₃ , Ph ₃ C)	—	367, 368
ArBu ^t N≡Mo(NBu ^t Ar) ₂ (Ar = 3,5-Me ₂ C ₆ H ₃)	MeI Me ₃ SiOTf	ArBu ^t N≡Mo(NBu ^t Ar) ₂ ⁺ X [−] R' = Me R' = Me ₃ Si	92 89	369 369
Me ₃ Si-N≡M(N≡N-SiMe ₃) ₂ (M = Mo, W)	MeOTf, Me ₃ SiOTf	Me ₃ Si-N≡M(N≡N-SiMe ₃) ₂ ⁺ OTf [−] (R' = Me, Me ₃ Si)	79–93	370
H-B-N≡M(N≡N) ₂ (M = Mo, W)	MeOTf Ph ₃ CPF ₆	H-B-N≡M(N≡N) ₂ ⁺ X [−] R' = Me R' = CPh ₃	70 —	371 372
N≡Re(S ₂ CNEt ₂) ₂ (PMe ₂ Ph)	Ph ₃ CPF ₆	[Ph ₃ CN≡Re(S ₂ CNEt ₂) ₂ (PMe ₂ Ph)] ⁺ PF ₆ [−]	85	373

Table 13 (continued).

Starting compound	Imidating reagent	Product	Yield (%)	Ref.
	Ph_3CBF_4		53	374
	Ph_3CBF_4 MeOTf BuBr		$\text{R}' = \text{CPh}_3$ 60 $\text{R}' = \text{Me}$ 58 $\text{R}' = \text{Bn}$ 41	375 375 375
	$\text{R}'\text{OTf}$ ($\text{R}' = \text{Me, Et, Me}_3\text{Si}$), $[\text{Me}_3\text{O}]\text{BF}_4$, $[\text{Et}_3\text{O}]\text{BF}_4$, MeI		—	366, 376, 377
	MeOTf		90	378
	Ph_3CPF_6		55	379
	Me_3SiOTf		92	380

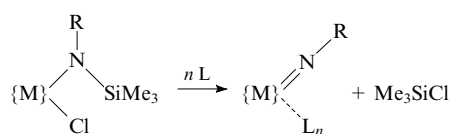
2. Transition metal amides

Intramolecular imidation methods based on the transformation of amido ligands have been reported. In this case, imido ligands are formed upon either 1,2-elimination of fragments of the initial amide groups or intramolecular interligand transfer of a hydrogen atom or trialkylsilyl groups.

a. Synthesis of imido complexes with elimination of an amido group fragment

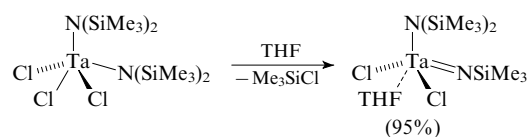
An imido ligand may be formed from an amide ligand upon elimination of molecules such as trialkylsilyl halides, primary and secondary amines, alkanes, hydrogen halides, *etc.* Depending on the structure of the starting amido complex and the nature of the leaving molecule, these reactions may be induced thermally or chemically. In some cases, a combination of these variants is used.

Trimethylsilylamidometal chloride easily eliminate chlorotrimethylsilane in the presence of various n-donor compounds L. The formation of a stronger Si—Cl bond and steric crowding in the metal coordination environment arising upon the formation of adducts with n-donors are apparently the driving forces of the process.

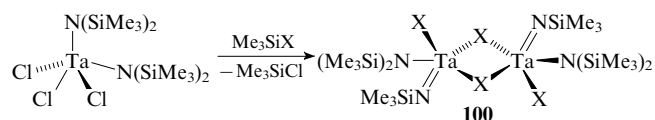


On treatment of the complex $\text{TiCl}_3[\text{N}(\text{SiMe}_3)_2]$ with pyridine, a Me_3SiCl molecule is eliminated to give the imido complex

$\text{Me}_3\text{SiN}=\text{TiCl}_2(\text{py})_2$.³⁸¹ The same is observed for the tantalum diamido complex $\text{TaCl}_3[\text{N}(\text{SiMe}_3)_2]$ on treatment with tetrahydrofuran.³⁸²

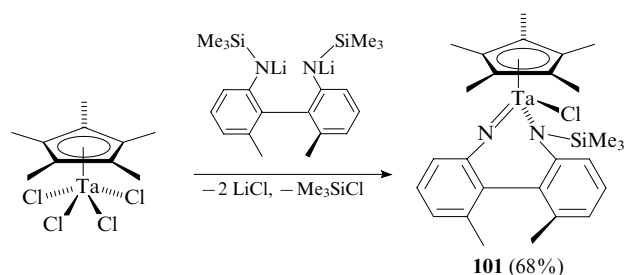


Elimination of chlorotrimethylsilane can take place spontaneously in the synthesis of bis(trimethylsilyl)amido complexes or in parallel with other transformations. For instance, on treatment of $\text{TaCl}_3[\text{N}(\text{SiMe}_3)_2]$ with trimethylsilyl halides, elimination of trimethylsilyl chloride, resulting in dimeric imido complexes **100**, takes place in parallel with ligand exchange.^{163, 382}

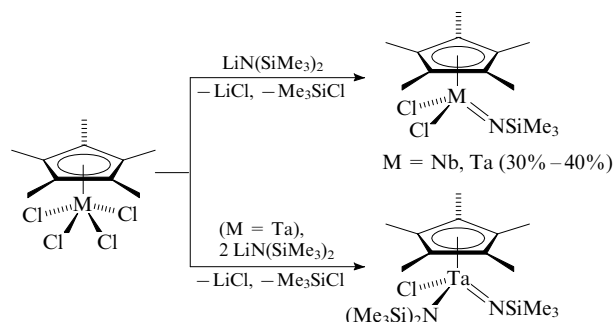


X = Br (25%), I (75%).

Upon the reaction of equimolar amounts of the complex $(\eta^5\text{-C}_5\text{Me}_5)\text{TaCl}_4$ and dilithium derivative of 2,2'-bis(trimethylsilylamino)biphenyl, amido–imido complex **101** was isolated; the complex is obviously formed upon spontaneous elimination of chlorotrimethylsilane from the reaction intermediate.³⁸³

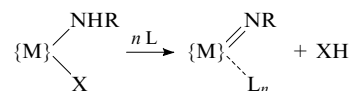


The reaction of the complexes $(\eta^5\text{-C}_5\text{Me}_5)\text{MCl}_4$ ($\text{M} = \text{Ta}, \text{Nb}$) with one³⁸⁴ or two¹⁶⁷ equivalents of lithium hexamethyldisylazide proceeds in a similar way



It is noteworthy that spontaneous elimination of chlorotrimethylsilane is apparently the key step in the formation of the imido complexes in the reaction of transition metal polyhalides with bis(trimethylsilyl)amines (see Section II.1.c).

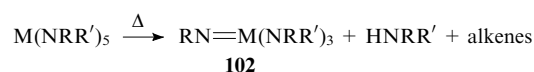
Polyamido (more rarely, alkylamido) complexes eliminate amines (alkanes) on treatment with n -donor compounds or on heating, resulting in the formation of imido products.



$\text{X} = \text{NHR}, \text{Alk}.$

Examples of the use of this synthetic approach are listed in Table 14.

In some cases, thermolysis of polyamido complexes leading to imido products occurs in a more complicated way. Thus thermolysis of homoleptic sterically hindered complex $\text{Nb}(\text{NMeBu}^n)_5$ involves elimination of butylmethylamine and but-1-ene, which affords mixed amido-imido complex **102** in low yield.³⁹¹ Thermolysis of the complexes $\text{Ta}(\text{NR}_2)_5$ proceeds in a similar way.^{392, 393}



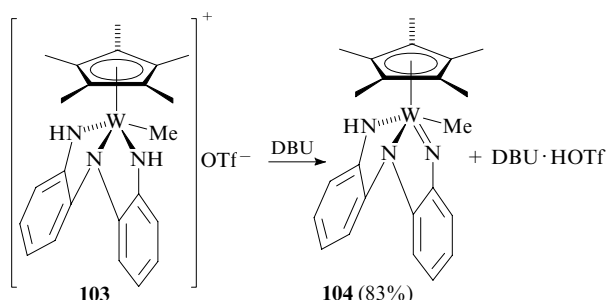
$\text{M} = \text{Nb}$: $\text{R} = \text{Bu}^n$, $\text{R}' = \text{Me}$;

$\text{Me} = \text{Ta}$: $\text{R} = \text{R}' = \text{Et}$ (35%–47%), Pr^n , Bu^n ; $\text{R} = \text{Bu}^n$, $\text{R}' = \text{Me}$.

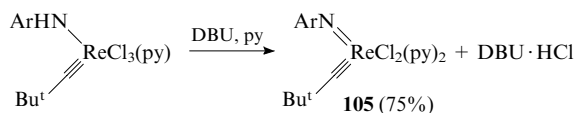
Table 14. Synthesis of transition metal imido complexes from amides by elimination of amines and alkanes.

Starting compound	Reaction conditions	Product	Yield (%)	Ref.
$(\text{Bu}_3\text{SiNH})_3\text{TiCl}$	THF, Δ	$\text{Bu}_3\text{SiN}=\text{Ti}(\text{NHSiBu}_3)\text{Cl}(\text{THF})$	83	385
	py, Δ		76	386
$(\text{Ar} = 2,6\text{-Pr}_2\text{C}_6\text{H}_3)$				
	4-pyrrolidinopyridine (L)		40–70	387, 388
$(\text{M} = \text{Zr}, \text{Hf}; \text{Ar} = 2,6\text{-Pr}_2\text{C}_6\text{H}_3)$				
	4-pyrrolidinopyridine (L)		40 (Zr)	325, 387, 388
$(\text{M} = \text{Ti}: \text{R} = 2,6\text{-Pr}_2\text{C}_6\text{H}_3, 2,6\text{-Ph}_2\text{C}_6\text{H}_3; \text{M} = \text{Zr}: \text{R} = 2,6\text{-Bu}_2\text{C}_6\text{H}_3)$				
$\text{Cp}_2\text{Zr}(\text{NHR})(\text{NHR}')$	THF, Δ	$\text{Cp}_2\text{Zr}(\text{THF})(\text{N}=\text{NR})$	69–72	389
$(\text{R} = \text{Bu}^t, \text{R}' = \text{Me}; \text{R} = 2,6\text{-Me}_2\text{C}_6\text{H}_3, \text{SiMe}_2\text{Bu}^t, \text{R}' = \text{CH}_2\text{Bu}^t)$				
	py, Δ		68	45
$(\eta^5\text{-C}_5\text{Me}_5)_2\text{U}(\text{NHR})(\text{NHR})$	THF, Δ	$(\eta^5\text{-C}_5\text{Me}_5)_2\text{U}(\text{THF})(\text{N}=\text{NR})$	—	390
$(\text{R} = \text{Bu}^t, \text{Et}, 2,6\text{-Me}_2\text{C}_6\text{H}_3)$				

Neutral and cationic monoalkyl- and monoarylamido complexes can be deprotonated under the action of nitrogenous bases to give the corresponding imido products. The cationic complex **103** is deprotonated with diazabicyclo[5.4.0]undecene (DBU) to give neutral imido complex **104**.¹³²

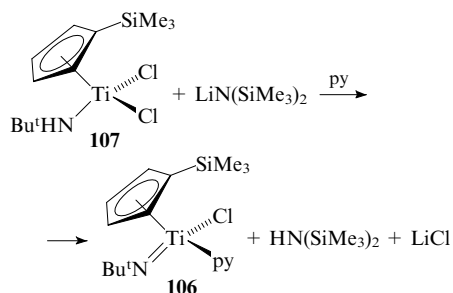


The amidocarbene complex $\text{Bu}^t\text{C}\equiv\text{Re}(\text{NHC}_6\text{H}_3\text{Pr}_2^i-2,6)\cdot\text{Cl}_3(\text{py})$ is also deprotonated with DBU in the presence of pyridine to give imidocarbene complex **105**.³⁹⁴

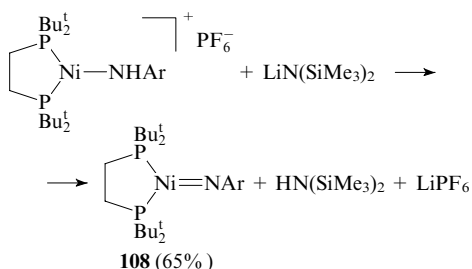


$\text{Ar} = 2,6\text{-Pr}_2\text{C}_6\text{H}_3$.

Half-sandwich titanium imido complex **106** was prepared by deprotonation of *tert*-butylamido complex **107** with lithium hexamethyldisilazide.³⁹⁵

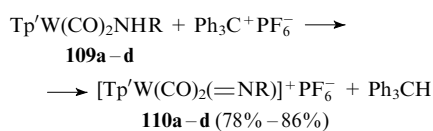


The only, to our knowledge, nickel complex **108** with a terminal imido group was synthesised in a similar way.³⁹⁶



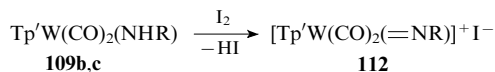
$\text{Ar} = 2,6\text{-Pr}_2\text{C}_6\text{H}_3$.

Examples of transformations of monoamido complexes into imido complexes upon abstraction of a hydride ion are known. Thus amido carbonyl complexes **109** are converted into cationic imido products **110a–d** under the action of trityl cation.^{372, 397}

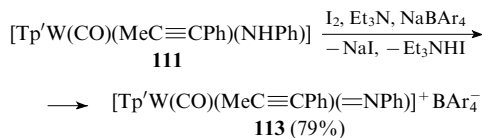


$\text{R} = \text{Bu}^n$ (a), Bu^t (b), Ph (c), CH_2Ph (d).

The complexes $\text{Tp}'\text{W}(\text{CO})_2(\text{NHR})$ (**109b,c**) and the related complex $\text{Tp}'\text{W}(\text{CO})(\text{PhC}\equiv\text{CMe})(\text{NHPh})$ (**111**) are oxidised to the corresponding imido derivatives **112** and **113** under the action of molecular iodine.³⁹⁸



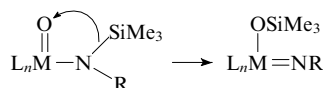
$\text{R} = \text{Bu}^t$ (b), Ph (c).



$\text{Ar} = \text{C}_6\text{H}_3(\text{CF}_3)_{2-3,5}$.

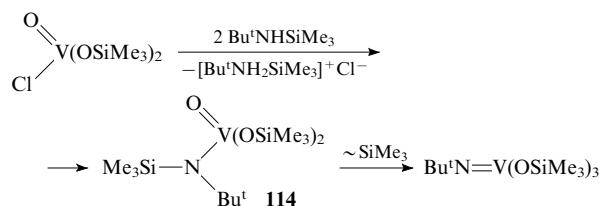
b. Synthesis of imido complexes through intramolecular migration of an amido group fragment

In some cases, imido complexes of Group 5–7 transition metals are formed upon intramolecular rearrangement of amido, mainly oxotrimethylsilylamido, complexes. In the synthesis of these complexes, spontaneous 1,3-migration of the trimethylsilyl group from the nitrogen atom of the amido ligand to the oxo group often takes place.

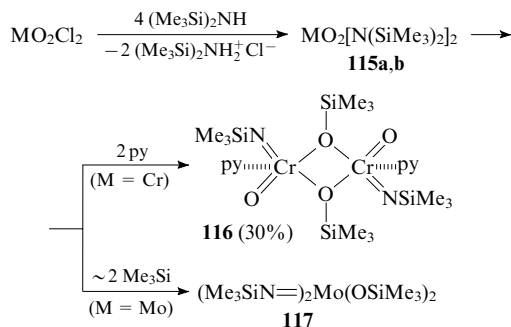


Thus, the reaction of VOCl_3 with three equivalents of $\text{NaN}(\text{SiMe}_3)_2$ results in the imido complex $\text{Me}_3\text{SiN}=\text{V}(\text{OSiMe}_3)_3$. $[\text{N}(\text{SiMe}_3)_2]_2$.³⁹⁹ Presumably, the reaction involves intermediate formation of the unstable oxotriamido complex $\text{O}=\text{V}[\text{N}(\text{SiMe}_3)_2]_3$, which is spontaneously rearranged to the final product.

The reaction of the oxo complex $\text{O}=\text{V}(\text{OSiMe}_3)_2\text{Cl}$ with two equivalents of *tert*-butyl(trimethylsilyl)amine yielded the complex $\text{Bu}^t\text{N}=\text{V}(\text{OSiMe}_3)_3$. This product may have formed upon 1,3-migration of the trimethylsilyl group in the intermediate oxo-amido complex **114**.¹⁵⁰



The reaction of chromyl chloride with hexamethyldisilazane has been shown to furnish dioxoamido d⁰-complex **115a**. Treatment of the latter with excess pyridine results in its reduction accompanied by 1,3-migration of the trimethylsilyl group to give dimeric imido d¹-complex **116**, the structure of which was con-

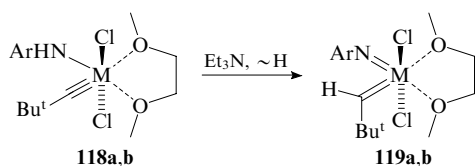


$\text{M} = \text{Cr}$ (a), Mo (b).

firmed by X-ray diffraction.¹⁹⁰ The reaction of molybdenum dioxodichloride with hexamethyldisilazane yields diimido complex **117**. By analogy with the previous case, this outcome was attributed to the intramolecular rearrangement of dioxodiamido complex **115b**.

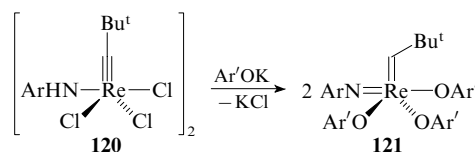
The formation of the rhenium imido complex $(\text{Me}_3\text{SiN}=\text{O})_2\text{Re}(\text{OSiMe}_3)_2[\text{N}(\text{SiMe}_3)_2]$ in the reaction of ReO_3X ($\text{X} = \text{Cl}, \text{OSiMe}_3$) with three equivalents of $\text{LiN}(\text{SiMe}_3)_2$ apparently also includes 1,3-migration of the SiMe_3 group.⁴⁰⁰

Yet another type of intramolecular rearrangement resulting in imido complexes is observed for monoarylamidocarbene complexes. In particular, it was shown that triethylamine induces interligand migration of the proton in amidocarbene complexes of molybdenum (**118a**)¹⁹¹ and tungsten (**118b**),^{193,401} resulting in imidocarbene complexes **119a,b**.



$\text{M} = \text{Mo}$ (**a**), W (**b**); $\text{Ar} = 2,6\text{-Pr}_2\text{C}_6\text{H}_3$.

Rhenium amidocarbene complexes behave in a similar way. On treatment of dimer **120** with six equivalents of potassium polyhalogenophenoxides, proton migration from the amido group to the carbene group to give imidocarbene complexes **121** takes place in addition to the replacement of chlorine atoms.⁴⁰²

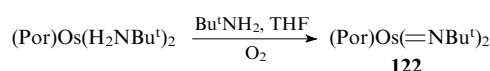


$\text{Ar} = 2,6\text{-Pr}_2\text{C}_6\text{H}_3$; $\text{Ar}' = 2,6\text{-Cl}_2\text{C}_6\text{H}_3$ (67%), C_6F_5 (78%), C_6Cl_5 (48%).

3. Transition metal complexes with other types of nitrogen-containing ligands

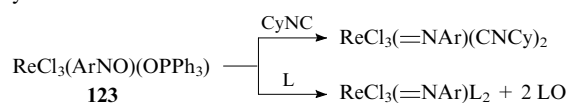
Metal complexes with other types of nitrogen-containing ligands can also be used to synthesise imido complexes. In particular, examples of transformation of metal-coordinated primary amines, nitriles, nitrosoarene, nitrosyl and some other ligands into imido ligands have been reported.

Thus osmium porphyrin complexes containing coordinated *tert*-butylamine are oxidised under aerobic conditions to give imido derivatives **122**.⁴⁰³



$\text{Por} = \text{TTP}$ (68%), TPP (70%), 4-Cl-TPP (75%),
3,4,5-(MeO)₃- TPP (72%) ($\text{Ar} = 3,4,5\text{-(MeO)}_3\text{C}_6\text{H}_2$,
see notation in Table 10).

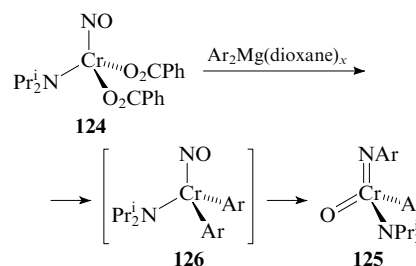
Rhenium nitrosoarene complex **123** is converted into imido complexes under the action of oxophilic tertiary phosphines or isocyanides.⁴⁰⁴



$\text{L} = \text{Ph}_3\text{P}, \text{PhEt}_2\text{P}$.

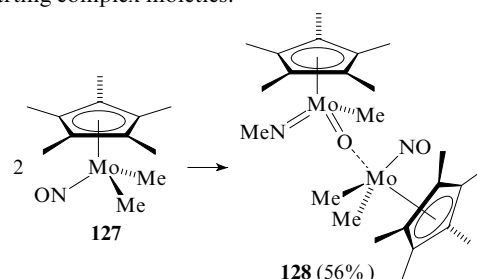
Examples of spontaneous rearrangements of dialkyl(aryl)-nitroso complexes of Group 6 metals involving nitrogen–oxygen bond cleavage and resulting in imido complexes have been

described. The reaction of nitrosyl complex **124** with diarylmagnesium leads to imido complex **125**⁴⁰⁵ with one σ -aryl ligand, which was characterised by X-ray diffraction. This product is believed to result from the rearrangement of unstable intermediate bis(σ -aryl) complex **126**.



$\text{Ar} = 2\text{-MeC}_6\text{H}_4$.

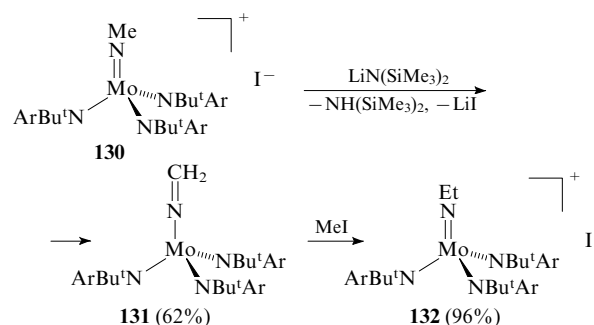
A similar transformation occurs on storage of dimethylnitrosyl complex **127** in solution. According to X-ray diffraction data, the rearrangement of complex **127** gives dimer **128** comprising fragments of the intramolecular rearrangement product and the starting complex moieties.⁴⁰⁶



Replacement of the counter-ion in the cationic complex *trans*- $[\text{CrCl}(\text{MeCN})(\text{dmpe})_2]^+(\text{BPh}_4)^-$ (dmpe is $\text{Me}_2\text{PCH}_2\text{CH}_2\text{PMe}_2$) on treatment with barium triflate in methanol involves a redox process resulting in the ethylimido d²-complex *trans*- $[\text{EtN}=\text{CrCl}(\text{dmpe})_2]^+(\text{OTf})^-$ in parallel with the protonation of the coordinated acetonitrile molecule.⁴⁰⁷ The formation of the ethylimido d²-complex was confirmed by both spectroscopy and X-ray diffraction.

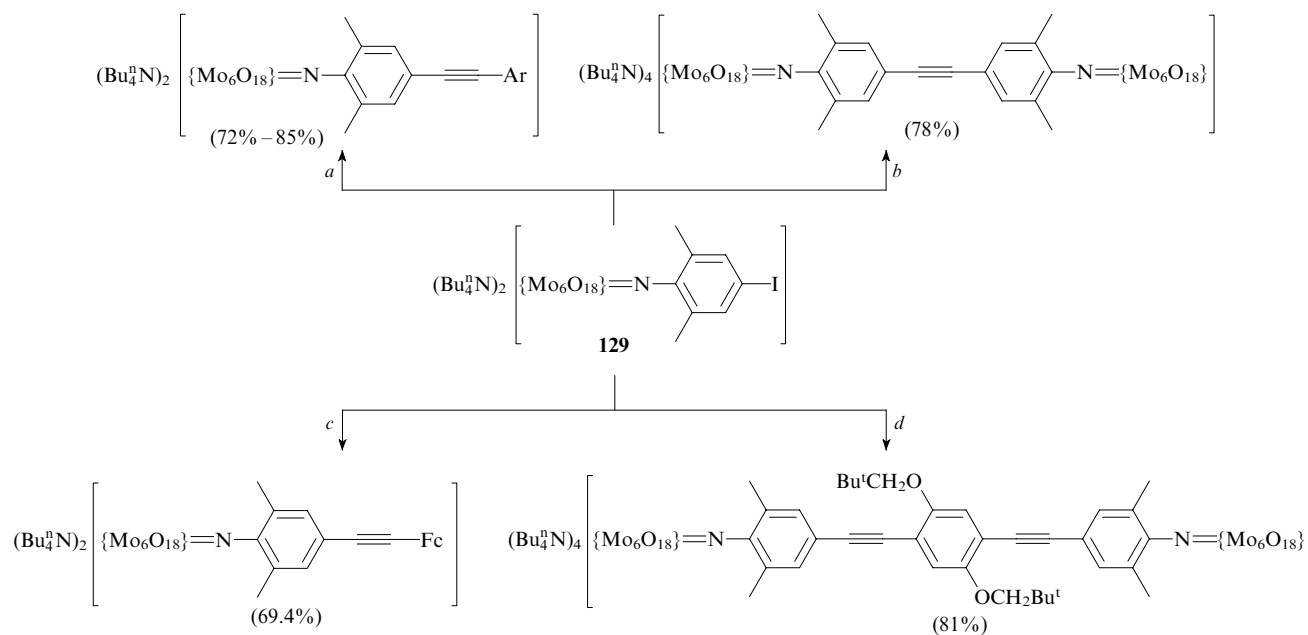
Examples of modification of an imido ligand directly within the complex are documented. It was demonstrated that imido complex **129** can be used in the palladium-catalysed Sonogashira cross-coupling, which opens the way to various metal complexes containing conjugated systems of multiple bonds^{408–410} (Scheme 14).

Recently, the possibility of elongation of the carbon chain in the alkylimido group by one methylene unit as a result of consecutive deprotonation and alkylation of the cationic methyl-imido complex **130** was demonstrated. It was shown that the complex can be deprotonated to the ketimido derivative **131**, which, in turn, is readily alkylated with methyl iodide to give compound **132**, a homologue of the starting complex.³⁶⁹



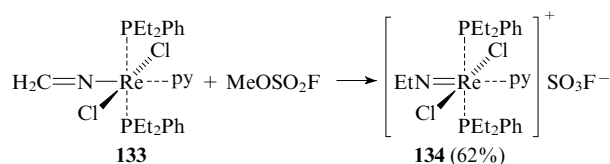
$\text{Ar} = 3,5\text{-Me}_2\text{C}_6\text{H}_3$.

Scheme 14

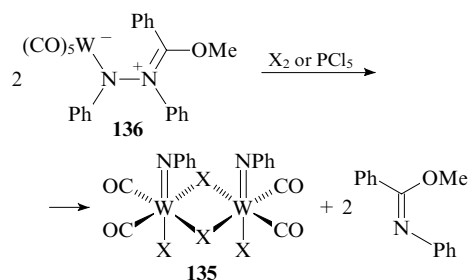


(a) $\text{HC}\equiv\text{CAr}-\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ ($\text{Ar} = 3,5\text{-Bu}_2\text{C}_6\text{H}_3$, $4\text{-MeC}_6\text{H}_4$), CuCl , Et_3N ; (b) $(\text{Bu}_4\text{N})_2[\{\text{Mo}_6\text{O}_{18}\}=\text{N}(4\text{-HC}\equiv\text{C}-2,6\text{-Me}_2\text{C}_6\text{H}_2)]-\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, CuI , Et_3N , K_2CO_3 ; (c) $\text{HC}\equiv\text{CFc}-\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, CuI , Et_3N ; (d) $3,6\text{-(HC}\equiv\text{C)}_2\text{-1,4-(Bu}^t\text{CH}_2\text{O)}_2\text{C}_6\text{H}_2-\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, CuI , Et_3N , K_2CO_3 .

We would like to add that the possibility of converting metal ketimides into imido complexes was first demonstrated for complex **133**. In particular, this was found to be readily methylated with methyl fluorosulfate to give cationic complex **134**.⁴¹¹



For the synthesis of tungsten imido carbonyls **135**, zwitterionic complex **136** can be used. The latter is smoothly oxidised with iodine, bromine or phosphorus pentachloride with N–N bond cleavage to give binuclear complexes **135** with bridging halogen atoms.^{412–415}



$\text{X} = \text{I}$ (76%), Br (13%), Cl (63%).

IV. Conclusion

The chemistry of transition metal imido complexes has long aroused particular interest owing to the remarkable ability of imido ligands to stabilise transition metals in higher oxidation states. The introduction of imido ligands into the coordination environment allowed, for example, preparation and characterisation of organic derivatives of chromium(VI) and manga-

nese(VII), *i.e.*, the elements the oxides of which are classical oxidants used in organic chemistry.

Over the last 15 years, the focus has moved toward the application of transition metal imides, which has, in turn, stimulated the development of new methods for the synthesis of metal imido complexes of diverse structural types. Currently, the reactions of a broad range of nitrogen-containing reagents with transition metal compounds have been studied in sufficient detail, the features of these reactions were revealed and their synthetic potential was demonstrated.

A wide diversity of imido complexes was attained, first of all, owing to the use of intermolecular imidation methods. Currently, it can hardly be expected that the range of imidating reagents would be extended; further development of intermolecular imidation methods is possible, most of all, through the use of new transition metal-containing substrates and new types of imido ligands, in particular, heteroarylimido ligands. The progress in this field may also be connected with modern quantum-mechanical calculations of potential energy surface fragments. Such calculations are now virtually missing, and detailed structures of the transition states often remain obscure.

The methodology of intramolecular imidation has been developed less extensively than the intermolecular imidation strategy; therefore, there are grounds for expecting fruitful development of this line of research. In our opinion, the most interesting prospects are related to selective inner-sphere modification of the imido ligands, for example, functionalisation, elongation of the organic group, design of polymeric or dendrimeric molecules. Examples of such modifications are still few, but further development of this field would favour the synthesis of new promising compounds and material based on them.

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^a — *Russ. J. Coord. Chem. (Engl. Transl.)*

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Organolithium and organomagnesium compounds of the naphthalene series in organic synthesis

A F Pozharskii, O V Ryabtsova

Contents

I. Introduction	709
II. General features	709
III. Synthesis and reactions of naphthylmetals	716
IV. Naphthylmetals in cross-coupling reactions	732
V. Conclusion	733

Abstract. The review summarises procedures for the synthesis of organolithium and organomagnesium compounds of the naphthalene series, including binaphthyls, the properties of these compounds and their use in organic synthesis. The bibliography includes 283 references.

I. Introduction

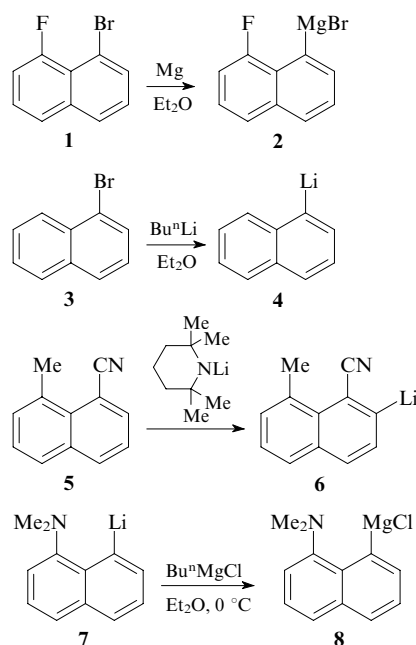
Organometallic, primarily, lithium and magnesium, derivatives of naphthalene play an exceptionally important role in organic synthesis. In recent years, these compounds have been widely used in the synthesis of chiral binaphthyl catalysts and complex natural compounds. Of special note are various 1,8-disubstituted naphthalenes necessary for studying the *peri* effects. However, reviews of a vast literature on the synthesis of organometallic derivatives of naphthalene are lacking. Scarce data are available in monographs.^{1–6} The main aim of the present review is to close this gap as regards Li and Mg derivatives of naphthalene. The review summarises data published predominantly in the last two decades. An earlier literature is cited if the corresponding data remain to be important and are of principal significance.

II. General features

1. Synthesis

There are four main methods for the synthesis of organolithium and -magnesium compounds of the naphthalene series: (i) the reactions of the corresponding metal with naphthyl halides, (ii) the reactions of commercial organolithium or -magnesium compounds with naphthyl halides, (iii) direct deprotonation of aromatic C–H bonds and the formation of C–M bonds (CH-metallation) and (iv) transmetallation. Examples of the reactions are presented in Scheme 1.

The first of the above-mentioned procedures is most often used for the synthesis of organomagnesium compounds (Grignard reagents), for example, **1** → **2**.⁷ It was proposed to use chemical activation of magnesium with the aim of increasing the product



Scheme 1

yield.[†] Of various methods for magnesium activation, the method of auxiliary reagents is the most widely used procedure. This method is based on an increase in the reactivity of inert aryl halides by adding more active alkyl halide, which rapidly reacts with magnesium and activates its surface. 1,2-Dibromoethane has gained wide acceptance as an auxiliary reagent, in the presence of which even chloronaphthalenes are involved in the Grignard reaction.⁸ Rieke magnesium prepared by reduction of anhydrous MgBr_2 or MgCl_2 with sodium or potassium in THF is an efficient reagent.^{8,9}

The synthesis of 1- and 2-lithium-substituted naphthalenes by the reactions of metallic lithium with halonaphthalenes also gives good results, although this method is nowadays rarely used and only if the presence of another stronger base, for example, of butyllithium, in the mixture is undesirable.¹⁰

The second procedure presented in Scheme 1 (**3** → **4**) is used primarily for the synthesis of organolithium compounds. This method has gained wide acceptance due to the pioneering studies by Gilman.¹¹ Commercial lithium alkyls (*n*-, *sec*- or *tert*-butyl-

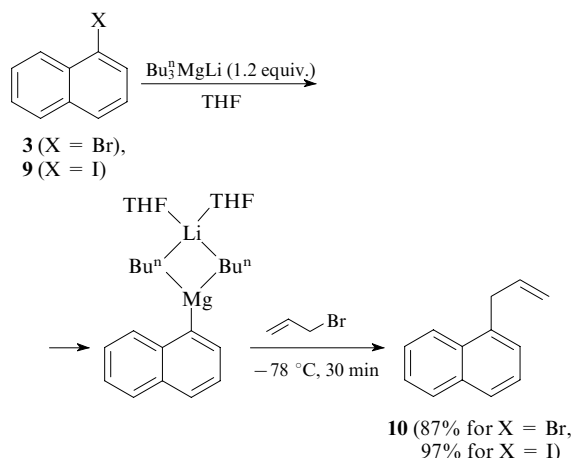
A F Pozharskii, O V Ryabtsova Department of Chemistry, Rostov State University, ul. Zorge 7, 344090 Rostov-on-Don, Russian Federation.
Fax (7-8632) 24 59 05, tel. (7-8632) 97 51 46, e-mail: APozharskii@rsu.ru (A F Pozharskii), alabrica@mail.ru (O V Ryabtsova)

Received 17 October 2005

Uspekhi Khimii 75 (8) 791–819 (2006); translated by T N Safonova

[†] Methods for magnesium activation were covered in detail in the review.⁸

lithium) are generally used as organometallic reagents. In this connection, it should be kept in mind that the synthesis of lithium-substituted naphthalenes from commercial reagents used after a long storage can be accompanied by side reactions.¹² Metal–halogen exchange reactions of aryl halides can be performed with the so-called *ate*-complexes R_3MgLi instead of lithium alkyls.¹³ In this case, the exchange of the bromine and iodine atoms occurs at 0 and -78°C , respectively. Mild conditions of the exchange reactions and their high rate allow one to perform these reactions with substrates containing functional groups active toward lithium alkyls (CN, CONR_2 , CO_2R , *etc.*). Most studies of metal–halogen exchange in aryl halides dealt with metallation of substituted phenyl halides. However, the results of the reactions with halides **3** and **9** giving rise to 1-allylnaphthalene (**10**) in high yield show that this method is also applicable to naphthyl halides.



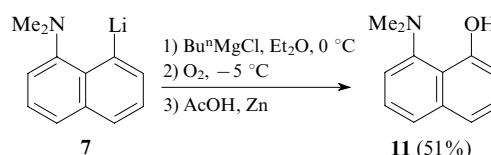
Iodine atoms are most readily involved in exchange with metals; bromine atoms are the second in activity (see, the example with compounds **3** and **9**). Attempts to perform metal–halogen exchange reactions with 1-chloronaphthalene failed.¹¹ Fluorine is virtually not replaced with metal.[‡]

Metallation based on direct ionisation of C–H bonds gives good results in two cases: (i) if the naphthalene ring contains a strong electron-withdrawing substituent, for example, the cyano group (see the synthesis of 2-naphthyllithium **6** from cyanide **5**^{14,15}) and (ii) if the ring contains the so-called directing groups, which coordinate the organometallic reagent, thus lowering the activation energy of metallation (see numerous examples in Sections II.4 and III.3–III.11). Ionisation of C–H bonds is most often performed with the use of Bu^nLi ,¹⁶ Bu^sLi ^{17,18} or Bu^iLi ¹⁶ (selected references are given). Examples of the use of MeMgI ,¹⁸ MeLi ,^{16,18} $n\text{-C}_5\text{H}_{11}\text{Li}$,¹⁹ PhLi ^{17,20} and a Bu^nLi – Bu^iOK mixture (the superbasic reagent LICKOR)^{21–24} for this purpose were documented. Lithium amides, such as lithium tetramethylpiperidide (LTMP)^{14,25–27} or lithium diisopropylamide (LDA),¹⁸ are particularly useful when the strength of the base should be combined with its low nucleophilicity as in the transformation **5** → **6** (see Scheme 1). Compounds of the naphthyloxazoline series were subjected to metallation with ethoxyvinyl lithium (EVL)²⁸ (reactions with other bases afforded addition products to the aromatic system, see Section III.11).^{22,29,30}

Unsubstituted naphthalene is subjected to metallation with difficulty and non-selectively. For example, prolonged reflux of this compound with an excess of Bu^nLi in diethyl ether afforded 1- and 2-lithium-substituted naphthalenes in a ratio of 7 : 3 in a total yield of as low as 20%.³¹ The use of the LICKOR system (as a stronger base) led to an increase in the total yield;²¹ however, after

the addition of CO_2 , the reaction products contained considerable amounts of isomeric dicarboxylic acids along with small amounts of tricarboxylic acids. The reactions in high-boiling solvents, for example, in decalin (see Section II.5), lead to the addition of organometallic reagents to the naphthalene system.

Transmetallation is widely used for the introduction of heavy metals (see examples in Section III.1). In addition, this reaction is used for the transformations of organolithium compounds into their magnesium-containing analogue (**7** → **8**, Scheme 1).^{32,33} In particular, the oxidative synthesis of naphthols (for example, of **11**)³⁴ and Kumada cross-coupling involve this reaction (see Section IV.1).



On the whole, the mechanism of formation of metal naphthalenes is analogous to that for other lithium and magnesium arenes.⁵ It should be noted that the one-electron transfer plays a considerable role in metal–halogen exchange,³⁵ and the surface factors are of importance in the synthesis of Grignard reagents.³⁶

2. Influence of solvents and coordinating additives

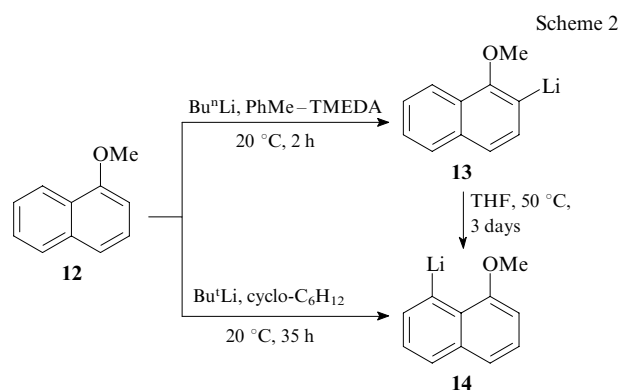
Diethyl ether, THF (more rarely, 2-methyltetrahydrofuran³⁷), anisole, toluene, hexane, tertiary amines and their mixtures generally serve as solvents in the synthesis of organomagnesium³ and -lithium^{2,4,5} compounds of the naphthalene series.⁴ The choice of the solvent is mainly determined by the ability of the metallating agents to undergo aggregation. On the whole, a decrease in aggregation leads to smaller dispersion of the negative charge in the alkyl carbanion, which increases its activity in metallation reactions. It is also important that a decrease in aggregation leads to an increase in coordinative unsaturation of the lithium ion, whose typical coordination number, like that of the magnesium ion, is four. Due to this fact, metal can interact with the adjacent groups, including C–H σ -bonds (agostic interactions),³⁰ thus decreasing the activation barrier to the reaction and resulting in its higher selectivity.

For example, Bu^nLi exists in a hydrocarbon medium as a hexamer, whereas it forms tetramers in diethyl ether and THF.^{2,5,20,25,38} A further decrease in aggregation of Bu^nLi is achieved by the addition of the following coordinating additives to the reaction mixture: diazabicyclo[2.2.2]octane (DABCO),⁴ hexamethylphosphoramide (HMPA),^{28,39,40} N,N,N',N',N'' -pentamethyldiethylenetriamine (PMDTA)²⁰ or tetramethylethylenediamine (TMEDA),^{21,41,42} TMEDA being most widely used. The latter compound promotes the transformation of *n*-butyllithium into the dimeric form.^{20,41,43,44} Attempts to transform Bu^nLi into the monomeric form failed even in THF in the presence of 1 equiv. of PMDTA.²⁰ In this connection, it is clear why, for example, metallation of 1-methoxynaphthalene occurs slowly and in low yield in hydrocarbons, whereas this reactions readily proceeds in the presence of TMEDA⁴⁰ or with the use of Et_2O and THF.^{45,46}

3. Kinetic and thermodynamic control

The direction of metallation of naphthalenes can be influenced by the temperature. For example, the reaction of Bu^nLi with 1-methoxynaphthalene (**12**) in Et_2O , THF or a PhMe –TMEDA mixture at room temperature or lower temperatures produces predominantly 1-methoxy-2-naphthyllithium (**13**) (Scheme 2).^{41,45} Heating of compound **13** leads to its isomerisation into more stable 1-methoxy-8-naphthyllithium (**14**). Calorimetric measurements demonstrated that the energy difference between the 1,2- and 1,8-isomers is 1.9 kcal mol^{-1} (Ref. 47) (this difference estimated by PM3 calculations⁴¹ is twice larger, $3.95\text{ kcal mol}^{-1}$). Presumably, the $\text{Li}\cdots\text{O}$ distance in derivative

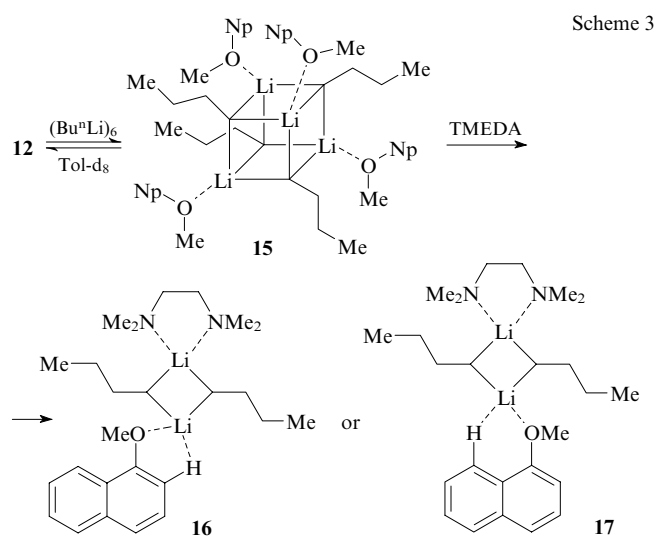
‡ Under particular conditions, chloro- and fluoronaphthalenes can react with phenyllithium and other strong bases to form dehydronaphthalenes (see Section III.14); the reactions of metallic lithium with chloro- and fluoronaphthalenes are accompanied by reductive processes giving rise to radical anions and dianions and elimination of halogen.²



14 is shorter than that in compound **13**, which provides its higher stability.

The direction of metallation of 1-methoxynaphthalene (1-MeONp) depends also on the nature of the metallating agent and the solvent. For example, the addition of BuⁿLi to 1-methoxynaphthalene in toluene-d₈ (Tol-d₈) at –65 °C (or at room temperature) does not lead to lithiation;⁴¹ instead, the reaction affords, apparently, complex **15**, in which the methoxy oxygen atom of substrate **12** is coordinated to the lithium ion (Scheme 3). This assumption is supported by downfield shifts of the protons of the MeO group ($\Delta\delta = 0.05$ ppm) and the H-2 proton of naphthalene ($\Delta\delta = 0.11$ ppm) in the ¹H NMR spectra. The addition of one equivalent of TMEDA to this complex causes reorganisation of the latter to form aggregates **16** or **17**. The latter serve as models of transition states for abstraction of the H-2 and H-8 protons, respectively. Quantum-mechanical calculations⁴¹ demonstrated that transition state **16** lies substantially lower than transition state **17**, metallation rather than complexation being the rate-determining step of the process. These conditions are referred to as the kinetic control.⁴¹

Metallation of 1-methoxynaphthalene with *tert*-butyllithium proceeds more slowly and affords exclusively 8-lithium derivative **14** (see Scheme 2). In this case, the NMR spectra did not reveal complexation. Nevertheless, it is hypothesised that the formation of *peri*-complex **17** does occur but very slowly, and this complex is present in solution at an insignificant equilibrium concentration. It is the formation of complex **17** that is the rate-determining step, whereas metallation of the C–H bond occurs rather rapidly. This assumption is evidenced by the fact that the kinetic isotope effect was not observed in the reaction of BuⁿLi with a mixture of 8-D- and 8-H-methoxynaphthalenes, whereas the isotope effect in 2-metallation of a mixture of 2-D- and 2-H-methoxynaphthalenes



Np is 1-naphthyl.

in the BuⁿLi–TMEDA system is as high as 15±3. These conditions were classified as the thermodynamic control conditions. In the reaction with 1-methoxynaphthalene, *sec*-butyllithium behaves as BuⁿLi.⁴¹

4. Influence of directing groups

As a rule, substituents in the naphthalene ring, particularly, those containing heteroatoms direct metallation to the *ortho* or *peri* position or, more commonly, simultaneously to both positions. These substituents are called directing groups. The methoxy group in compound **12** provides a classical example. Data on other directing groups are summarised in Table 1. The directing effect of the group is determined by the following two main factors: (i) the ease of coordination of this group to the organometallic reagent determining its orientation for deprotonation, and (ii) the electron-withdrawing properties of this group resulting in an increase in CH-acidity of the adjacent protons.

Only a few directing groups promote selective *peri*-lithiation. Among them are primarily dialkylamino and dialkylaminomethyl groups. This is not surprising taking into account the relatively low electronegativity of the nitrogen atom and a weak ‘acidifying’ ability of such groups (see also selective *peri*-lithiation of 1-naphthyllithium, Section II.8). To the contrary, due to a high electronegativity, substituents containing the carbonyl group (OCONR₂ or CONR₂) facilitate the replacement with metal primarily of the

Table 1. Yields of the *peri* and *ortho* isomers produced in the reactions of electrophiles with lithiated 1-R-naphthalenes.

R	Metallation conditions	Electrophile	Yield (%)		Ref.
			<i>peri</i>	<i>ortho</i>	
OH	Bu ⁿ Li, tetrahydropyran (THP), 20 °C	Me ₂ S ₂	50	19	48
OMe	Bu ⁿ Li, Et ₂ O–n-C ₆ H ₁₄ , 20 °C	CO ₂	8	20	45, 49
OMe	Bu ⁿ Li, Et ₂ O–n-C ₆ H ₁₄ –TMEDA, 20 °C	CO ₂	0.4	60	45
OMe	Bu ⁿ Li, n-C ₅ H ₁₂ –cyclo-C ₆ H ₁₂ , 20 °C	CO ₂	19.4	0.6	45
OMe	LICKOR, THF, –78 °C	D ₂ O	0	92	22
OCH ₂ OMe	LICKOR, THF, –78 °C	D ₂ O	0	95	22
(OCH ₂) ₂ CH ₂ SiMe ₃	Bu ⁿ Li, Et ₂ O, 20 °C	Me ₃ SiCl	0	87	50
OCONEt ₂	Bu ^s Li, TMEDA–THF, –78 °C	MeI	0	90	51
NH ₂	Bu ⁿ Li, Et ₂ O	CO ₂	20	0	52
NMe ₂	Bu ⁿ Li, Et ₂ O, 20 °C	DMF	76	0	34
CH ₂ NMe ₂	Bu ⁿ Li, Et ₂ O–n-C ₆ H ₁₄ , 20 °C	Ph ₂ CO	60	6	53
CH(OMe) ₂	Bu ⁿ Li, Et ₂ O, –78 to 0 °C	MeI	27	13	54
CH(NEt ₂)OLi	Bu ⁿ Li, C ₆ H ₆ , refluxing	MeI	2	33	54
CONEt ₂	Bu ^s Li, TMEDA–THF, –78 °C	Me ₃ SiCl	0	80	25
CONPr ₂	Bu ^s Li, THF, –78 °C	D ₂ O	0	93	16

ortho-protons. Changes in the reaction conditions can substantially influence the direction of metallation. For example, the reaction of BuⁿLi or Bu^tLi with 1-methoxynaphthalene in the presence of TMEDA affords predominantly the 2-Li derivative, whereas the reaction of compound **12** with Bu^tLi in a purely hydrocarbon medium (n-pentane–cyclohexane) produces a mixture of the 8-Li and 2-Li isomers in a ratio of 97:3, although the total yield of the products is at most 20% (see Table 1).

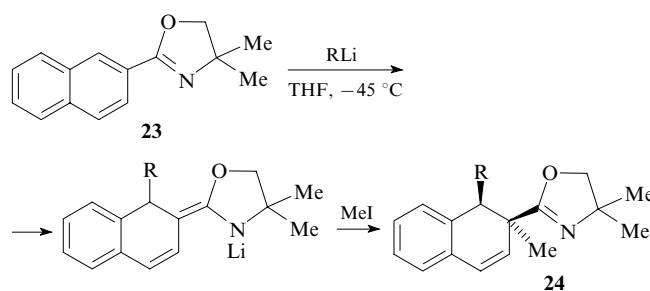
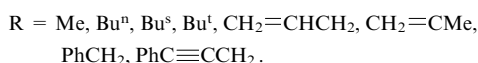
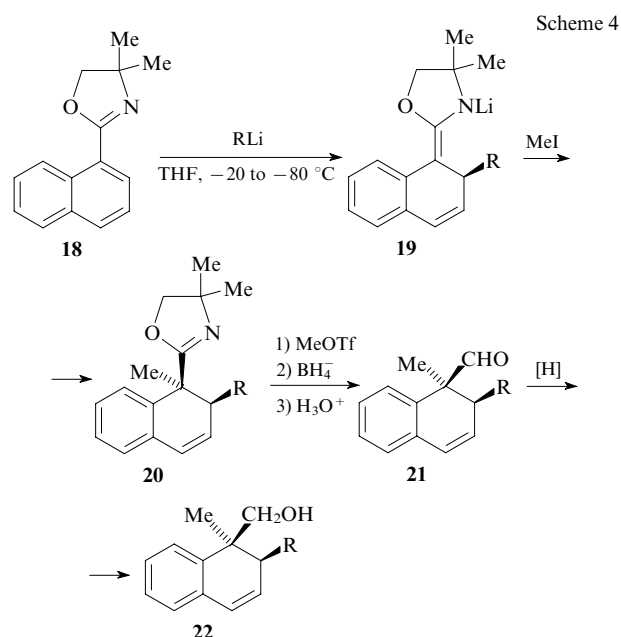
The hierarchy of the directing groups taking into account, in particular, their relative directing ability and stability to organometallic reagents was discussed in the review²⁵ for compounds of the benzene series.

5. Side reactions

The character of side reactions substantially depends on the procedure for the synthesis of organometallic compounds. For example, CH-metallation of naphthalenes containing electron-withdrawing substituents in the naphthalene moiety leads predominantly to the addition of the metallating agent to the aromatic system. Naphthyloxazolines provide a typical example.^{12,19,55} For instance, (1-naphthyl)oxazoline **18** reacts with lithium alkyls in THF at low temperature to form azaenolates **19**, which give oxazoline derivatives of 1,2-dihydronaphthalene **20** (generally, as the only diastereomer) in 60%–99% yields after the addition of iodomethane.¹² This reaction can be used for the stereospecific synthesis of optically active derivatives of hydrogenated naphthalenes, in particular, of aldehydes **21** and alcohols **22** (Scheme 4).

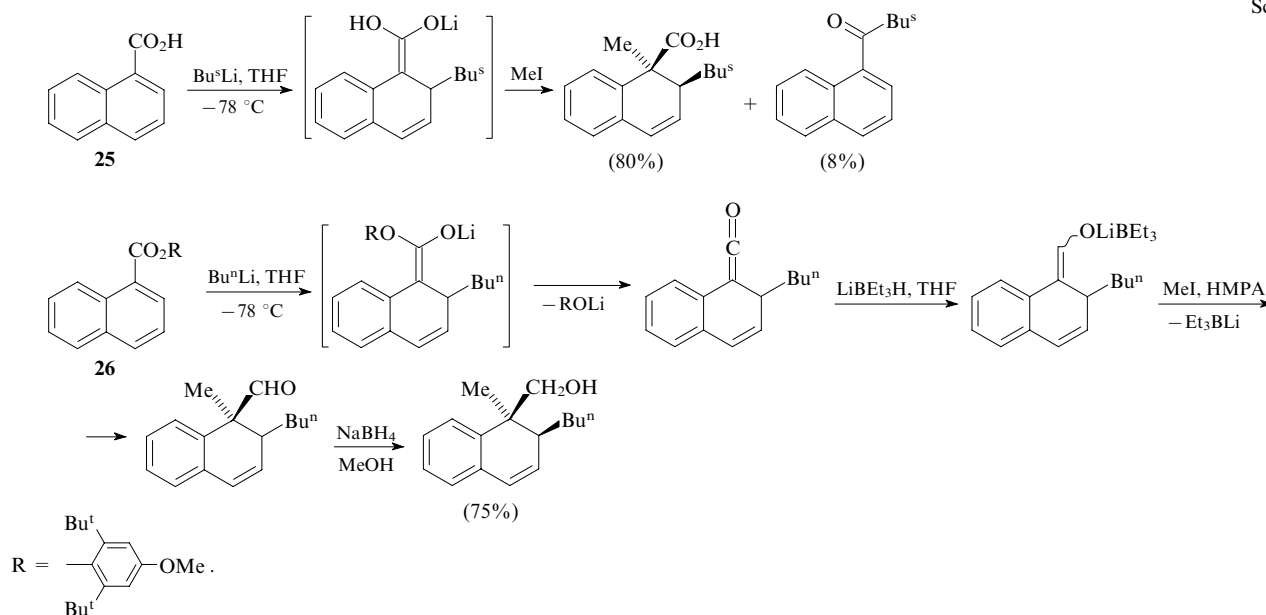
The procedure for the preparation of lithium alkyls is responsible for whether or not these transformations occur successfully. For example, the addition of commercial or long-stored RLi occurs slowly and ambiguously. The best results were obtained in the reactions with lithium alkyls prepared *in situ* by treatment of methylithium with the corresponding stannanes R₄Sn. Apparently, this is associated with the formation of the *ate*-complex R₄Sn·MeLi, in which the nucleophilicity of alkyl anions is substantially higher. In these transformations, lithium dialkylamides,^{56,57} lithiosilane (PhMe₂SiLi)⁵⁸ or vinylolithium⁵⁹ can be used instead of lithium alkyls.

(2-Naphthyl)oxazoline **23** behaves analogously to the 1-isomer, the attack of the nucleophile occurring exclusively on position 1 of the naphthalene ring. Methylation of intermediate azaenolate affords the oxazoline derivative of dihydronaphthalene **24**.^{12,55,56}

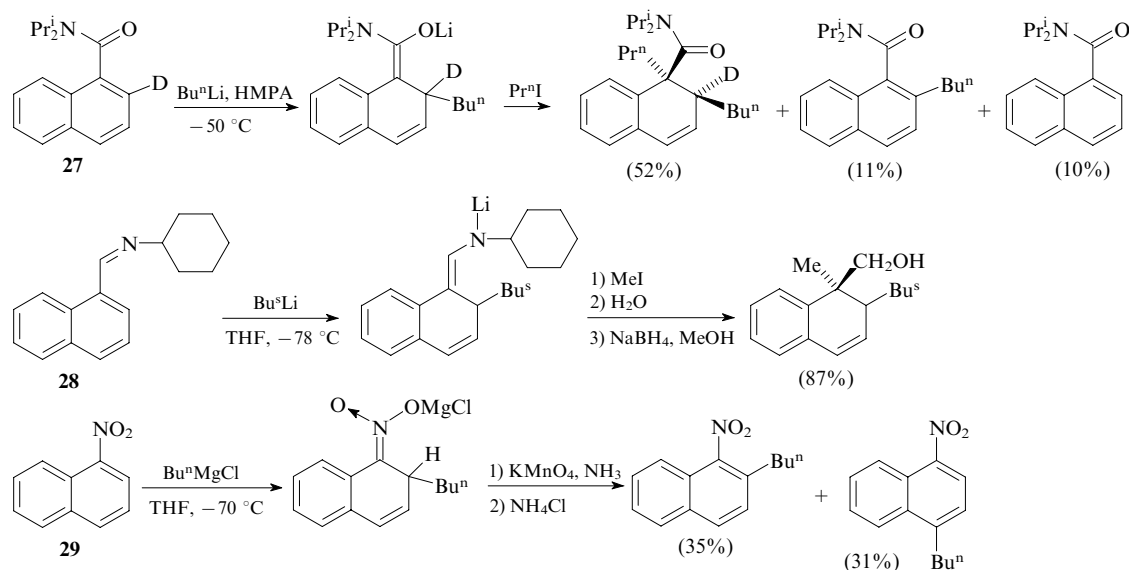


The CO₂H,⁶⁰ CO₂R,^{61–64} COR,^{61–64} CONR₂,^{12,16} CH=NR,^{65–67} NO₂,^{68–70} SO₂R⁷¹ and BR₂ groups⁷² also promote the addition of metallating agents to the naphthalene π-system. Selected examples of the addition of metallating agents to naphthalene derivatives **25**–**29** are shown in Scheme 5. In essence, the carboxamide group is the only electron-withdrawing

Scheme 5

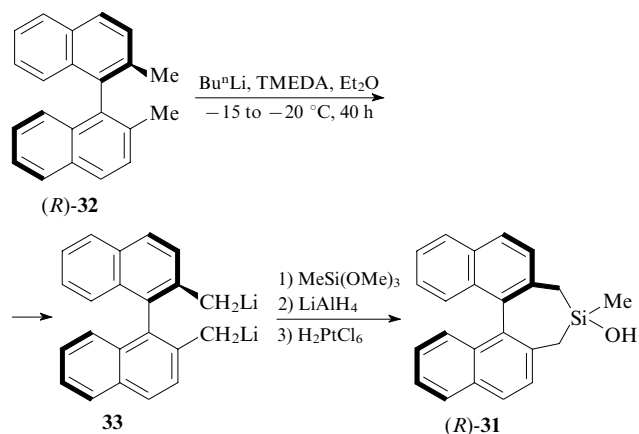


Scheme 5 (continued)

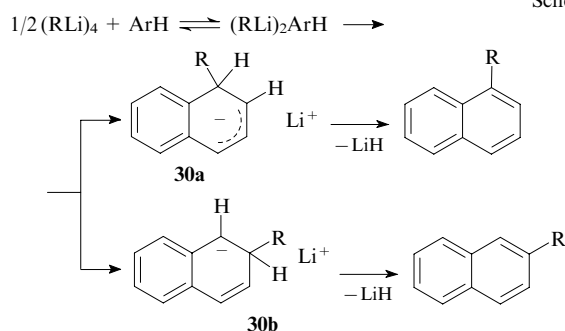


substituent providing a rather high percentage of metallation (for more details, see Section III.10).^{16, 25, 73, 74}

At high temperature, alkyllithium reagents can add to unsubstituted naphthalene.^{75–77} For example, heating of a mixture of equimolar amounts of naphthalene and Bu^nLi , Bu^sLi or Bu^iLi (decalin, 20 h) at 165 °C afforded the corresponding monoalkylnaphthalenes in 15%, 20% or 30%–45% yields, respectively, the replacement occurring predominantly (> 90%) at the α position. The reaction with Bu^iLi additionally produces di(*tert*-butyl)naphthalene (30%–50%). Kinetic measurements led to the conclusion that alkylation is preceded by the rapid formation of the $(\text{RLi})_2\text{ArH}$ complex, which is slowly transformed into adducts **30a** and **30b**. At high temperature, the latter undergo fast aromatisation accompanied by elimination of lithium hydride to form 1- and 2-alkylnaphthalenes (Scheme 6).



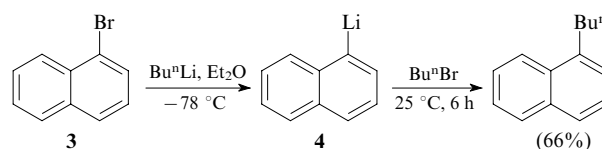
Scheme 6



Let us mention other side reactions, which will be considered below. For example, the activated MeO and Me_2N groups in naphthalene derivatives can be replaced with a metallating agent (see Sections III.8 and III.11).^{78, 79} In the presence of a halogen atom ($\text{Br}^{77, 80}$ or F^{81}) in the *ortho* position with respect to the metal atom, the corresponding aryne can be formed (see Section III.14). In addition, when preparing organometallic compounds, it should be remembered that these compounds can undergo protolysis under the action of the solvent or the reagent (for example, of acetone⁸²).

Metallation of alkylnaphthalenes can give also benzyl-type anions, many of which are of interest on their own. For example, organosilicon compound **31** was prepared from 2,2'-dimethyl-1,1'-binaphthyl (**32**) through the intermediate formation of dilithium derivative **33**.^{25, 83–85}

In the synthesis of lithium-substituted naphthalenes by metal–halogen exchange, the products can undergo alkylation with the resulting alkyl halide.^{86–88} For example, 1-naphthyllithium (**4**), which was prepared by treatment of 1-bromonaphthalene with butyllithium at low temperature, is transformed at room temperature into 1-butynaphthalene in good yield.⁸⁷



The Schlenk equilibrium is characteristic of the Grignard reagents:³

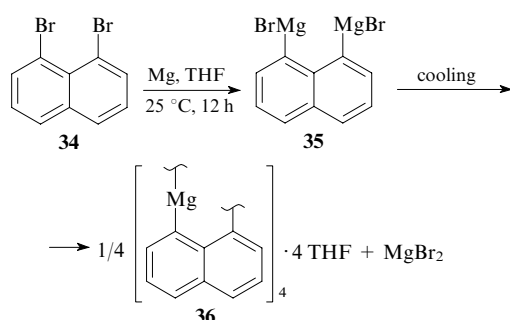


For example, the reaction of 1,8-dibromonaphthalene (**34**) with magnesium in THF produces 1,8-di(bromomagnesio)naphthalene (**35**), which is transformed into tetramer **36** upon cooling of the solution. The structure of the latter compound was established by ^1H and ^{13}C NMR spectroscopy and X-ray diffraction.³⁷ The reaction of compound **35** with D_2O produces 1,8- D_2 -naphthalene in a quantitative yield, and the reaction of this compound with an excess of Me_3SnCl gives mono- and 1,8-bis(trimethylstannyl)naphthalenes.^{37, 89}

Table 2. Selected geometric parameters of lithium-substituted naphthalenes and comparison with lithium-substituted benzenes (X-ray diffraction data).

Compound	Substituents in the aromatic moiety	Ligand	CSD refcode	Bond lengths and distances /Å		Angle /deg		Ref.
				<i>d</i> (see ^a)	δ (see ^b)	Li—C—Li	α (see ^c)	
4	1-Li	TMEDA	HIGQUJ	2.206; 2.246	0.578; 1.845	71	83	
7	8-Li, 1-NMe ₂	THF	QOYZOT	2.207; 2.223	0.373; 1.052	64	39	91
7	8-Li, 1-NMe ₂	Et ₂ O	—	2.224; 2.232	—	—	—	92
12	8-Li, 1-OMe	THF	QESQUA	2.162; 2.231	0.284; 1.689	66	63	28
37	2-Li, 1-CONPr ₂ ⁱ	THF	QOGBET	2.162; 2.389	0.032; 1.870	70	54	93
38	—	—	GIBTOA	2.216; 2.247	0.249; 0.527	74	15	94
39b	—	—	PUDLUV	2.322; 2.242	1.022; 1.366	63	90	95
40	2-CONPr ₂ ⁱ	Et ₂ O	QOGBAP	2.176; 2.303	0.371; 1.604	67	57	93

^a *d* Are the C—Li bond lengths; ^b δ is the deviation of the lithium atom from the plane of the aromatic ring; ^c α is the angle between the plane of C₂Li₂ and the plane of the naphthalene (or benzene) ring.



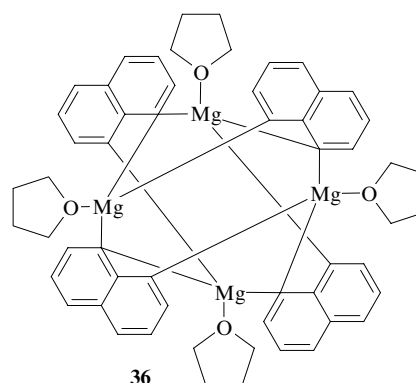
Gilman and Brannen⁹⁰ found that treatment of 1-naphthyl-lithium or 1-naphthylmagnesium bromide with various electrophiles, for example, with SiCl₄ or CO₂, often affords 1,1'-binaphthyl and perylene as by-products in low yields (< 3%). Presumably, naphthalene–naphthalene coupling occurs according to the free-radical mechanism and is associated with one-electron oxidation of metal naphthalenes.

There are many other specific side transformations, which depend on the nature of the substrate, the metallating agent and the reaction conditions. These transformations are considered below as needed.

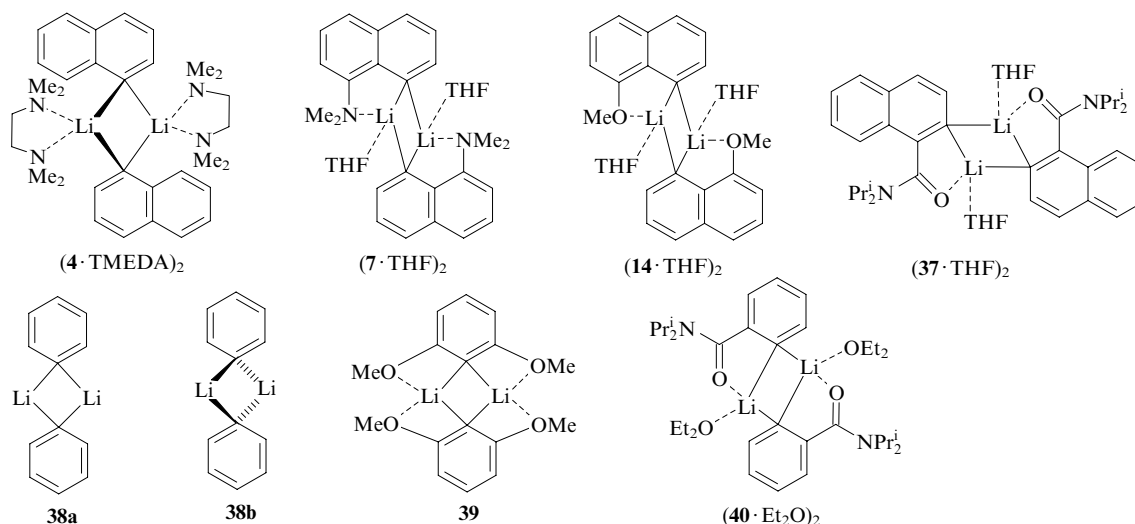
6. Crystal structures of organometallic compounds

The Cambridge Structural Database (CSD, February 2005 release) contains data on one organomagnesium derivative of naphthalene **36** (PEFXIH) and four lithium-naphthalenes

(Table 2, Fig. 1). Compound **36** is a tetranuclear cluster with the symmetry *S*₄. The magnesium atoms form a distorted tetrahedron.



Each naphthalene fragment is located above one of the tetrahedron faces and is bound to three Mg atoms by two *peri*-carbon atoms. One carbon atom forms a σ -bond with the Mg atom, and another carbon atom forms a three-centre two-electron bond with two other Mg atoms. Each Mg atom is additionally coordinated by one THF molecule (standard Grignard reagents are coordinated by two solvent molecules). The crystals are stabilised by a large number of disordered solvent molecules. In the absence of the latter (for example, upon evacuation), crystals are destroyed.

**Figure 1.** Schematic representation of dimeric lithium-substituted naphthalenes and benzenes.

In crystals, all lithium-substituted naphthalenes have a dimeric structure (see Fig. 1). Dimerisation occurs due to coordination of the Li atoms by two *ipso*-carbon atoms, resulting in the formation of the rhomboid quasi-ring C_2Li_2 . Both solvent molecules (THF, Et_2O or TMEDA) and the chelating groups present in the ring [NMe_2 (**7**), MeO (**14**) or $CONR_2$ (**37**)] can serve as two other ligands for Li. In the dimer $(4 \cdot TMEDA)_2$, whose naphthalene ring contains no chelating groups, the α angle is nearly equal to 90 degrees (83°). Intramolecular chelation leads to a substantial decrease in this angle (see the data for dimers **7**, **14** and **37**, Table 2) and a decrease in the deviation of the Li atoms from the plane of the aromatic rings. In each dimer, the naphthalene fragments are virtually coplanar. In all lithium-substituted naphthalenes, the C—Li bond length varies only slightly (2.2–2.3 Å). These tendencies are typical also of phenyllithium (**38**) and its derivatives **39** and **40**. However, it should be noted that calculations (MNDO)⁹⁶ performed for the nonsolvated dimer $(PhLi)_2$ in the gas phase demonstrated that ‘planar’ structure **38a** is more favourable than ‘perpendicular’ structure **38b**.⁹⁷

7. NMR spectra

One-dimensional ^1H , ^{13}C and ^6Li NMR spectra and two-dimensional ^1H - ^1H (COSY), ^{13}C - ^1H and ^6Li - ^1H (HOESY) spectra were measured for a number of lithium-substituted naphthalenes.^{20,41,98} All signals were unambiguously assigned based on the analysis of cross-peaks. As can be seen from Table 3, in the ^1H NMR spectra of complex **4**·TMEDA, the H-2 (8.57 ppm) and H-8 (8.47 ppm) protons are the most deshielded because of their close proximity to the electropositive substituent (the lithium atom). This tendency persists in the ^1H NMR spectra of 1-methoxy-2-naphthyllithium (**13**) and 1-methoxy-8-naphthyllithium (**14**), in which the H-3 (in **13**) and H-2 (in **14**) protons are the most deshielded. Analogous conclusions can be drawn based on ^{13}C NMR spectra (Table 4), the metallated carbon atom resonating at the lowest field. The ^1H and ^{13}C NMR spectroscopic data were used for the determination of the degree of aggregation of lithium-substituted naphthalenes in solution and for the elucidation of the mechanism of lithiation. For example, the ^{13}C NMR spectrum of 1-methoxy-8-naphthyllithium (**14**) in THF- d_8 at $-100^\circ C$ shows a signal for C-8 as a septet with the spin–spin coupling constant $^1J(^{13}C, ^7Li) = 19.3$ Hz. Taking into account the nuclear spin of the ^7Li isotope ($I = 3/2$), this is evidence that the dimeric structure $(14 \cdot THF)_2$ observed in the crystals is retained in solution.

Table 3. ^1H NMR spectra of selected lithium-substituted naphthalenes.

Compound	Solvent	T / $^{\circ}\text{C}$	δ (multiplicity of the signal, J /Hz)							Ref.
			H-2	H-3	H-4	H-5	H-6	H-7	H-8	
4 ·TMEDA	C ₆ D ₆	22	8.57 (d, 5.8)	7.56 (dd, 8.0; 5.8)	7.81 (d, 8.0)	7.93 (d, 8.0)	7.47 (ddd, 8.0; 6.8; 1.2)	7.57 (ddd, 8.0; 6.8; 1.2)	8.47 (d, 8.0)	98
13	THF-d ₈	32	4.05 (s)	8.12 (d, 7.3)	7.39 (d, 7.3)	7.73 (d, 8.0)	7.24 (dd, 7.3; 8.5)	7.33 (dd, 8.2; 8.5)	8.08 (dd, 8.2)	41
14	THF-d ₈	32	8.15 (d, 5.8)	7.18 (dd, —)	7.35 (d, 7.7)	7.27 (d, 8.1)	7.12 (dd, —)	6.68 (d, 7.6)	3.85 (s)	41

Table 4. ^{13}C NMR spectra of selected lithium-substituted naphthalenes.

Compound	Solvent	T / $^\circ C$	δ											Ref.
			C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	OMe	
4 ·TMEDA	C_6D_6	24	195.0	140.4	124.4	124.2	129.2	123.8	122.7	138.3	148.7	133.8	—	98
13	THF- d_8	32	163.0	163.0	141.0	119.3	126.3	121.6	122.3	120.1	124.0	133.7	58.1	41
14	THF- d_8	32	185.2	139.1	125.1	122.9	128.8	123.2	101.4	161.0	139.6	139.4	55.2	41

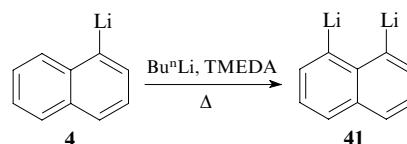
The NMR method was successfully used for the explanation of the direction of metallation of 1-methoxynaphthalene (**12**) and 1-naphthyllithium (**4**) giving rise to naphthylene-1,8-dilithium. The ^1H NMR spectrum of the complex **4**·MeLi is indicative of a stronger deshielding of the H-8 proton compared to H-2 (unlike the free 1-naphthyllithium molecule).⁹⁸

8. Quantum-mechanical calculations

Almost all quantum-mechanical calculations for Li and Mg derivatives of naphthalene were performed with the aim of explaining the regioselectivity of lithiation of naphthalenes.^{29,30,98–101} The optimal structures and the energies of isomeric lithium-substituted naphthalenes, primary substrate–metallating agent complexes and the corresponding transition states were calculated. Calculations were performed predominantly with the use of the semiempirical MNDO method.

Schleyer and co-workers⁹⁸ came up with one of the most fruitful ideas. They postulated the existence of agostic interactions between the coordinatively unsaturated lithium atom and σ electrons of the adjacent C—H bonds in the transition state of lithiation.³⁰ These interactions should lead to an elongation of the C—H bond and an increase in the positive charge on the hydrogen atom that is replaced. These parameters can easily be calculated and serve as an indication of the direction of metallation.

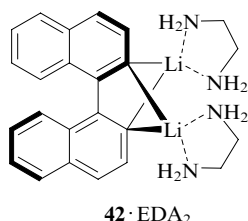
Let us consider lithiation of 1-naphthyllithium (**4**) giving rise exclusively to naphthylene-1,8-dilithium (**41**) as an example.⁹⁸



An analysis of the optimised structure of the complex $(4 \cdot EDA)_2$ (EDA is ethylenediamine) did not explain the pathway of this reaction and even, on the contrary, provided evidence that 2-metallation is preferable. Quantum-chemical calculations combined with experimental observations were used to resolve these contradictions. It was found that the addition of Bu^nLi to the dimer $(4 \cdot TMEDA)_2$ is accompanied by heat evolution but does not lead to the immediate formation of dilithium derivative **41**. For this purpose, it is necessary to perform subsequent prolonged heating of the reaction mixture. This suggests that repeated lithiation occurs inside the complex between 1-naphthyllithium

and the metallating agent (the role of such complexes in metallation reactions was discussed in the review¹⁰²). The structure of the complex with MeLi optimised by the MNDO method actually confirmed that the C-8—H-8 bond in this compound is activated toward metallation to a greater extent than the C-2—H-2 bond.

These calculations demonstrated that lithiation of 1-naphthol occurs predominantly at position 8; of 2-naphthol, predominantly at position 3; of 1,3-, 1,4- and 1,5-binaphthols and 1,4,5-trinaphthol, exclusively at the *peri* position adjacent to the OH group (for the reaction conditions, see Section III.3).^{29, 30} As mentioned above, 1-methoxynaphthalene (**12**) is lithiated predominantly at the C-2 atom under kinetically controlled conditions, whereas lithiation occurs at the C-8 atom under the thermodynamically controlled conditions. In the former case, this is due to the fact that the transition state corresponding to metallation at the C-2 atom is energetically more favourable (by ~ 6 kcal mol⁻¹). The latter case is attributed to higher stability of the 8-lithium derivative (by ~ 4 kcal mol⁻¹).⁴¹ The energies of the 2- and 8-lithium derivatives of 1-aminonaphthalene were estimated by the *ab initio* method.¹⁰¹ The relative stabilities of the structures of **42**·EDA₂ with the perpendicular and parallel orientation of the naphthalene moieties and the rotation barrier about the C-1—C-1' bond were evaluated by the MNDO method.^{99, 100}



III. Synthesis and reactions of naphthylmetals

Organomagnesium compounds of the naphthalene series have found use immediately after the historical discovery by Grignard. As early as 1903, Gattermann¹⁰³ synthesised 1-naphthaldehyde by the reaction of ethyl formate with α -naphthylmagnesium bromide. Beginning in 1930s, lithium-substituted naphthalenes came into use along with Grignard reagents. In the present review, a vast literature on these compounds is systematised according to the type of additional substituents in the ring. As a rule, these substituents have a strong effect not only on the synthesis of organometallic derivatives but also on their reactivity. All reactions of magnesium- and lithium-substituted naphthalenes can, in essence, be classified into four main types: (1) reactions with C-electrophiles, (2) reactions with heteroelectrophiles, (3) oxida-

tion reactions and (4) cross-coupling reactions. Since the latter reactions are of particular importance, they are considered in the special section (Section IV). As for the difference in the reactivity, there are no general rules, which allow one to decide whether lithium or magnesium naphthalenes are reagents of choice. In many cases, both these types of naphthylmetals give comparable results. However, there are also many examples when the reactions better proceed with either magnesium or lithium derivatives.

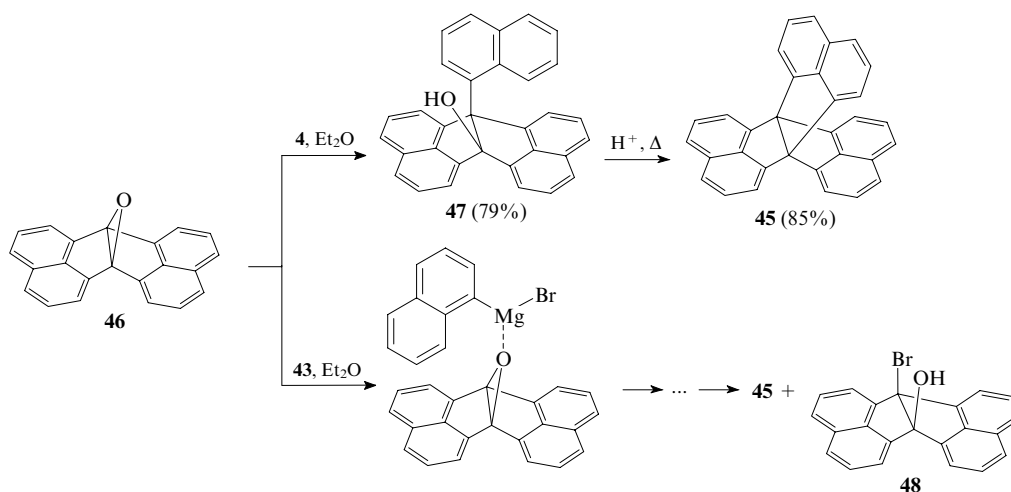
1. Naphthylmetals based on naphthalene and alkylnaphthalenes

General features of the procedures for the synthesis of Li and Mg derivatives of naphthalene were considered in Section II.1. The reactions of these derivatives with various alkylating and carbonyl-containing reagents are the most abundant. For example, the reaction of 8-methyl-1-naphthyllithium with dimethyl sulfate produces 1,8-dimethylnaphthalene in 90% yield.¹⁰⁴ Analogously, 1-naphthylmagnesium bromide (**43**) is smoothly alkylated with dialkyl sulfates and S_N1-active reagents to form compounds **44a–f**.

RX	Product 44	R	Yield (%)	Ref.
Me ₂ SO ₄	a	Me	68	105
Et ₂ SO ₄	b	Et	60	105
CH ₂ =C(Me)CH ₂ Cl	c	CH ₂ =C(Me)CH ₂	85	105
1-NpCH ₂ Br	d	1-NpCH ₂	—	106
1-FcCH ₂ N ⁺ Me ₂ EtBr ⁻	e	1-FcCH ₂	51	107
1-AdBr	f	1-Ad	2	108

The reaction of 2-methyl-1-naphthyllithium with ethylene oxide produces 1-(2-hydroxyethyl)-2-methylnaphthalene (67%).¹⁰⁹ Trisnaphtho[3.3.3]propellane (**45**) was synthesised by the reaction of 1-naphthyllithium (**4**) with epoxide **46** (Scheme 7).¹¹⁰ This reaction proceeds through the intermediate formation of alcohol **47**. The reaction with 1-naphthylmagnesium bromide (**43**) instead of the Li derivative affords a mixture of products **45** and **48** in a ratio of 1 : 1.8.

The reactions of CO₂ with 1-MgBr-, 2-MgBr- or 1,5-(MgBr)₂-containing naphthalenes produce the corresponding naphthalene-carboxylic or -dicarboxylic acids in good yields.¹¹¹ The reactions with lithium-substituted naphthalenes instead of Mg derivatives give comparable results.^{11, 112}

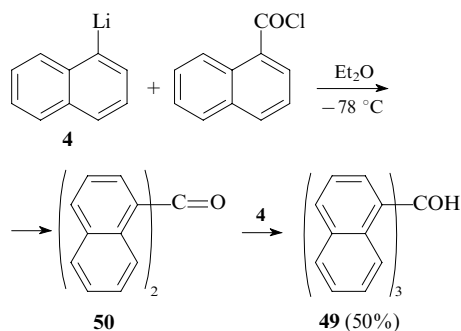


Scheme 7

Considerable study was given to formylation of magnesium- and lithium-substituted naphthalenes (data were briefly summarised in the review¹¹³). 2-(*N*-Methyl-*N*-formyl)pyridine,¹¹⁴ *N*-methylformanilide,^{46, 115} *N*-formylpiperidine,¹¹⁶ *N*-formylmorpholine¹¹⁷ and DMF^{118–120} are generally employed as formylating agents. As a rule, the reactions proceed rapidly and under mild conditions. However, in the reactions performed with a deficiency of a formylating agent, the resulting aldehyde can react with the starting organometallic compound to give the corresponding dinaphthylmethanol. The latter fact was used in the synthesis of 1,1'- and 2,2'-dinaphthylmethanols by treatment of 1- and 2-naphthylmagnesium bromides with 0.4–1.0 equiv. of ethyl formate.^{106, 121, 122}

Secondary and tertiary alcohols were synthesised by the reactions of 1-naphthylmagnesium bromides with propionic aldehyde,¹⁰⁵ aromatic aldehydes,¹²³ acetone, diethyl ketone, ethyl methyl ketone, di(1,1'-naphthyl) ketone¹²⁴ and acenaphthenequinone.¹²⁵ Analogous reactions were documented also for 2-naphthylmagnesium bromide¹²⁶ and lithium-substituted naphthalenes.¹²³

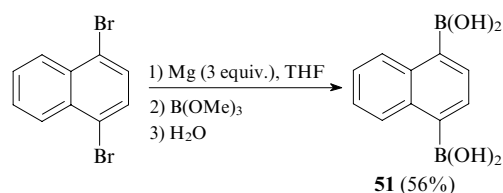
Tris(1-naphthyl)methanol (**49**) was prepared by the slow addition of 1-naphthoyl chloride to an ethereal solution of 1-naphthyllithium (**4**) at -78°C .¹⁰



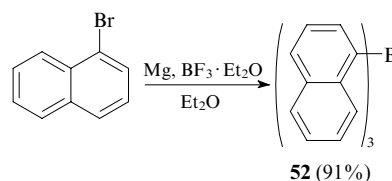
Tris(2-naphthyl)methanol was synthesised analogously from 2-naphthyllithium and 2-naphthoyl chloride in 56% yield.¹⁰ Evidently, both reactions proceed through the intermediate formation of binaphthyl ketone (for example, **50**), which rapidly reacts with the starting naphthyllithium. This hinders the use of this method for the synthesis of ketones of the naphthalene series. Earlier, Blicke¹²¹ has synthesised ketone **50** (in 40% yield) by the reaction of 1-naphthoyl chloride with 1-naphthylmagnesium bromide.⁸ However, in Blicke's opinion, a procedure of choice for the synthesis of ketones is based on the reactions of organometallic compounds with an appropriate nitrile. For example, the reaction of 1-naphthylmagnesium bromide with 1-naphthonitrile produces ketone **50** in 75% yield.

The synthesis of naphthonitriles by electrophilic cyanation of lithium-substituted naphthalenes with 1-cyanobenzotriazole was documented.¹²⁷

In recent years, the reactions of lithium and magnesium naphthalenes with heteroorganic compounds as electrophiles have acquired great importance. In particular, of special interest (due to the wide use of cross-coupling reactions) are naphthylboronic acids and trialkynaphthyl stannanes, which can be prepared by the reactions with lithium or magnesium naphthalenes. For example, 1- and 2-naphthylboronic acids are generated in good yields in the reactions of triisopropyl borate with 1- and 2-lithium-substituted naphthalenes, respectively.¹²⁸ Organomagnesium compounds can also be used, for example, in the synthesis of naphthalene-1,4- (**51**)¹²⁹ and naphthalene-1,5-diboronic acids¹³⁰ from the corresponding dibromonaphthalenes.



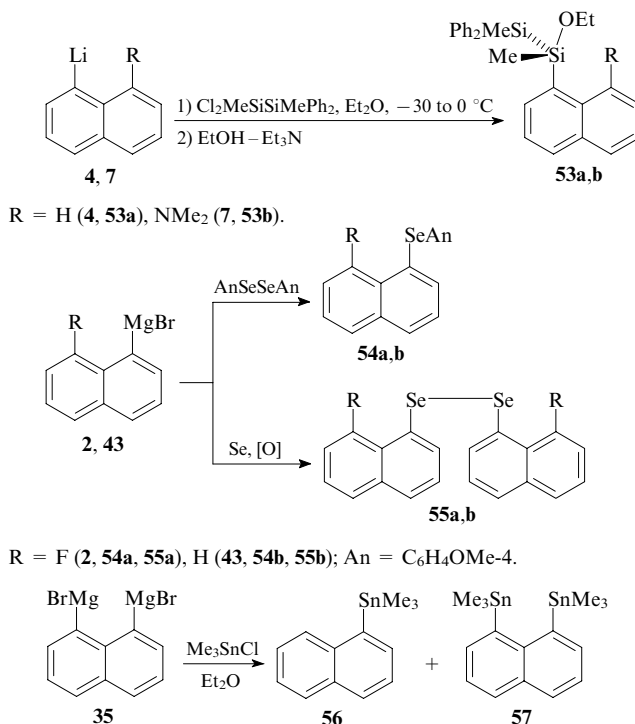
A convenient procedure was developed for the synthesis of tris(1-naphthyl)borane (**52**) by stirring a mixture of α -naphthyl bromide, magnesium and boron trifluoride etherate,¹³¹ which does not require the special preparation of α -C₁₀H₇MgBr. The reaction is completed within 24 h. The ultrasonic treatment of the reaction mixture leads to a decrease in the reaction time to 30 min.¹³¹



Noyori and co-workers¹³² used the Grignard reagent, which was prepared from 2,2'-dibromo-1,1'-binaphthyl, for the synthesis of the well-known BINAP ligand and its analogues (see Section III.15, Scheme 16).

Silylation,^{133, 134} selenenylation,^{7, 135, 136} stannylation^{37, 137} and chloromercuration¹³⁸ of lithio- and magnesionaphthalenes (Scheme 8) were documented. For example, the reaction of 1,1-dichloro-1,2-dimethyl-2,2-diphenyldisilane with 1-naphthyllithium derivatives **4** and **7** under an inert atmosphere followed by the treatment of the mixture with ethanol afforded naphthyl-ethoxydisilanes **53a,b**, from which stable naphthylsilylenes were generated.¹³³ The reactions of naphthylmagnesium bromides **2** and **43** with di(*p*-anisyl) diselenide produce 1-(*p*-anisyl)selenyl-naphthalenes **54a,b**.⁷ The reactions with a selenium powder and oxidising agents afford dinaphthyl diselenides **55**.^{7, 135} The reaction of 1,8-di(bromomagnesium)naphthalene (**35**) with an excess of trimethylchlorostannane produce a mixture of mono- (**56**) and

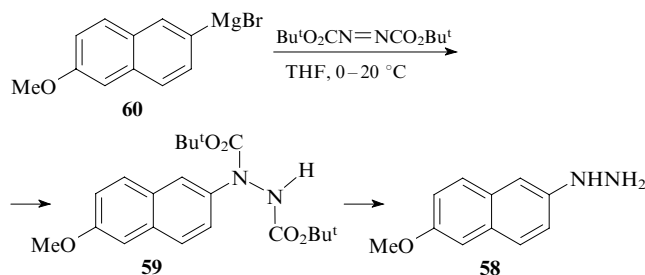
Scheme 8



§ Blicke failed to reproduce the earlier procedure proposed by Schmidlin and Massini¹⁰⁶ due, presumably, to the presence of an intolerable impurity of unconsumed magnesium.

1,8-bis(trimethylstannyl)naphthalenes (**57**) in 67% and 22% yields, respectively.³⁷

There is evidence for the possibility of electrophilic amination¹³⁹ and hydrazination¹⁴⁰ of lithium and magnesium naphthalenes. For example, 2-hydrazino-6-methoxynaphthalene (**58**) and its precursor **59** were prepared by the reaction of Grignard reagent **60** with di-*tert*-butyl azodicarboxylate.



Undoubtedly, naphthalene-1,8-dilithium (**41**) is the most important reagent. This compound is regularly used in the synthesis of various 1,8-disubstituted naphthalenes and *peri*-fused heterosystems. This compound was synthesised for the first time by Letsinger^{141, 142} in 1962 by the reaction of butyllithium with

1,8-dibromonaphthalene (**34**) in diethyl ether at room temperature. Katz^{143, 144} recommended to perform the synthesis of naphthalene-1,8-dilithium with the available reagent diiodonaphthalene. Metallation of 1-bromonaphthalene or unsubstituted naphthalene with an excess of butyllithium is also a convenient procedure for the synthesis of compound **41**.^{98, 145–147}

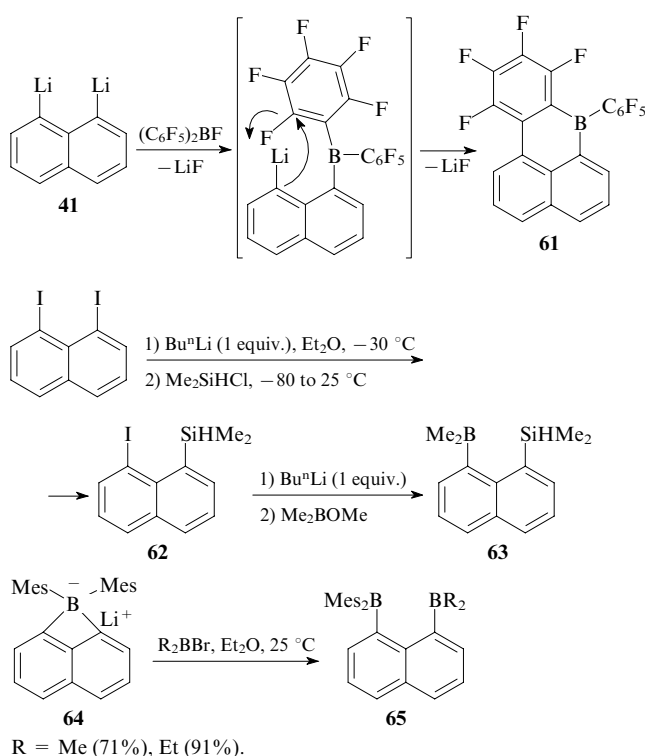
Main types of compounds prepared by the reactions of various electrophiles with naphthalene-1,8-dilithium are listed in Table 5. As can be seen from this table, all structures are symmetrical and are either 1,8-disubstituted naphthalenes or *peri*-cyclic systems. Asymmetrical compounds of this series can be synthesised by the stepwise replacement of the Li atoms in compound **41** (synthesis of unsymmetrical *peri*-cyclic compound **61**, Scheme 9),¹⁶³ stepwise lithiation–replacement of 1,8-dihalo-naphthalenes (synthesis of compounds **62** and **63**)¹⁶⁴ or cleavage of the anionic borate ring in *peri*-fused system **64** with dialkylboryl bromides. The last original approach to the synthesis of unsymmetrical 1,8-diborylnaphthalenes **65** was developed by Gabbaï and Hoefelmeyer.¹⁵⁶

Four-membered *peri*-metallacycles can be synthesised with the use of both naphthalene-1,8-dilithium and its magnesium analogue **35**. This approach was applied in the synthesis of the (1,8-Np)ML_n complexes (see Table 5).¹⁶² In this connection, it should be noted that 1,8-bis(trimethylstannyl)naphthalene (**57**) is

Table 5. Types of naphthalene derivatives prepared by the reactions of various electrophiles with naphthyl-1,8-dilithium (**41**).

Compound	Electrophile	Yield (%)	Ref.	Compound	Electrophile	Yield (%)	Ref.
					Pr ⁱ ₂ NBCl ₂	89	157
X = CPh ₂ OH	Ph ₂ CO	58	141		Pr ⁱ ₂ NPCl ₂	75	158
C(C ₆ H ₄ OMe-4) ₂ OH	(4-MeOC ₆ H ₄) ₂ CO	43	148				
C(C ₆ H ₄ Cl-4) ₂ OH	(4-ClC ₆ H ₄) ₂ CO	—	149	X = S	S ₈	35–40	159
HgCl	HgCl ₂	89	150	Se	Se	18–20	159
SiMe ₃	Me ₃ SiCl	83	89	Te	Te	8–12	159
SnMe ₃	Me ₃ SnCl	70	89	PPh	PhPCl ₂	59	158
BMe ₂	Me ₂ BOEt	47	143, 144		CH ₂ Cl ₂	18–21	160
BPh ₂	Ph ₂ BBr	—	150		R ₂ SiCl ₂ (R = CH ₂ SiMe ₃ , Bu ^s)	44–70	161
B(NR ₂) ₂ (R = Me, Et, Pr ⁱ)	(R ₂ N) ₂ BBr (R = Me, Et, Pr ⁱ)	—	151	R = CH ₂ SiMe ₃ , Bu ^s			
PPh ₂	Ph ₂ PCl	—	152		L _n MCl ₂	—	162
P(NMe ₂) ₂	(Me ₂ N) ₂ PCl	44	153	L _n M = Cp ₂ Ti, (Et ₃ P) ₂ Pt, (C ₅ Me ₅)(Ph ₃ P)Ir, (C ₅ Me ₅) ₂ Zr			
P(NEt ₂) ₂	(Et ₂ N) ₂ PCl	60	154				
	CO ₂	85	141, 145				
		14	155				
	B(OBu ^t) ₃	71	141				
	B(OBu ^t) ₃	60	142				
	Mes ₂ BF	39	156				
Li ⁺ (THF) ₄							

Scheme 9

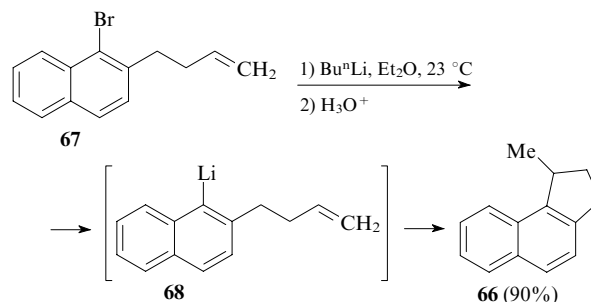


more easily produced from naphthalene-1,8-dilithium (**41**)⁸⁹ than from 1,8-di(bromomagnesio)naphthalene (**35**),³⁷ whereas the yield of 1*H*-cyclobuta[*de*]naphthalene increases to 30% (*cf.* 18%–21%, Table 5) in the reaction starting from 1,8-di(iodo-magnesio)naphthalene with the use of methylene ditoluenesulfonate as the electrophile.¹⁶⁰ Additional data on the use of naphthalene-1,8-dilithium in the synthesis of heteroorganic *peri*-disubstituted naphthalenes were reported in the review.¹⁶⁵

2. Naphthylmetals containing alkenyl and alkynyl groups

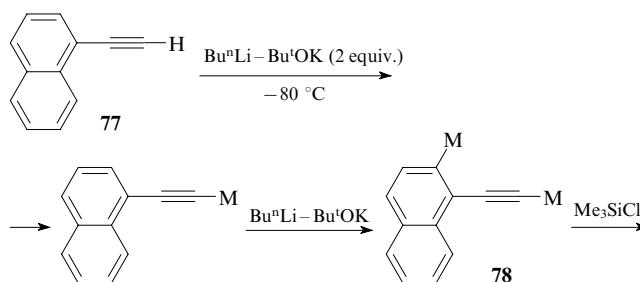
Lithium and magnesium derivatives of naphthalene containing alkenyl or alkynyl substituents in the naphthalene ring are scarce. The intramolecular addition of the carbanionic centre to a multiple bond is very typical of compounds containing an

unsaturated group adjacent to the Li atom. The formation of benz[e]indane **66** in high yield from bromide **67** is a typical example.¹⁶⁶ The intramolecular addition in intermediate **68** occurs according to Markovnikov's rule.

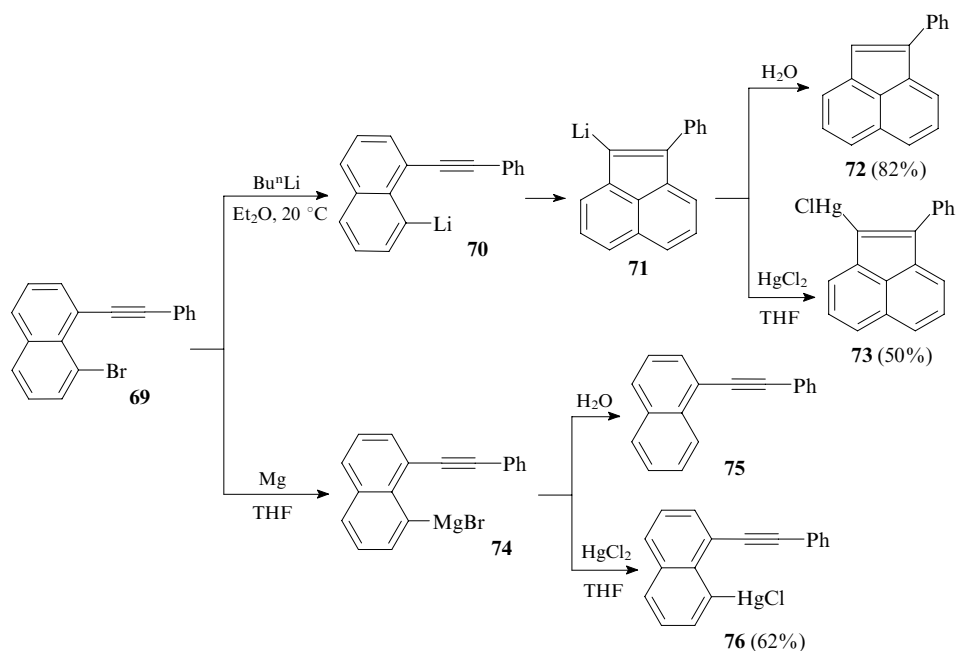


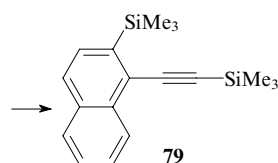
The reaction of butyllithium with 1-bromo-8-phenylethynyl-naphthalene (**69**) produced 8-lithio-derivative **70**, which was isomerised to give lithium acenaphthylene **71** (Scheme 10). This reaction can be applied in the synthesis of various acenaphthylene derivatives, for example, of compounds **72** and **73**. Magnesium analogue **74** does not undergo the above isomerisation and gives compounds of the naphthalene series, for example, derivatives **75** and **76**, under the actions of electrophiles (see Scheme 10).¹⁶⁷

Direct CH-metallation of ethynylnaphthalenes was studied along with metal–halogen exchange. Metallation of unsubstituted 1-naphthylacetylene (**77**) with 2 equiv. of LICKOR in a THF–hexane mixture (1:1) occurs exclusively at position 2 (compound **78**), as evidenced by the formation of bis(trimethylsilyl) derivative **79** in high yield after the addition of Me_3SiCl to the reaction mixture.²³



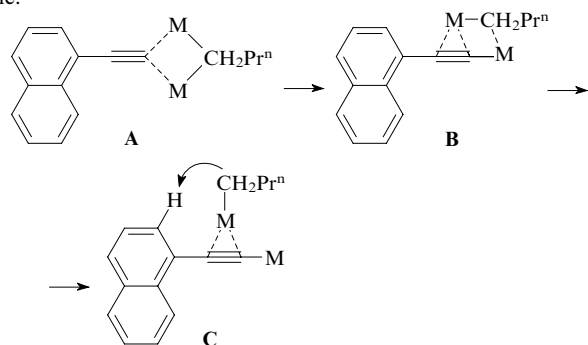
Scheme 10





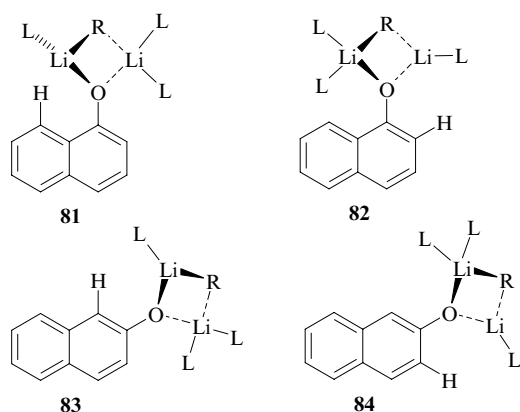
M = Li, K.

Under analogous conditions, 1-(3,3-dimethylbut-1-yn-1-yl)naphthalene (**80**) gives a mixture of metallation products, among which the 3-M derivative prevails (51%). Other isomers are distributed as follows: 4- and 5-M-substituted derivatives (in a total yield of 35%), 6- and 7-M-substituted derivatives (13%) and 2-metal derivative (1%). Interestingly, *peri*-lithiation products are absent in both cases, which is surprising in the light of the data on CH-metallation of other 1-R-naphthalenes.²³ The factors responsible for the difference in the behaviour of acetylenes **77** and **80** (as well as their benzene analogues) were studied in detail, including by theoretical methods. The *ortho*-directing effect of the metallated acetylenic group in the further metallation reaction was attributed to 'gliding' of the metallating agent along the triple bond toward the H-2 atom (A → B → C). It is assumed that the analogous motion toward the H-8 atom is sterically less favourable.

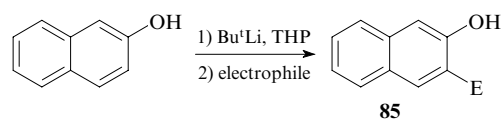


3. Naphthylmetals based on naphthols

Lithiation of naphthols with BuⁿLi or Bu^tLi occurs with different degrees of regioselectivity.^{29, 30, 48} Although the precise structures of metallated species are unknown, they have presumably the structures of complex lithium naphtholates **81**–**84**.

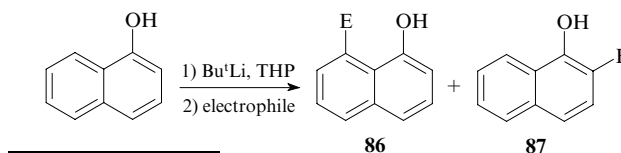


The highest selectivity is achieved in metallation of 2-naphthol, which gives only the corresponding 3-substituted derivative **85** in good yield after the subsequent treatment with *tert*-butyllithium in tetrahydropyran and an electrophile (Me₂NCHO, Me₂S₂ or MeI).^{29, 48}



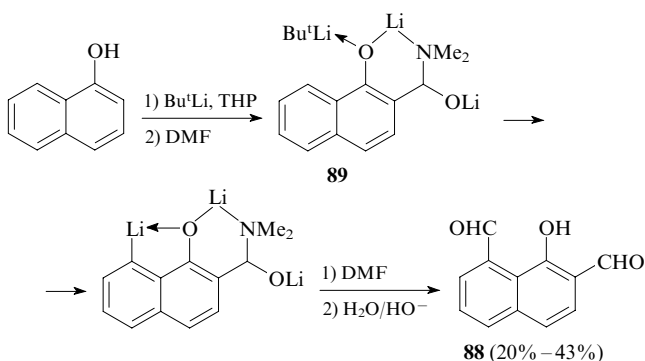
E = CHO, MeS, Me.

Under the same conditions, 1-naphthol gives a mixture of *peri*- (**86**) and *ortho*-lithiation products (**87**), with the former generally predominating.⁴⁸



E	Yield (%)	
	86	87
CHO	40	20
MeS	50	19
Me	8	38

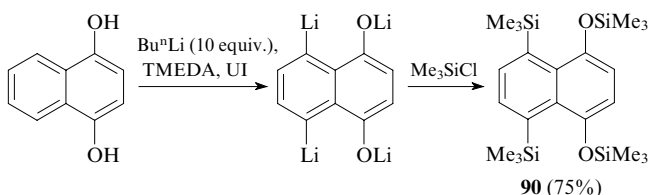
After metallation of 1-naphthol with a BuⁿLi–TMEDA system followed by the reaction with DMF, only 8-hydroxy-1-naphthaldehyde was found in 43% yield.³⁰ Metallation with a Bu^tLi–THP mixture followed by the addition of dimethylformamide afforded dialdehyde **88** (20%–43%), which is presumably generated from intermediate α-aminoalkoxide **89** as a result of lithiation.⁴⁸

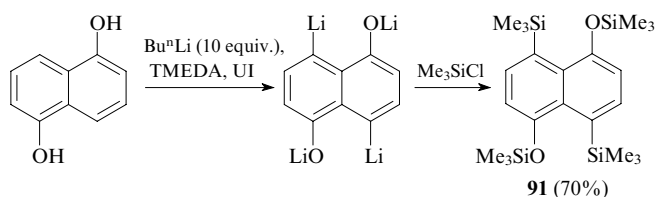


It is worthy of note that 2-naphthol does not react with *n*-butyllithium in TMEDA,³⁰ whereas the corresponding reaction in diethyl ether produces (after the addition of CO₂) 3-hydroxy-2-naphthoic acid (7%) and the starting compound (62%).¹⁶⁸

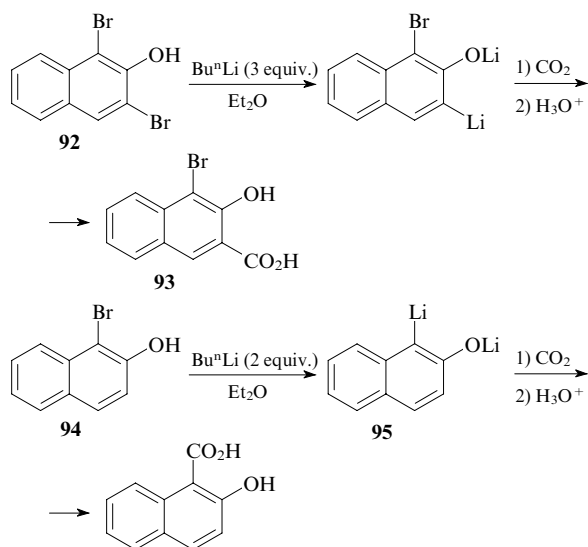
The yields of substituted naphthols strongly depend on the reaction conditions. The best results were obtained in the case of the fast addition of a 2M Bu^tLi solution in pentane to the concentrated naphthol solution. The theoretical interpretation of the direction of metallation of 1- and 2-naphthols is considered in Section II.8.

Lithiation of 1,3-, 1,4-, 1,5- and 1,6-dihydroxynaphthalenes and 1,4,5-trihydroxynaphthalene with a BuⁿLi–TMEDA system occurs exclusively at the *peri* position with respect to the 1-OH group, which was confirmed by the synthesis of the corresponding monoaldehydes in high yields. When the reaction is initiated with ultrasonic irradiation (UI), 1,4- and 1,5-dinaphthols are subjected to dilithiation, as evidenced by isolation of compounds **90** and **91** after the treatment of the reaction mixture with trimethylchlorosilane.





Metal–halogen exchange is also used for the preparation of lithium naphthols. For example, bromine at position 3 in 1,3-dibromo-2-naphthol (**92**) is replaced with lithium under the action of Bu^nLi , as evidenced by isolation of acid **93** after the treatment of the reaction mixture with CO_2 .¹⁶⁹ In this case, the direction of metallation is identical to that for unsubstituted 2-naphthol. In 1-bromo-2-naphthol (**94**), metal–halogen exchange is also more preferable than metallation of the C–H bond at position 3. This allows one to prepare 1-lithium derivative **95**, which is difficult to synthesise according to other procedures (see also Ref. 170).

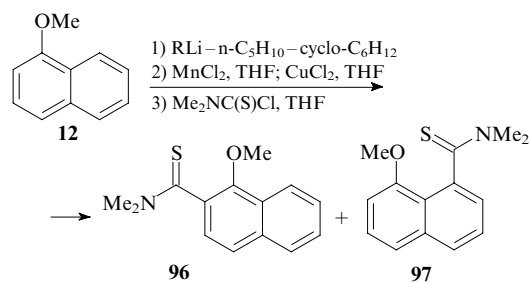


Analogous results were obtained by metallation of 4-bromo-1-naphthol and 4-, 6- and 8-bromo-2-naphthols.^{169, 171} Metallation of their derivatives containing the protected OH group provides additional possibilities for the synthesis of substituted naphthols (see Section III.4).

4. Metallation of alkoxy derivatives of naphthalene

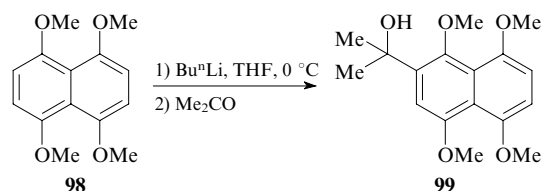
The factors determining the direction of lithiation of 1-methoxynaphthalene (**12**) were discussed in Sections II.3 and II.8. In the general case, the reaction with Bu^nLi or a Bu^nLi – Bu^tOK mixture occurs predominantly at position 2, whereas the reaction with *tert*-butyllithium occurs at position 8. There are contradictory data on the degree of regioselectivity of the reaction and the total yield of metallation products. For example, Shirley and co-workers^{45, 49} prepared a mixture of 1-methoxy-2-naphthalene- and 1-methoxy-8-naphthalenecarboxylic acids by the reaction of 1-methoxynaphthalene with Bu^nLi – TMEDA – Et_2O – $n\text{-C}_6\text{H}_{14}$ and Bu^tLi – $n\text{-C}_5\text{H}_{12}$ – $n\text{-C}_6\text{H}_{14}$ systems followed by the treatment of the reaction mixture with CO_2 in total yields of 60% and 20% in a ratio of 99:1 and 1:9, respectively. However, more recent studies^{41, 170} demonstrated that the total yield of the acids in such reactions is substantially higher, whereas the regioselectivity is, on the contrary, somewhat lower. In addition to the synthesis of alkoxynaphthalenecarboxylic acids,^{16, 33, 41, 169} lithium derivatives of 1-alkoxynaphthalenes were involved in H/D exchange,^{41, 67} alkylation,¹⁶ acylation,³³ trimethylsilylation,^{50, 67} trimethylstannylation,⁶⁷ iodination¹⁷² and the reactions with aldehydes.^{173, 174} In some cases, when the reactions of lithium derivatives **13** and **14** with electrophiles give unsatisfactory results, good results can be obtained by transforming lithium derivatives into manganese- or

copper-containing compounds. For example, the synthesis of thiocarbamoyl derivatives **96** and **97** was documented.¹⁷⁵

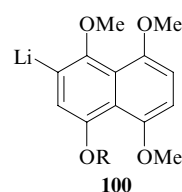


RLi	Yield (%)	
	96	97
Bu^tLi	29	60
Bu^nLi	79	13

The reaction of Bu^tLi with 1,4-dimethoxynaphthalene afforded *peri*- and *ortho*-lithiation products in a ratio of 2:1 (products were detected by transforming them into the corresponding aldehydes).¹⁷⁶ Lithiation of 1,4,5,8-tetramethoxynaphthalene (**98**) produced the 2-lithium derivative, which gave alcohol **99** after the treatment with acetone.

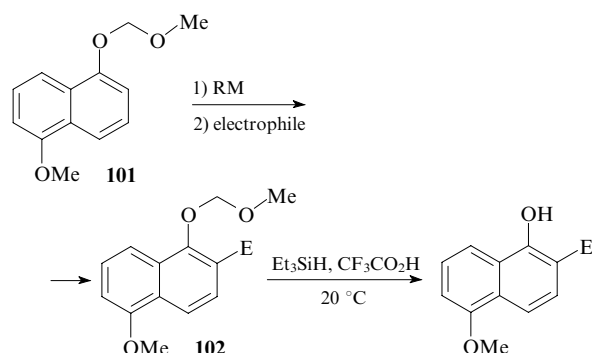


Interestingly, 2-lithium derivatives **100**, which were derived from the corresponding bromides, undergo protolysis in the presence of acetone.⁸² Apparently, the protolysis rate in this case is substantially higher than the rate of formation of the corresponding alcohols due to steric effects.



R = PhCH_2 , $\text{PhCH}_2\text{OCH}_2$, $\text{Me}_3\text{SiCH}_2\text{CH}_2\text{OCH}_2$ (SEM).

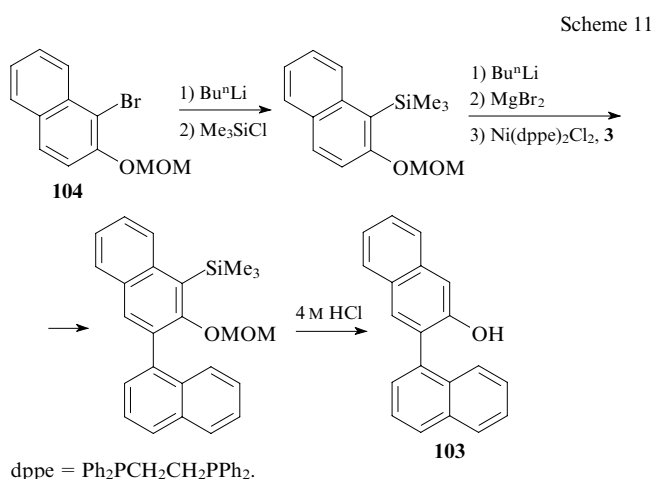
Unlike 1-methoxynaphthalene, methoxymethyl ether of 1-naphthol (1-MOMO-Np) is lithiated exclusively at the *ortho* position.¹⁷³ The directing effect of the 1-MOMO group is stronger than the effect of the methoxy group, as exemplified by compound **101**^{67, 177} (see also Ref. 178). After completion of the reaction, the methoxymethyl group can be removed by the reaction with triethylsilane in an acidic medium.¹⁷⁷



RM	Reaction conditions	Electrophile E		Yield of 102 (%)	Ref.
Bu ⁿ Li – Bu ^t OK	THF, –78 °C	D ₂ O	D	95	67
		Me ₃ SiCl	Me ₃ Si	93	67
		Me ₃ SnCl	Me ₃ Sn	98	67
Bu ⁿ Li – TMEDA	THF, 20 °C	Me ₂ NCHO	CHO	73	177
		Me ₂ SO ₄	Me	45	177
		Bu ⁿ CHO	Bu ⁿ CH(OH)	77	177

In the presence of 2-(trimethylsilyl)ethoxymethoxy (OSEM) and carbamoyloxy groups at position 1, lithiation of the ring occurs exclusively at position 2.⁵⁰

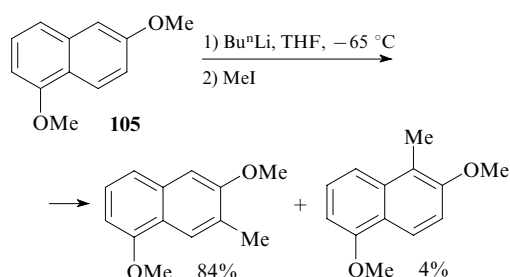
2-Methoxy-^{169, 179} and 2-ethoxynaphthalenes¹⁶⁸ are metallated with high selectivity at position 3. By contrast, lithiation of 2-MOMO-Np affords a mixture of 1- and 3-lithium isomers in a ratio of 3:4.¹⁸⁰ A substituent can be introduced at position 3 of this compound and the corresponding product can be prepared in good yield after the protection of the more active position 1. This strategy was successfully applied in the synthesis of 3'-hydroxy-1,2'-binaphthyl (**103**) from bromide **104** (Scheme 11).³²



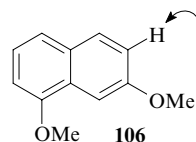
Metallation of 2-(trimethylsilyl)ethoxymethoxynaphthalene affords a mixture of 1- and 3-isomers in a ratio of 1:1 in a total yield of 80%.⁵⁰

In the reaction with BuⁿLi, 2,7-dimethoxynaphthalene, unlike 2-methoxynaphthalene, gives not only the 3-lithium-substituted derivative but also the 1-isomer (15%). In the presence of an excess of butyllithium, dilithiation can occur at positions 3 and 6.^{169, 181, 182}

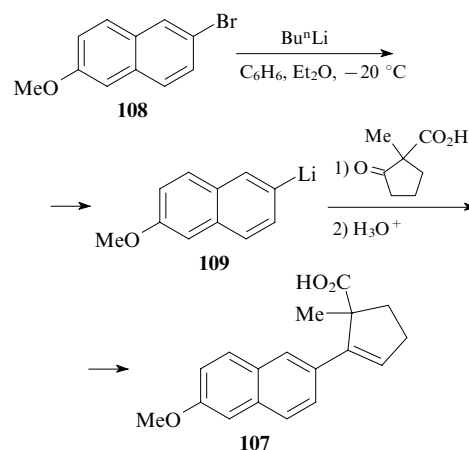
Study of the reaction of 1,6-dimethoxynaphthalene (**105**) demonstrated that the 6-methoxy group exerts the stronger directing effect than the 1-methoxy group.



This conclusion is also true for 1,7-dimethoxynaphthalene (**106**), which undergo metallation at position 6 (the yield of the product was 98%).^{49, 181, 183}

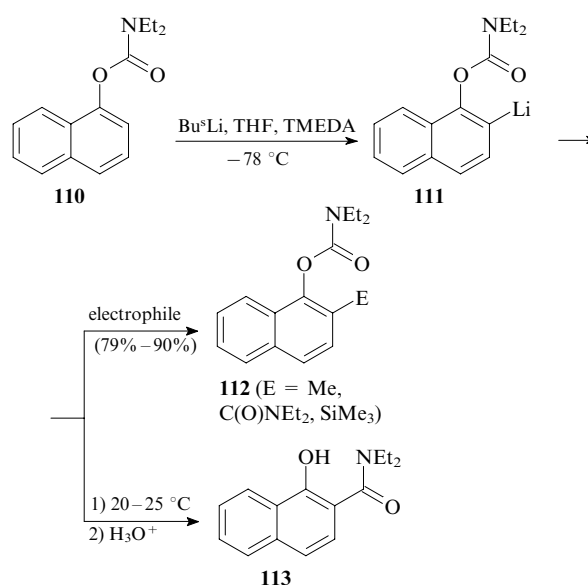


Metal derivatives of alkoxy-naphthalenes, which cannot be prepared by direct metallation of the C–H bond in alkoxy-naphthalenes, are generated from the corresponding bromonaphthalenes. The synthesis of compound **107** from 2-bromo-6-methoxynaphthalene (**108**) through lithium derivative **109** is a typical example.¹⁸⁴



Additional data on metal–halogen exchange in halogen-substituted alkoxy-naphthalenes are given in Table 6.

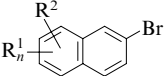
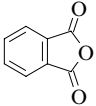
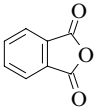
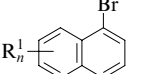
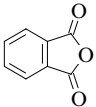
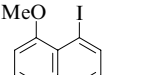
1-Naphthyl-*N,N*-diethylcarbamate (**110**) is metallated at –78 °C to form 2-Li derivative **111**, whose treatment with electrophiles affords compounds **112** in high yield.²⁵

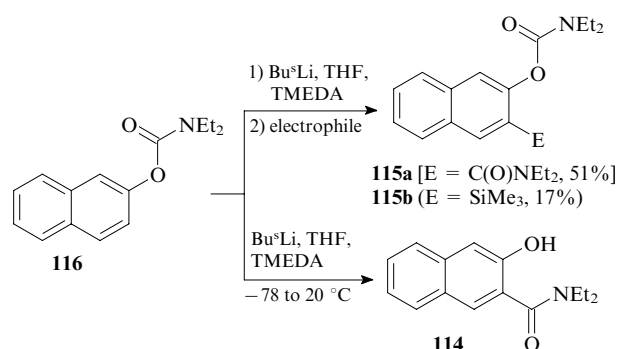


Since the nucleophilic site in the amide group is located on the carbonyl oxygen atom, such a high regioselectivity, apparently, indicates that carbamate **110** subjected to metallation has a conformation, in which the C=O bond is directed toward the C-2 rather than C-8 atom. At room temperature, naphthyllithium **111** is isomerised to give α-naphthol derivative **113**.

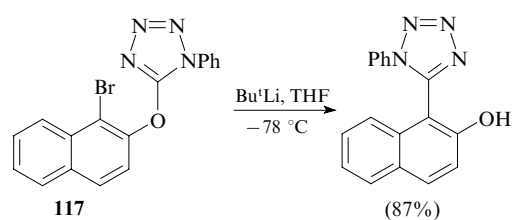
This rearrangement giving rise to β-naphthol **114** is typical also of the 3-lithium derivative of 2-naphthyl-*N,N*-diethylcarbamate. However, taking into account low yields of compounds **115**, metallation of derivative **116** is less regioselective.²⁵

Table 6. Reactions based on metal–halogen exchange in alkoxy-naphthalenes.

Substrate	R ¹	R ²	Metallating agent	Electrophile	Product ^a	Yield (%)	Ref.
	1,4-(OMe) ₂	5-OCH ₂ Ph	Bu ⁿ Li	B(OMe) ₃	B(OH) ₂	—	185
	1,4-(OMe) ₂	5-OMe	Bu ^t Li	PhCHO	CH(OH)Ph	82	186
	1-OCH ₂ Ph	5-OMe	Mg	Me ₃ SiC≡CCH ₂ Br	Me ₃ SiC≡CCH ₂	77	186
	1,4-(OMe) ₂	H	Bu ^t Li		2-HO ₂ CC ₆ H ₄ CO	56	187
	1,4-(OMe) ₂	3-Me	Bu ⁿ Li	ClCO ₂ Et	CO ₂ Et	86	188
	6-OMe	H	Mg		2-HO ₂ CC ₆ H ₄ CO	69	189
	6-OMe	H	Mg	CO ₂ , DMF, EtCN	CO ₂ H, CHO, C(O)Et	70, 80, 50	119
	6-OEt	H	Mg			50	190
	—	—	Bu ⁿ Li	AcN(Me)OMe	2,7-Ac ₂	52, 66	191
	—	—	—	—	—	—	—
	3-OMe	—	Mg		2-HO ₂ CC ₆ H ₄ CO	80	192
	2-OMe	—	Bu ⁿ Li	CO ₂	CO ₂ H	70	169
	2-OMe	—	Bu ⁿ Li	B(OPr ⁱ) ₃	B(OH) ₂	63	193
	4-OCH ₂ Ph-5-OMe	—	Bu ⁿ Li	HC(O)N(Me)OMe	CHO	89	194
	7-CH ₂ OMe	—	—	—	—	—	—
	—	—	Mg	D ₂ O	D	70	49

^a Substituents introduced instead of the halogen atom are given.

An analogous rearrangement was observed in the reaction of *tert*-butyllithium with 1-bromo-2-(1-phenyltetrazol-5-yloxy)-naphthalene (**117**).¹⁹⁵



The behaviour of organometallic derivatives of naphthyl triflates and naphthyl tosylates is considered in Section III.14.

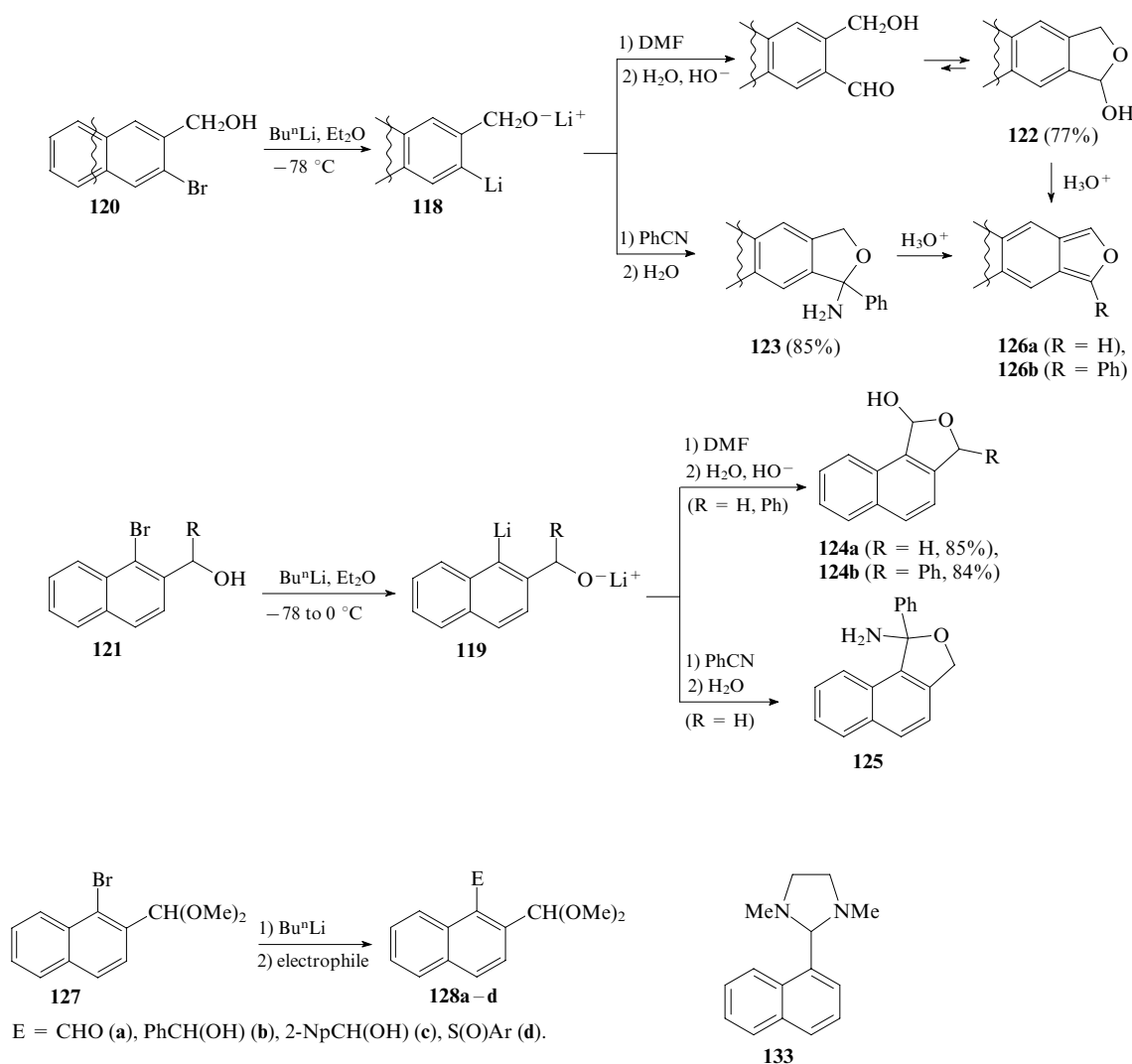
5. Metallation of hydroxymethylnaphthalenes

Data on direct CH-metallation of hydroxymethylnaphthalenes are lacking. The corresponding lithium-substituted naphthalenes **118** and **119** were prepared from bromides **120** and **121** by metal–halogen exchange. Lithiated derivatives were used for the generation of partially hydrogenated naphthofurans **122–125**, which, in turn, were used for the preparation of *ortho*-quinonoid naphthofurans, for example, **126a,b**, the latter being highly active as dienes (Scheme 12).^{196–198}

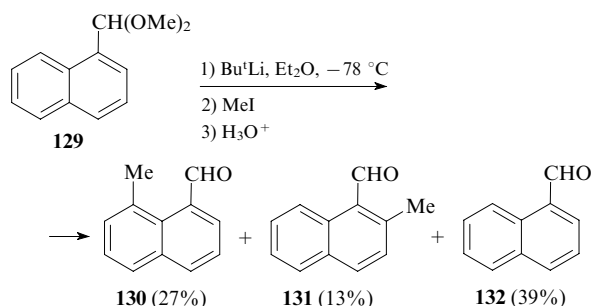
6. Metallation of naphthaldehydes and their latent forms

The synthesis of organometallic derivatives of naphthaldehydes requires the pre-protection of the aldehyde group. Good results were obtained with the use of metal–halogen exchange, for example, in acetals. The successive treatment of bromide **127** with butyllithium and dimethylformamide affords aldehyde **128a** in almost quantitative yield. The reactions with benzaldehyde and 2-naphthaldehyde as electrophiles¹⁹⁶ produce alcohols **128b,c**, whereas the reactions with aryl isopropyl sulfenates, ArS(O)OPrⁱ, afford diaryl sulfoxides **128d**.¹⁹⁹

Scheme 12



CH-Metallation of naphthaldehyde acetals gives less satisfactory results. For example, the successive treatment of 1-dimethoxymethylnaphthalene (**129**) with *tert*-butyllithium and iodomethane followed by hydrolytic cleavage of the acetal afforded a mixture of aldehydes **130–132**.⁵⁴



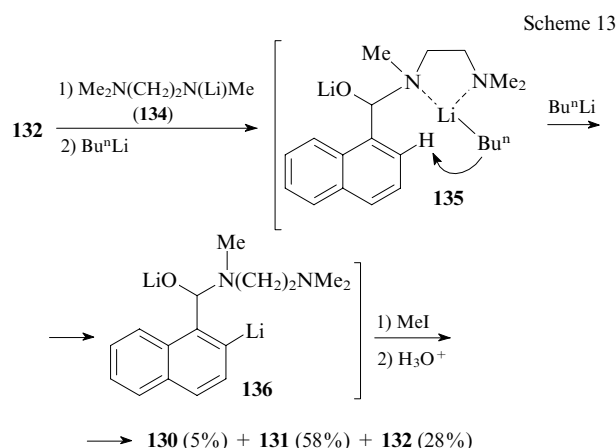
It is worthy of note that *peri*-metallation dominates over *ortho*-metallation by a factor of more than two. The use of amins (for example, compounds **133**) instead of acetals leads to a decrease in the yield of compounds **130–132** to 6%, 12% and 15%, respectively.

Similar results were obtained by metallation of 2-substituted analogues of compounds **129** and **133**.⁵⁴

Metallation of Schiff bases (for example, of compound **28**, see Section II.5) leads primarily to the addition of the metallating agent rather than to metallation.⁵⁴

An original procedure for metallation of naphthaldehydes is based on the preliminary transformation of these compounds into the corresponding α -amino alkoxides by treatment with lithium (dimethylaminoethyl)methylamide (**134**).^{54, 200, 201} For example, metallation of amino alkoxide **135** derived from 1-naphthaldehyde (**132**) with an excess of butyllithium occurs predominantly at position 2 to form dilithium derivative **136**, whose methylation followed by hydrolysis affords a mixture of naphthaldehydes **130–132**, with compound **131** predominating (Scheme 13). The method is based on the fact that amino alkoxide **135** contains the 'built-in' chelating group, whose action is analogous to that of TMEDA. The transformation of lithium derivative **136** into boronic ester followed by oxidation with oxygen or hydrogen peroxide afforded 2-hydroxy-1-naphthaldehyde in 12%–17% yield.²⁰⁰

Metallation of 2-naphthaldehyde according to this procedure gave a mixture of the 3-Li and 1-Li derivatives in a ratio of $\sim 3:1$. The reaction of this mixture with iodomethane produces the corresponding methyl derivatives, whereas the treatment of this

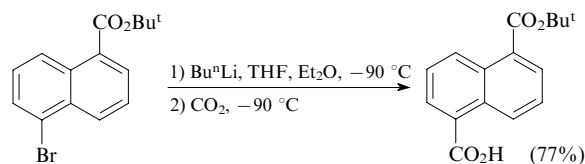


mixture with sulfur affords 3-thio-2-naphthaldehyde in 94% yield.²⁰¹

The use of lithium diethylamide, pyrrolidide, piperidide or *N*-methylpiperazide instead of compound **134** gives worse results.⁵⁴

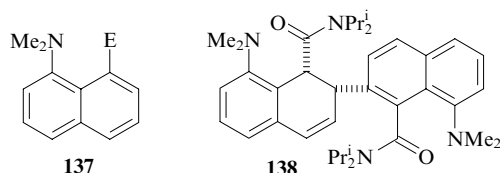
7. Metallation of naphthalenecarboxylic acids and their esters

Since the reactions of metallating agents with naphthalenecarboxylic acids or their esters afford addition products to the naphthalene ring (see Scheme 5), the corresponding metal derivatives are prepared by metal–halogen exchange at low temperature.²⁰²



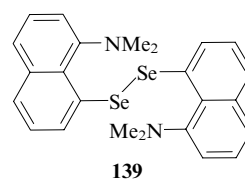
8. Metallation of aminonaphthalenes

The most pronounced directing effect of the amino groups on metallation is observed for 1-dimethylaminonaphthalene. The treatment of this compound with Bu^nLi or Bu^tLi ^{16, 173} in diethyl ether affords exclusively 8-lithium derivative **7**,²⁰³ whose structure was established by X-ray diffraction. The reactions of compound **7** with different electrophiles, including CD_3OD , CO_2 , Ph_2CO , Ac_2O , DMF , BF_3 ,³⁴ Me_2AlCl ,²⁰⁴ MnCl_2 ,¹⁷⁵ MeNCS ,¹⁷⁵ Me_3SnCl , Me_3SiCl , R_2SnBr_2 ,²⁰³ $(p\text{-Tol})_2\text{SbBr}$,²⁰⁵ $\text{Pr}_2^i\text{NCOCl}$,¹⁶ $\text{Cl}_2\text{MeSiSiMePh}_2$ ¹³³ or $\text{F}_2\text{MeSi} - \text{SiMePh}_2$,²⁰⁶ produce the corresponding 1- NMe_2 -8-*E*-naphthalenes **137**. In the synthesis of 8-carbamoylnaphthalenes, it is necessary to add a suspension of compound **7** to carbamoyl chloride because the addition in the reverse order leads to the formation of binaphthyl derivative **138**.¹⁶

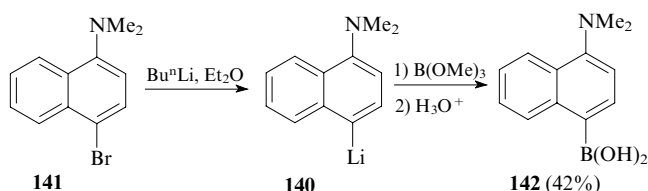


$E = \text{D}, \text{CO}_2\text{H}, \text{CHO}, \text{C}(\text{O})\text{Me}, \text{C}(\text{O})\text{NPr}_2^i, \text{Ph}_2\text{C}(\text{OH}), \text{BBu}_2^n, \text{C}(\text{S})\text{NHMe}, \text{SiMe}_3, \text{SnMe}_3, \text{etc.}$

The treatment of compound **7** with selenium followed by oxidation of the reaction mixture affords diselenide **139**.¹³⁶

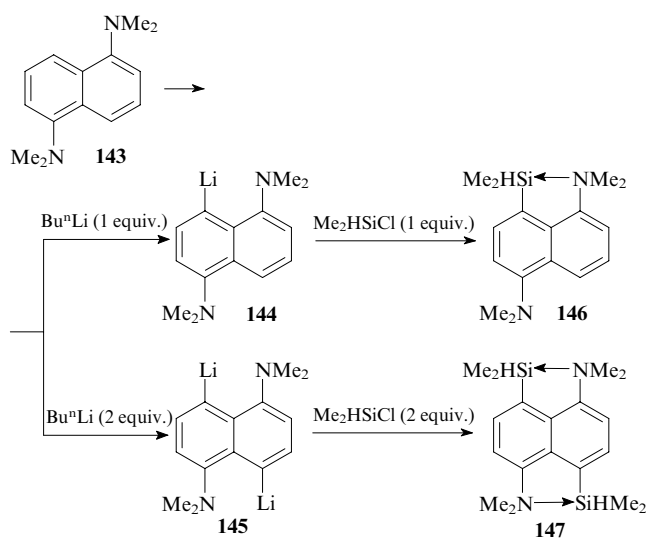


The synthesis of other lithium derivatives of 1-dimethylaminonaphthalene (for example, **140**) is based on metal–halogen exchange. This procedure was applied in the synthesis of boronic acid **142** from 4-bromo-1-dimethylaminonaphthalene (**141**).²⁰⁷

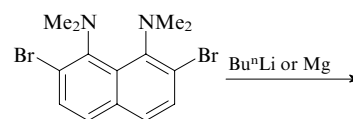


2-Bromomagnesio-6-dimethylaminonaphthalene was prepared from 2-bromo-6-dimethylaminonaphthalene by metal–halogen exchange. Taking into account low activity of the latter, the Grignard reaction was carried out in the presence of the auxiliary reagent, dibromoethane.⁸

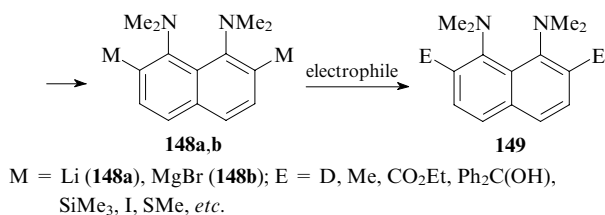
The reaction of 1,5-bis(dimethylamino)naphthalene (**143**) with *n*-butyllithium produces either 4-lithium (**144**) or 4,8-dilithium derivatives (**145**) depending on the amount of *n*-butyllithium. The reactions of compounds **144** and **145** with halosilanes [$\text{Si}(\text{OMe})_3\text{Cl}$, Ph_2SiHCl , Me_2SiHCl , *etc.*] were used for the synthesis of *peri*-substituted derivatives of naphthalenes **146** and **147** containing $\text{N} \rightarrow \text{Si}$ bonds.²⁰⁸



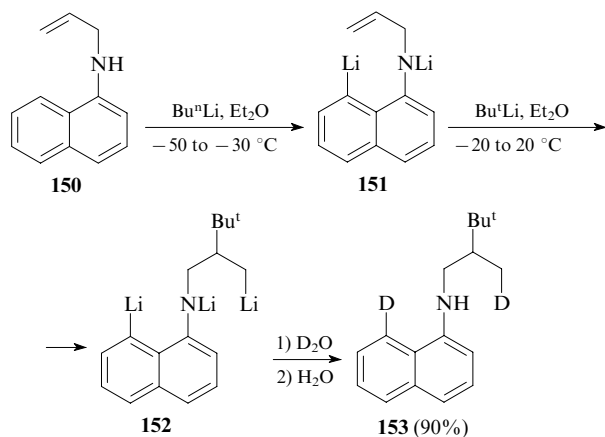
1,8-Bis(dimethylamino)naphthalene ('proton sponge') is not metallated by butyllithium.²⁰⁹ However, its 4-lithium,²¹⁰ 2-lithium and 2,7-dilithium derivatives^{88, 211} and their MgBr analogues can easily be prepared by metal–halogen exchange. Compounds **148a, b** are of particular importance. The reactions of the latter compounds with electrophiles produce 2,7-disubstituted proton sponges **149**, which are difficult to synthesise according to other procedures and which are of fundamental importance.^{88, 211}



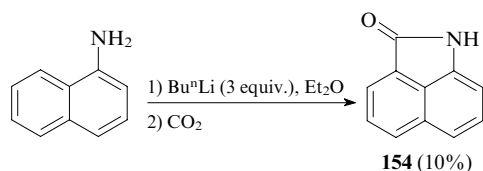
Scheme 14



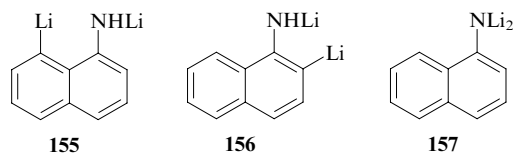
Metallation of naphthalenes containing a secondary or primary amino group as a substituent is complicated because of the initial formation of N-anions. Nevertheless, these compounds also generally undergo lithiation at the *peri* position.^{102,212} For example, the reaction of 1-allylaminonaphthalene **150** with an excess of BuⁿLi produces dianion **151**, whose treatment with *tert*-butyllithium affords trianion **152**, and the latter is transformed into compound **153** under the action of D₂O.²¹²



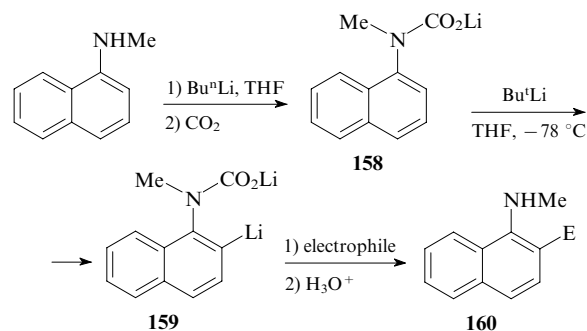
The reaction of 1-aminonaphthalene with BuⁿLi followed by the treatment with CO₂ gives rise to naphtholactam **154** in low yield.⁵²



According to *ab initio* calculations, *peri*-lithiated dianion **155** is 14.4 kcal mol^{−1} more stable than *ortho* isomer **156** and 27.3 kcal mol^{−1} more stable than dilithium naphthylamide (**157**).¹⁰¹



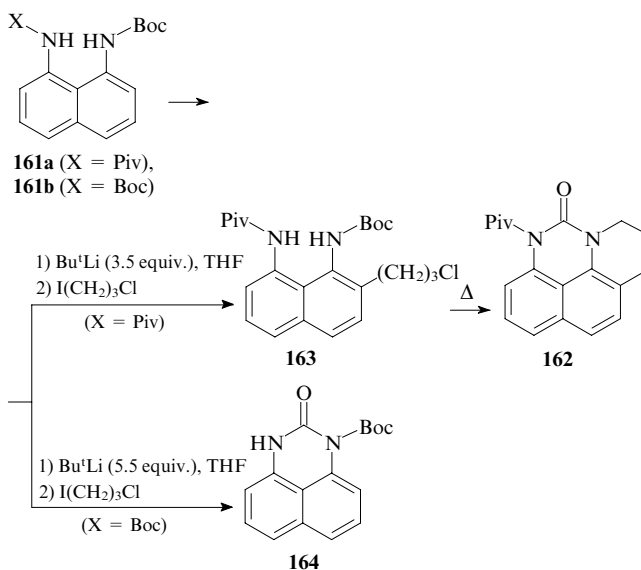
Katritzky *et al.*²¹³ developed a general one-pot procedure for *ortho*-lithiation of aminonaphthalenes (Scheme 14) providing great scope for their functionalisation. According to the proposed procedure, 1-methylaminonaphthalene is initially lithiated with *n*-butyllithium and then transformed into lithium carbamate **158** by the reaction with CO₂. Lithiation of the latter with *tert*-butyllithium occurs selectively at position 2 to form compound **159**, whose treatment with various electrophiles gives 2-substituted 1-naphthylamines **160** in a total yield of 48%–61%.



E = PhCH₂, Ph₂C(OH), PrⁱCH(OH), BuⁿNHCO.

Analogously, 2-methylaminonaphthalene can be transformed into 3-substituted derivatives but in lower yields.

The transformation of *peri*-diamine **161a** into urea derivative **162** by the successive treatment with butyllithium and 3-chloro-1-iodopropane is yet another example of *ortho*-lithiation.²¹⁴ Evidently, intermediate chloride **163** is generated by alkylation of the corresponding 2-lithium derivative. It is worthy of note that if both amino groups in *peri*-diamine contain the *tert*-butoxycarbonyl substituents (compound **161b**), cyclisation of diamine **161b** giving rise to 1-Boc-perimidone **164** occurs instead of metallation of the naphthalene moiety.

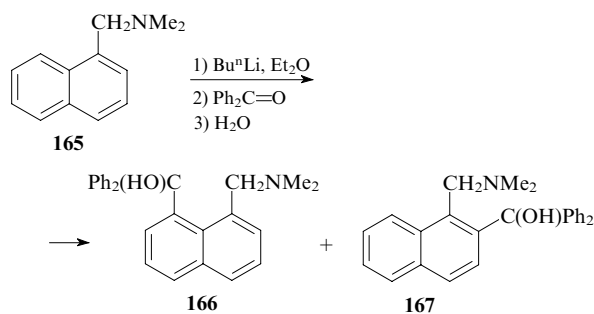


9. Nitronaphthalenes

Data on Li and Mg derivatives of nitronaphthalenes are lacking. As a rule, the reactions of organomagnesium reagents with nitronaphthalenes afford addition products to the naphthalene ring (see Scheme 5).^{68–70,215–217} The treatment of the latter with dichlorodicyanobenzoquinone (DDQ)⁶⁸ or KMnO₄⁷⁰ gives alkylnitronaphthalenes.

10. Dialkylaminomethyl- and dialkylaminocarbonylnaphthalenes

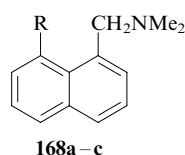
Metallation of 1-dimethylaminomethylnaphthalene (**165**) with butyllithium followed by the reaction of the resulting 8-lithium derivative with benzophenone afforded alcohol **166** in 58% yield. In addition, *ortho* isomer **167** was found in the reaction mixture, but attempts to isolate this isomer in pure form failed (presumably, the ratio of the *peri*- to *ortho*-lithiation products is 91 : 9).⁵³



The same alcohols were prepared in good yields from bromides through metal–halogen exchange.⁵³

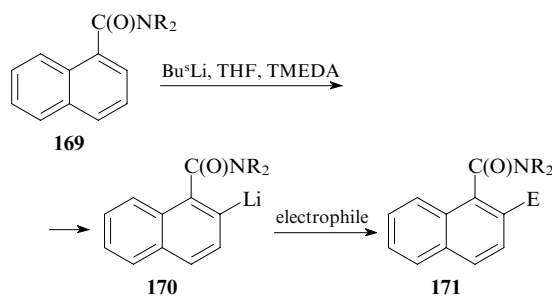
Analogous experiments with 2-dimethylaminomethylnaphthalene demonstrated low selectivity of metallation (the ratio of the 3- to 1-substitution products was 55:45).

Clayden *et al.*¹⁶ used 1-dimethylaminomethyl-8-naphthyllithium in the synthesis of 8-carbamoyl-1-dimethylaminomethylnaphthalenes **168a,b**.[¶] The lithium derivative was prepared by the reaction of compound **165** with *tert*-butyllithium.¹⁶ The synthesis of compound **168c** was documented.²⁰⁵



R = C(O)NEt₂ (a), C(O)NPr₂ⁱ (b), (*p*-Tol)₂Sb (c).

As mentioned above (see Section II.4), the carboxamide group is one of few electron-withdrawing groups, which promote the efficient metallation of the naphthalene moiety. For example, the reactions of 1-naphthamides **169** with *sec*-butyllithium produce 2-lithium derivatives **170**; its treatment with electrophiles gives 2-substituted 1-naphthamides **171** generally in good yields (Table 7).



ortho-Lithiation is particularly favoured by low temperature (to $-100\text{ }^{\circ}\text{C}$) and the reverse order of mixing of the reactants (a solution of the substrate is added to the metallating agent).²²⁴

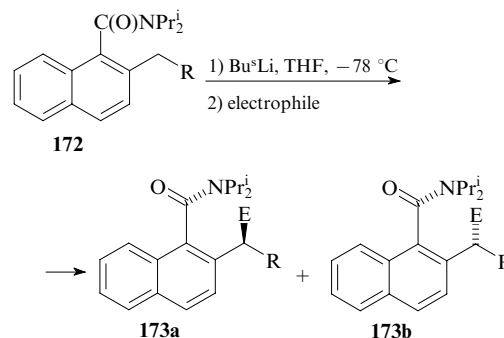
Based on the existence of atropisomerism in the series of *N,N*-dialkyl-2-*R*-1-naphthamides, Beak and co-workers²²³ studied asymmetric deprotonation of *N,N*-dihexyl-1-naphthamide under the action of Bu^sLi in the presence of chiral diamine, *viz.*, (–)-sparteine. Subsequent methylation and ethylation of the 2-lithium derivative obtained after lithiation afforded atropoisomers of *N,N*-dihexyl-2-alkyl-1-naphthamides with 50% and 55% *ee*, respectively.²²³

It is worthy of note that under the above-mentioned conditions, position 8 is not subjected to lithiation and no indication of the nucleophilic addition at the aromatic ring is observed. To achieve *peri*-metallation, various 2-substituted 1-naphthamides were tested as substrates. However, in none of the experiments,

Table 7. Reactions of 2-lithio-1-naphthamides **170** with electrophiles.

R	Electrophile	E	Yield of 171 (%)	Ref.
Et	1) TosN ₃ , 2) NaBH ₄	NH ₂	74	218, 219
Et	1) O ₂ , 2) H ₃ O ⁺	OH	34	220
Et	1) LiCu(CN)NMePh, 2) O ₂	NMePh	61	221
Et	Me ₃ SiCl	Me ₃ Si	80	25
Pr ⁱ	D ₂ O	D	93	16
Pr ⁱ	EtI	Et	82	85
Pr ⁱ	Pr ⁿ I	Pr ⁿ	78	85
Pr ⁱ	MeCHO	MeCH(OH)	92	74, 222
CH(Pr ⁿ)Bu ⁿ	MeCHO	MeCH(OH)	35	74
<i>n</i> -C ₆ H ₁₃	MeI	Me	30	223

did *peri*-metallation occur. Lithiation of 2-ethyl- and 2-propyl-1-carboxamides **172** afforded solely the corresponding benzyl anion; its treatment with electrophiles gave rise to a mixture of stereoisomers **173a** and **173b**, with one of them substantially predominating.⁸⁵ High stereoselectivity of metallation is attributed to the almost perpendicular orientation of the carboxamide fragment relative to the naphthalene moiety, resulting in stereochemical induction.

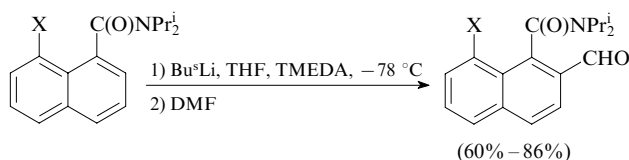


R = Me, Et; E = D, Alk, Me₃Si, Me₃Sn, *etc.*

Due to a high kinetic isotope effect in metallation reactions of naphthalene derivatives ($k_{\text{H}}/k_{\text{D}} > 80$ at $-78\text{ }^{\circ}\text{C}$), *N,N*-diisopropyl-2-D-1-carboxamide (**27**) would be expected to undergo *peri*-metallation. However, the reaction of this compound with BuⁿLi or Bu^sLi led only to the addition of the nucleophile at position 2 (see Scheme 5).^{16, 73} In the presence of the Buⁱ or Bn substituents at the nitrogen atom, the α -proton abstraction from the *N*-benzyl group was observed.^{73, 225}

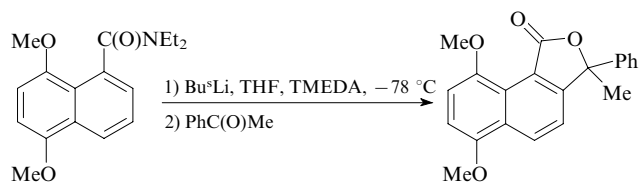
Nowadays, the only procedure for the preparation of thermodynamically less stable 8-lithio-1-naphthamides is based on bromine–lithium exchange in 8-bromo-1-naphthamides.²²⁶ Recall also that the carboxamide group can be introduced at the *peri* position with respect to the already present substituent by the reaction of the corresponding carbamoyl chloride with 1-*R*-8-naphthyllithium.¹⁶

The 1-carboxamide group is superior to other groups,¹⁶ including the methoxy group,^{226, 227} in the directing ability.

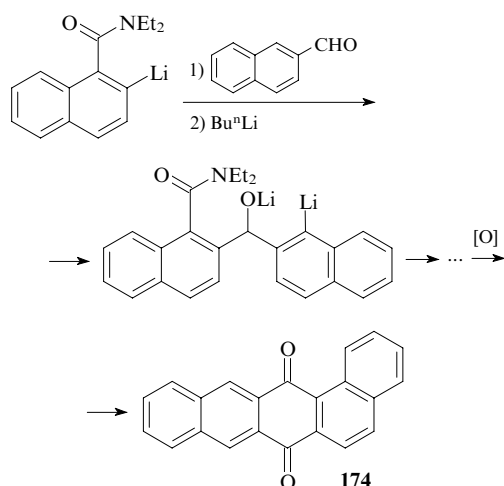


X = CH₂NMe₂, NMe₂, OMe.

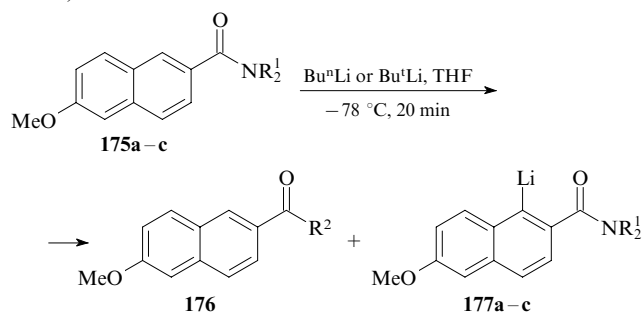
¶ According to the IUPAC nomenclature, these compounds are called *N,N*-dialkyl-8-(*N,N*-dimethylaminomethyl)-1-naphthamides.



The distinguishing feature of the carboxamide group is that it is stable to the action of organolithium compounds only at lowered temperature. At high temperature, the carboxamide group can be subjected to the nucleophilic attack. This fact was used in the synthesis of isomeric benzanthraquinones (for example, of compound **174**,²²⁸ dibenzanthracenes²²⁶ and cholanthrenes²²⁴) and a series of other polynuclear arenes²¹⁹ (see also the review²⁵).

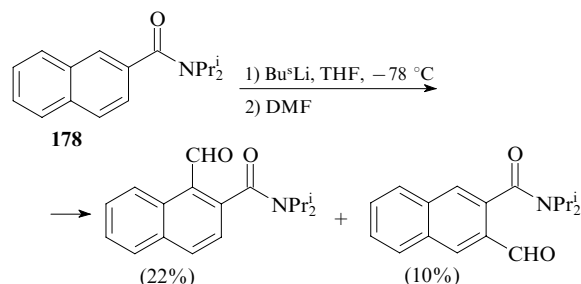


Metallation of 2-naphthamides is very sensitive to the reaction conditions and steric factors. For example, compounds containing methyl groups at the amide nitrogen atom (compound **175a**) do not undergo metallation, and the reaction affords ketone **176** as virtually the only product regardless of the nature of the metallating agent (Bu^nLi or Bu^tLi). Metallation of compounds containing the *N*-isopropyl group (**175c**) gives only Li derivative **177c**, whereas diethylamide **175b** can form both ketone (in the reaction with Bu^nLi) and the Li derivative (in the reaction with Bu^tLi).²²⁹



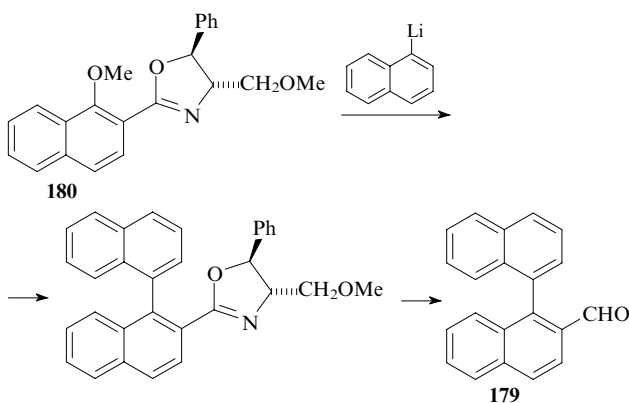
$\text{R}^1 = \text{Me}$ (a), Et (b), Pr^i (c); $\text{R}^2 = \text{Bu}^n$ or Bu^t .

N,N-Diethyl-2-naphthamide containing the unsubstituted naphthalene ring reacts with Bu^tLi at -45°C to form a mixture of products, *viz.*, the product of the addition of the nucleophile to the naphthalene ring (50%), the 1-lithium derivative (30%) and *tert*-butyl 2-naphthyl ketone (10%).^{12, 25} Approximately the same ratio of metallation products was observed in the reaction with *N,N*-diisopropyl-2-naphthamide (**178**) with the only difference that the reaction occurs at positions 1 and 3.²³⁰

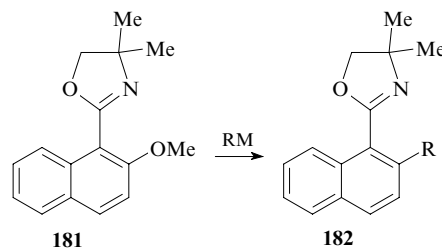


11. Naphthyloxazolines

As mentioned above, the oxazoline substituent promotes the addition of various metallating agents to the naphthalene ring (see Section II.5). In some cases, the oxazoline substituent activates the adjacent group (for example, the methoxy group) toward the nucleophilic substitution (Meyers's reaction).^{78, 231} In particular, this reaction was used for the preparation of 1,1'-binaphthyl-2-carbaldehyde (**179**) starting from (1-methoxy-2-naphthyl)oxazoline **180**.²³²

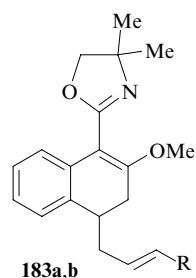


In the reactions with C- and N-nucleophiles, the methoxy group in (2-methoxy-1-naphthyl)oxazoline **181** is replaced to give compounds **182**.¹²



$\text{RM} = \text{MeLi}$, Bu^nLi , Bu^sLi , Bu^tLi (94%–98%),
syn- $\text{MeCH}=\text{CHLi}$ (60%), Me_2NLi , Pr_2NLi ,
 PhMgBr (98%–100%).

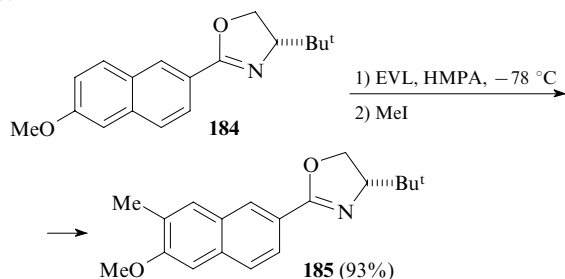
It is interesting that the reaction of compound **181** with allyllithium leads to the addition of the nucleophile at position 4 to give 3,4-dihydronaphthalenes **183a,b**. The latter can be subjected to aromatisation with DDQ.^{66, 78}



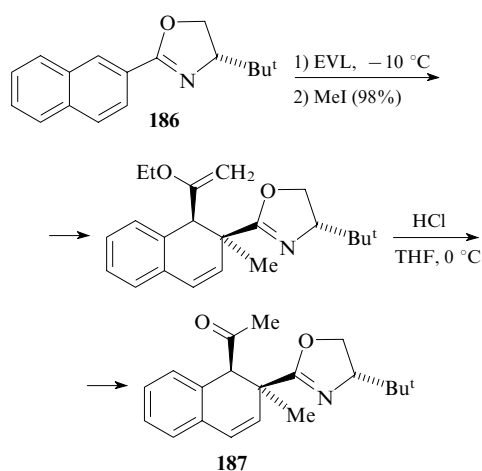
$\text{R} = \text{H}$ (a), SiMe_3 (b).

The replacement of the NMe_2 group in (2-dimethylamino-1-naphthyl)oxazolines with Bu^tLi was documented.^{78, 79}

The only example of successful metallation of naphthyloxazolines by the reaction of compound **184** with ethoxyvinyl lithium (EVL) in the presence of hexamethylphosphoramide was documented. Contrary to expectation, the reaction occurs at the *ortho* position with respect to the 6-methoxy group, and the addition of iodomethane to the reaction mixture affords 7-methyl derivative **185**.^{28, 233}

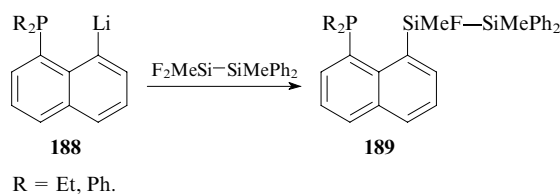


This anomalous situation remains to be explained. However, in the absence of HMPA and at higher temperature ($-10\text{ }^\circ\text{C}$), ethoxyvinyl lithium also adds to the naphthalene moiety of compound **186** at positions 1 and 2, and the treatment of the resulting compound with MeI and a hydrochloric acid solution yields 1,2-dihydronaphthalene **187**.²³⁴



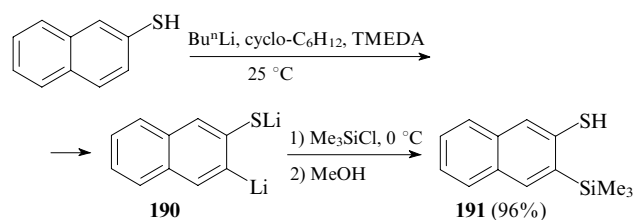
12. Metallation of phosphorylated naphthalenes

Data on organometallic derivatives of phosphorylated naphthalenes are scarce. For example, the use of 1-lithium-substituted 8-phosphinonaphthalenes **188** in the synthesis of pentacoordinate phosphodisilanes **189** was documented,²⁰⁶ however experimental details were not reported.

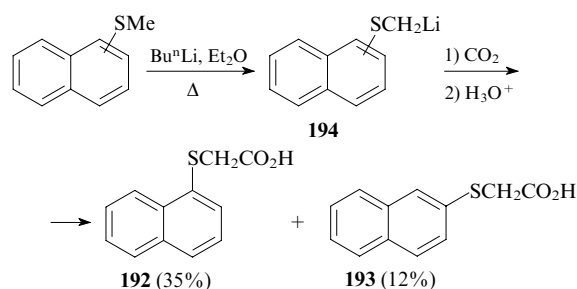


13. Sulfur-containing naphthalenes

Metallation of naphthalene-2-thiol with *n*-butyllithium affords solely 3-lithium derivative **190**, which was detected as compound **191**.²³⁵

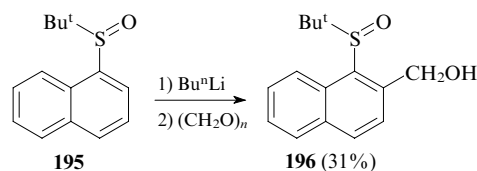


Metallation of 1- and 2-methylthionaphthalenes occurs at the methyl group, whereas the naphthalene ring remains intact, as evidenced by isolation of acids **192** and **193** after carbonisation of the reaction mixture. This is quite understandable because the sulfur atom better stabilises the adjacent carbanionic centre in compound **194** through the unoccupied 3d orbitals.

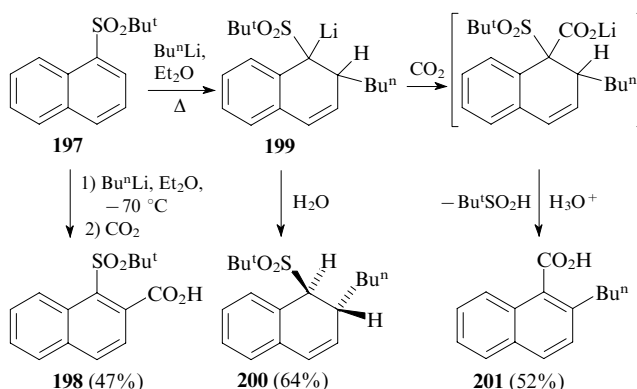


Nevertheless, 2-ethylthionaphthalene undergoes metallation at the ring, and carbonisation of the resulting compound affords 3-ethylthio-2-naphthoic acid.²³⁶

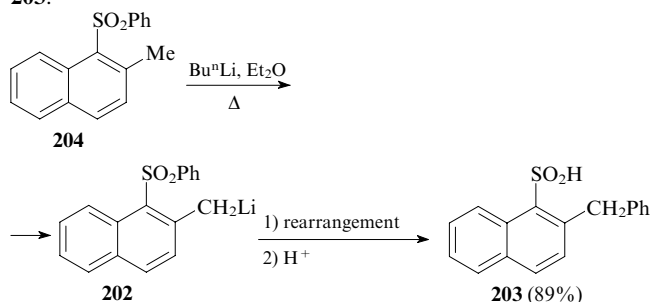
tert-Butyl 1-naphthyl sulfoxide (**195**) is metallated with *n*-butyllithium at the *ortho* position, which is confirmed by the isolation of alcohol **196** after the treatment of the mixture with paraformaldehyde.¹⁹⁹



At $-70\text{ }^\circ\text{C}$, *tert*-butyl 1-naphthyl sulfone (**197**) is metallated with Bu^nLi or MeLi to form the 2-lithium derivative, whose carbonisation affords carboxylic acid **198**.⁷¹ At high temperature, the reaction with MeLi proceeds analogously, whereas the reaction with Bu^nLi gives addition product **199**, which is transformed into either *trans*-1-*tert*-butylsulfonyl-2-butyl-1,2-dihydronaphthalene (**200**) or 2-butyl-1-naphthoic acid (**201**) depending on the subsequent treatment of the mixture (with H_2O or CO_2).



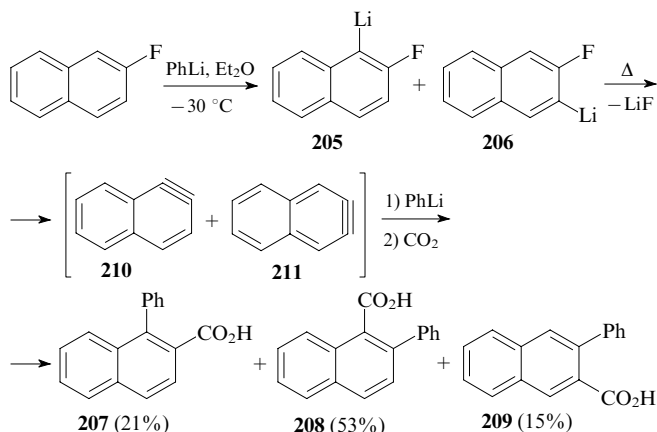
In the presence of the methyl group adjacent to the arylsulfonyl group, the initially formed benzyl-type anion **202** is rearranged into the corresponding benzylnaphthalenesulfinic acid **203**.²³⁷



In addition to sulfone **204**, the reaction was performed with 2-SO₂Ph-1-Me-, 2-SO₂Ph-3-Me and 1-SO₂Ph-8-Me-naphthalenes. Naphthalene-1-sulfamides undergo metallation at position 2.²³⁸

14. Halogen-containing naphthylmetals. Formation of dehydronaphthalenes

The following two types of halogen-containing naphthylmetals should be distinguished: compounds containing the metal and halogen atoms in the *ortho* positions with respect to each other and compounds in which these atoms are more distant from one another. In the former case, metallation giving rise to metal *o*-halonaphthalenes can be followed by elimination of metal halide to form 1,2- and 2,3-dehydronaphthalenes, which is facilitated by heating. Naphthyne can add a metallating agent at the triple bond. These compounds can also be trapped by special scavengers of the furan type. For example, the reaction of 2-fluoronaphthalene with phenyllithium produces a mixture of 1- (**205**) and 3-lithium derivatives (**206**), whose heating followed

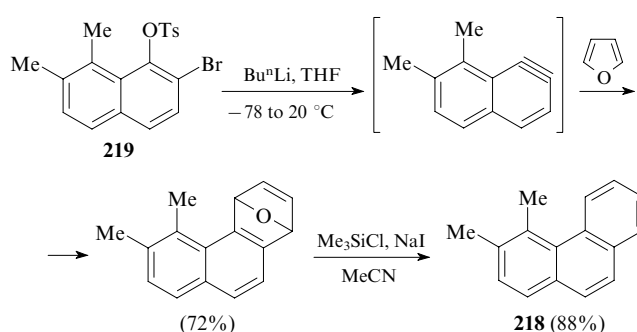


by treatment with CO₂ affords a mixture of naphthalenecarboxylic acids **207** – **209**.²³⁹

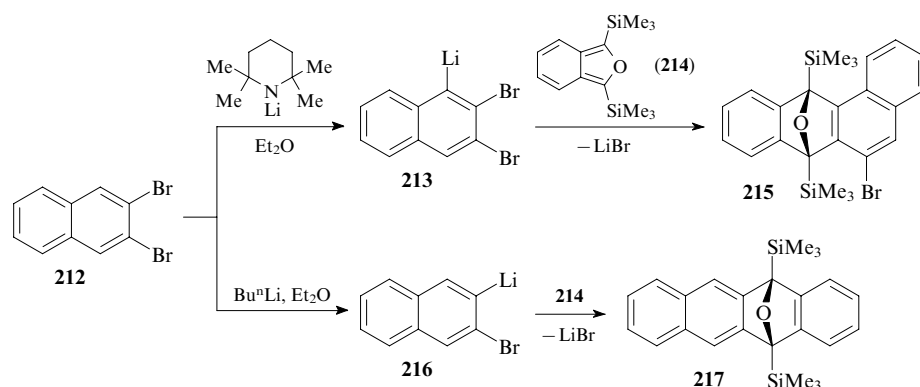
Evidently, acids **207** and **208** are derived from 1,2-naphthyne (**210**), whereas their isomer **209** is generated from 2,3-naphthyne (**211**). Under these conditions 1-fluoronaphthalene, as well as 1- and 2-chloronaphthalenes, behave analogously (although the reaction time in the case of the chlorides is substantially longer).²³⁹ Lithium alkyls^{81, 239} and lithium amides^{27, 240} can be used as metallating agents instead of phenyllithium although the specific features of each reagent should be taken into account. For example, the reaction of 2,3-dibromonaphthalene (**212**) with lithium tetramethylpiperidide results in CH-metallation giving rise to 1-lithium derivative **213**. After elimination of the LiBr molecule, the latter compound is transformed into 3-bromo-1,2-naphthyne, which gives compound **215** after the addition of isobenzofuran **214**. By contrast, the treatment of dibromide **212** with butyllithium affords 2-lithium 3-bromonaphthalene (**216**) as a result of metal – halogen exchange. In the presence of isobenzofuran **214**, the latter compound is transformed into tetracene derivative **217** through 2,3-naphthyne (**211**) (Scheme 15).

An analogous approach was successfully applied in the synthesis of 5,6,11,12-tetraphenylnaphthacene (rubrene) and its analogues starting from 2,3-dibromo-1,4-diphenylnaphthalene.⁸⁰

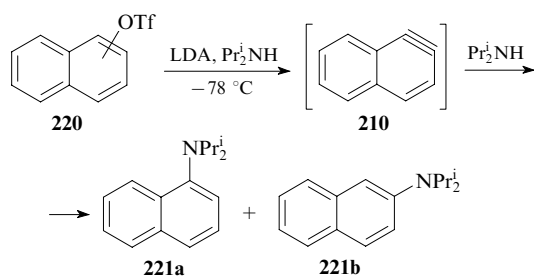
The introduction of the lithium atom at the *ortho* position with respect to good leaving groups, such as OTf or OTs, also leads to the formation of naphthyne.^{241, 242} The synthesis of 1,2-dimethylphenanthrene (**218**) from *o*-bromotoluenesulfonate **219** is a typical example.



To generate naphthyne from naphthyl triflates through CH-metallation, it is necessary to use strong low-nucleophilic bases (such as LDA). For example, the reactions of 1- and 2-naphthyl triflates (**220**) with LDA in an excess of diisopropylamine produce exclusively 1,2-naphthyne (**210**), which adds diisopropylamine to form 1- and 2-diisopropylaminonaphthalenes **221a** and **221b** in a total yield of 86 % in a ratio of 8 : 92.



Scheme 15



This reaction gives naphthalene as a by-product (7%–8%).²⁴³

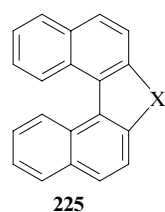
At rather low temperature (below -45°C), metal *o*-halonaphthalenes are quite stable and can be used in various standard transformations, for example, in the synthesis of 2-bromo-1-fluoronaphthalene from 1-fluoronaphthalene.⁸¹

Halogen-containing metal naphthalenes, in which the metal and halogen atoms are distant from each other (including *peri*-substituted compounds), have no specific features (see the reactions involving 1-MgBr-4-Br,¹¹¹ 1-MgBr-6-Br,¹ 1-MgBr-8-Br,^{7, 123} 1-MgBr-8-Cl¹²³ and 1-Li-4,5-F₂-naphthalenes²⁴⁴).

15. Metal derivatives of binaphthyls

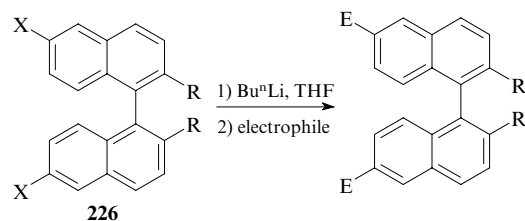
Organolithium and -magnesium derivatives are widely used for the synthesis of binaphthyls (see Section IV) and their functionalisation. The synthesis of 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP, **222a**) is a prominent example. This chiral ligand was used for the design of efficient metal complex catalysts for asymmetric hydrogenation.^{245, 246} Racemic or optically active dihalides **223** serve as the starting compounds in the synthesis of BINAP. These reagents are lithiated with BuⁿLi or BuⁿLi at low temperature,^{99, 247} and then the resulting dilithium derivative **42** is treated with diphenylchlorophosphine. The Grignard reagents can also be used. The latter are transformed into diarylphosphinyl derivatives **224**, which are reduced to the target compounds **222a–c** (Scheme 16).¹³² In the reactions of dihalides **223** with one equivalent of a metallating agent [BuⁿLi (see Ref. 247) or Mg (see Ref. 132)] followed by the treatment with an electrophile, only one-half of the molecule is subjected to functionalisation, which provides a route to unsymmetrically substituted 1,1'-binaphthyls.

Dinaphthoheterols **225** were synthesised by the reactions of dichlorosilanes, dichlorogermanes and other 1,1-bifunctional reagents with dilithium derivative **42**.²⁴⁸



X = SiMe₂, GeMe₂, PPh, AsPh, etc.

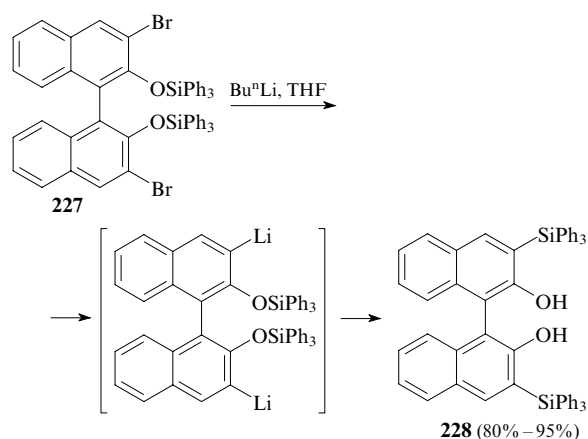
Other positions in 1,1'-binaphthyls are most often functionalised by metal–halogen exchange (for example, in the case of 6,6'-dihalides **226**^{249–253} or isomeric 4,4'-dihalides²⁵⁴).



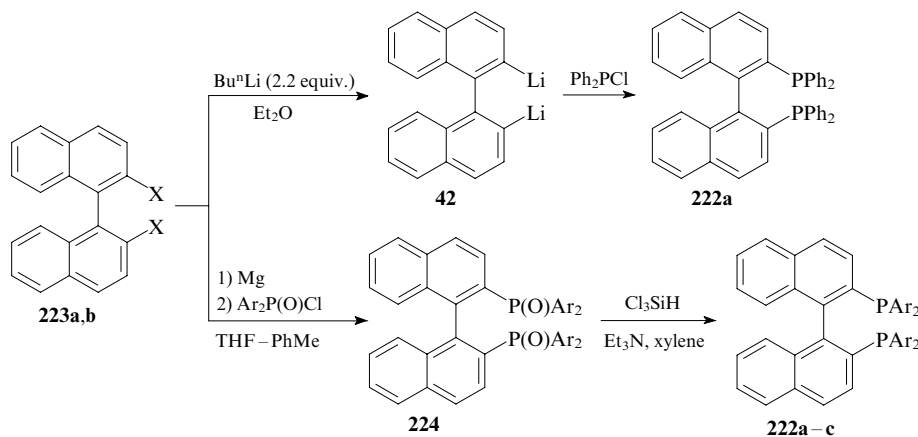
X = Br, I; R = H, OMe, OEt, OC₁₂H_{25-n}, OMOM;

E = I, CHO, CF₃, Me₃Si, B(OH)₂, etc.

Lithiation of 2,2'-bis(triphenylsilyloxy)-3,3'-dibromobinaphthyl (**227**) is accompanied by the migration of the Ph₃Si groups to positions 3 and 3' to form compound **228**.²⁵⁵

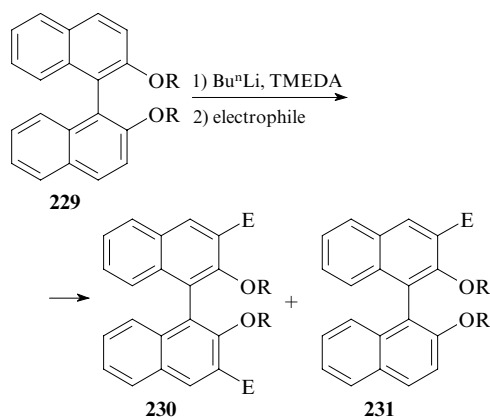


Scheme 16



X = Br (**223a**), I (**223b**); Ar = Ph (**222a**), 4-MeC₆H₄ (**222b**), 4-BuⁿC₆H₄ (**222c**).

Direct CH-lithiation of 2,2'-dialkoxy-1,1'-binaphthyls **229** was documented. Metallation occurs at positions 3 and 3', and the addition of an electrophile to the resulting compound affords compounds **230** (sometimes, with an impurity of monosubstituted product **231**).^{250, 256–264}

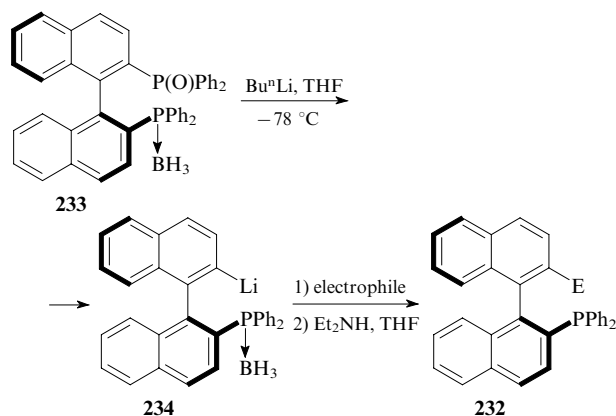


R = Me, Et, n-C₁₂H₂₅, MOM, C(O)NEt₂;

E = Hal, CHO, CO₂H, C(OH)Ph₂, B(OH)₂, etc.

It is interesting that lithiation of 2'-methoxy-1,1'-binaphthyl-2-carboxylic acid with BuⁿLi occurs at the *ortho* position with respect to the carboxy group.²⁶⁵

Hayashi and co-workers²⁶⁶ developed a procedure for the synthesis of optically pure 2'-substituted 2-diphenylphosphino-1,1'-binaphthyls **232**. This method is based on the treatment of the phosphine borane complex **233** with an excess of BuⁿLi giving rise to monolithium derivative **234**, whose treatment with electrophiles affords binaphthyls **232** in good yields.



E = D, I, SiMe₃, SnMe₃, etc.

The use of compounds containing the PPh₂ or P(O)Ph₂ groups instead of PPh₂·BH₃ as the starting reagents give worse results.

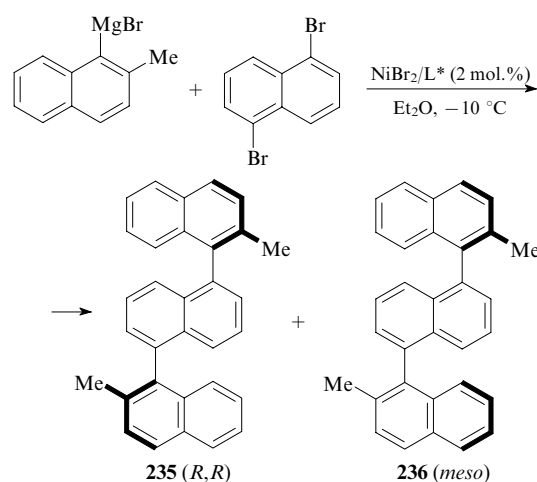
IV. Naphthylmetals in cross-coupling reactions

In recent years, organolithium and -magnesium compounds of the naphthalene series have been widely used in cross-coupling reactions, primarily, for the synthesis of binaphthyls, polynaphthyls and arynaphthalenes. There are several general approaches to these reactions. These approaches are based on catalytic, non-catalytic and oxidative cross-coupling of metal naphthalenes. The main catalytic methods are based on (1) Kumada cross-coupling,²⁶⁷ in which aryl halides (including naphthylmagnesium halides) are used, (2) Negishi cross-coupling (recent publications were summarised in the study²⁶⁸), (3) Stille cross-coupling²⁶⁹ and (4) Suzuki cross-coupling.²⁷⁰ In the last three methods, organo-

series are used, respectively, as the starting compounds. Although only the Kumada method is within the scope of the present review, it should be remembered that the synthesis of Zn, Sn and B derivatives of naphthalene generally involve the use of lithium-substituted naphthalenes in earlier steps.

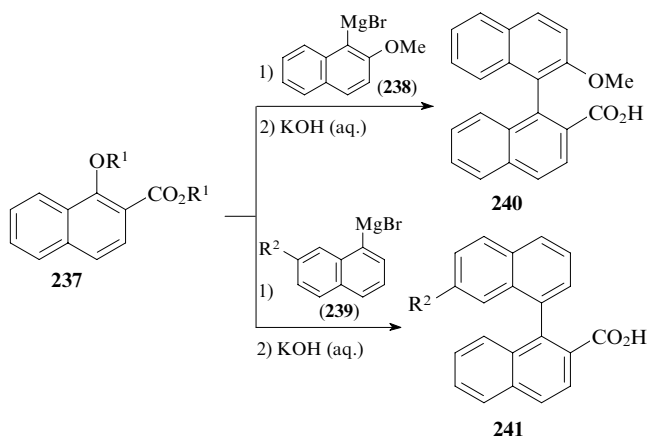
1. Catalytic reactions

The application of the Kumada reaction in the synthesis of binaphthyls was described above (see Scheme 11). In the presence of the chiral ferrocenylphosphine nickel catalyst, which was prepared *in situ* from nickel bromide and (*S*)-1-[(*R*)-2-(diphenylphosphino)ferrocenyl]ethyl methyl ether (L*), this reaction proceeds with high enantioselectivity (95%–98% *ee*) and produces chiral binaphthyls,^{271, 272} ternaphthalenes²⁷³ and arynaphthalenes.²⁷⁴ For example, the reaction of 2-methyl-1-naphthylmagnesium bromide with 1,5-dibromonaphthalene gives ternaphthalene **235** and its *meso* isomer **236** in a ratio of 84:16 in a total yield of 89%. (Similar results were obtained for 1,4-dibromonaphthalene.²⁷³)



2. Non-catalytic reactions

The synthesis of 1,1'-binaphthyls by Meyers's reaction (see Section III.1.1, the synthesis of compound **179**) is a typical example of non-catalytic transformations. The Japanese chemists successfully used 1-alkoxy-2-naphthalenecarboxylates **237** as the substrates.^{275–277} It was demonstrated that if the group R¹ in compound **237** is rather bulky (for example, Prⁱ), organometallic reagents **238** or **239** do not virtually attack the ester group; instead, 1,1'-binaphthyls **240** or **241** are generated in high yield.



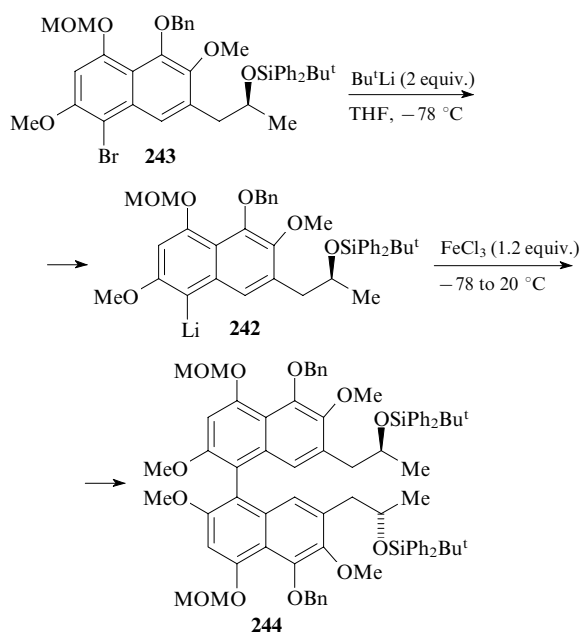
R¹ = Alk, Ar; R² = H, OMe.

If the substituent R¹ is chiral (for example, menthyl), stereochemical induction takes place, and the reaction affords

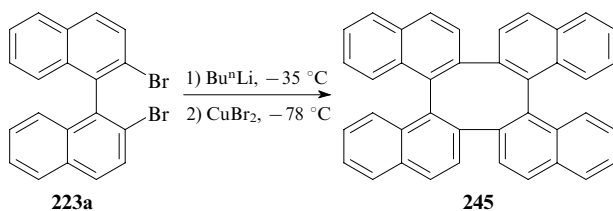
binaphthyl with high optical purity. Other modifications of these reactions were described in the publications.^{278, 279}

3. Oxidative coupling

Several procedures were developed for oxidative cross-coupling of naphthalenes with the aim of preparing binaphthyls. One of these methods is based on the direct reaction of oxidising agents with naphthylmetals. The advantage of this method is high activity of the latter compounds, which allows one to perform the synthesis at low temperature, thus preventing racemisation and retaining labile substituents in the substrate. For example, naphthyllithium **242**, which was prepared from bromide **243**, was transformed into binaphthyl **244** under the action of FeCl₃, and compound **244** was used for the synthesis of the phytotoxic plant pigment phlei-chrome.²⁸⁰

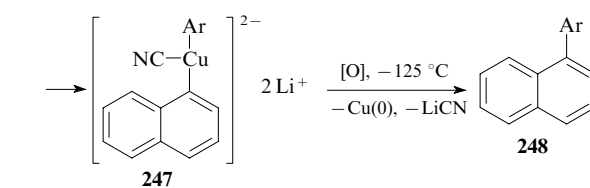
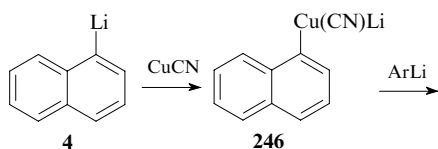


In addition to FeCl₃, cobalt and copper chlorides were tested as oxidising agents but with less success. It should be noted that 2,2'-dilithio-1,1'-binaphthyl (**42**), which was prepared from dibromide (*R*)-(+)-**223a**, was oxidised with CuBr₂ to form cyclooctatetraene derivative (*R*)-(+)-**245** in 16% yield with 90% *ee*.²⁸¹



An efficient procedure for the synthesis of biaryls (including arynaphthalenes and binaphthyls) is based on the transformation of lithium-substituted naphthalenes into cuprates followed by their oxidation.^{282, 283}

For example, the reaction of 1-naphthyllithium (**4**) with monovalent copper cyanide produces cuprate **246** (lower order cuprate). The reaction of the latter with another lithium aryl affords higher order cuprate **247**, whose oxidation with oxygen at low temperature gives the target compounds **248** generally in good yield.



Ar = 2,6-Me₂C₆H₃ (72%), 3-F-4-MeC₆H₃ (76%),
1-C₁₀H₇ (82%), 2-MeO-1-C₁₀H₆ (80%).

A considerable advantage of this reaction is that it is insensitive to steric factors and can be used for the preparation of highly functionalised compounds. It is interesting that the best results were obtained with the use *tert*-butyllithium for the synthesis of 1-naphthyllithium from 1-bromonaphthalene.

V. Conclusion

The above discussion demonstrated that organolithium and organomagnesium compounds of the naphthalene series find increasing application in organic synthesis. This refers to both rather simple functionalisations and the synthesis of various compounds with very complex structures. In many cases, the synthetic methods based on the reactions of lithium and magnesium naphthalenes provide the only route to the target compounds as, for example, in the synthesis of naphthylboronic acids, substituted binaphthyls, numerous *peri*-disubstituted naphthalenes and, particularly, polyfused systems containing small *peri*-rings. It should be noted that a search for new directing groups with the aim of increasing the selectivity of CH-metallation of the naphthalene ring, the development of convenient procedures for metal-halogen exchange in chloronaphthalenes, investigation of the structures of organometallic compounds and, in particular, of the nature of the so-called 'agostic interactions' and the further development of cross-coupling reactions of these compounds are still of importance in this field of science.

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Optically active supramolecular systems based on porphyrins

V V Borovkov, N Zh Mamardashvili, Y Inoue

Contents

I. Introduction	1
II. 'Host–guest' systems based on monomeric porphyrins	1
III. 'Host–guest' systems based on dimeric and oligomeric porphyrins	5

Abstract. The published data on supramolecular complexes of porphyrins with optically active organic molecules are systematised. The key principles, mechanisms and driving forces of complexation and factors responsible for effective control over formation of supramolecular systems are considered. The bibliography includes 105 references.

I. Introduction

Among the immense diversity of 'host–guest' interactions, complexation of tetrapyrrole chromophores with chiral organic molecules has recently received considerable attention.^{1–27} The interest in these processes is largely determined by the necessity of identification and separation of chiral biologically active substrates. Porphyrins with rigid macrocycles and predetermined arrangement of substituents that specifically interact with different types of 'guest' molecules are ideally suited for the solution of this problem.

Mutual arrangement of porphyrin fragments in a supramolecular system can be controlled by chemical modifications of the macrocycle or by change in the solvent polarity. The relative positions of tetrapyrrole chromophores change during host–guest complex formation, exciton interactions appear between their π -electronic systems, which is accompanied by the corresponding spectral changes. This allows the successful use of diverse spectral analytical methods for the study of intermolecular interactions.

The examples of porphyrin-based host–guest systems documented in the literature illustrate the broad potential of their practical applications. However, no adequate rationale for the electronic or structural factors that control the complexation is available so far.

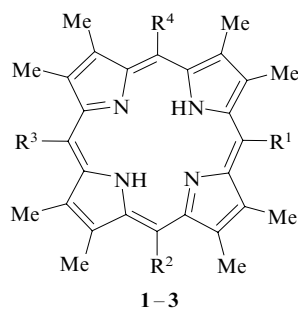
This review is the first generalisation and analysis of the results of investigations into porphyrin-based optically active supramolecular systems published over the past decade. The main principles, mechanisms and driving forces involved in the for-

mation of supramolecular systems and factors that efficiently control this process are considered.

II. 'Host–guest' systems based on monomeric porphyrins

Optically active host–guest systems based on monomeric porphyrins are conventionally divided into two main types, *viz.*, systems with achiral or racemic porphyrins ('hosts') that interact with optically active guest molecules and systems based on chiral porphyrins. The formation of supramolecular systems can be detected by various spectral analytical methods.

Host–guest systems based on monomeric porphyrins possess interesting properties. Thus fully substituted porphyrins **1–3** with a saddle-shaped structure of the macrocycle as a result of steric repulsion between neighbouring substituents exist in the form of two enantiomers; their interconversions yield a racemic mixture. This equilibrium can be shifted towards the formation of a particular structure (*de* > 98%) upon interaction with mandelic acid enantiomers.^{28, 29} This interaction involves the formation of H-bonds between the carboxy groups of the acid and the nitrogen atoms in the pyrrole fragments of the porphyrin macrocycle. The supramolecular host–guest complexes formed (1:2) possess a strong induced circular dichroism (CD) signal in the region of the Soret band. The sign of the CD signal correlated with the absolute configuration of the chiral centre of the guest. An interesting property of porphyrins **1–3** is their ability to retain the induced optical activity upon substitution of achiral acetic acid for chiral mandelic acid.



1: $R^1 = 2,6-(\text{MeO})_2\text{C}_6\text{H}_3$, $R^2 = R^3 = R^4 = \text{Ph}$;

2: $R^1 = R^3 = 2,6-(\text{MeO})_2\text{C}_6\text{H}_3$, $R^2 = R^4 = \text{Ph}$;

3: $R^1 = R^2 = R^3 = 2,6-(\text{MeO})_2\text{C}_6\text{H}_3$, $R^4 = \text{Ph}$.

V V Borovkov, Y Inoue Osaka University, Entropy Control Project, Japan Science and Technology Agency, Kamishinden 4-6-3, Toyonaka-shi, 5600085 Osaka, Japan. Fax (81-6) 6836 16 36, tel. (81-6) 6836 00 63, e-mail: victrb@inoue.jst.go.jp (V V Borovkov), inoue@chem.eng.osaka-u.ac.jp (Y Inoue)

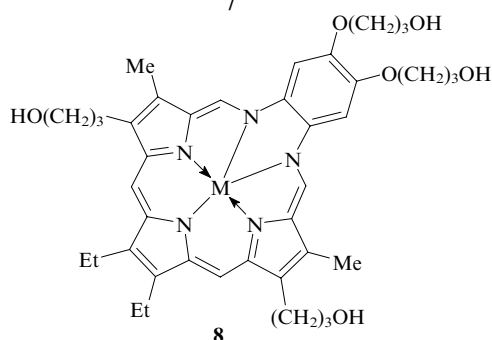
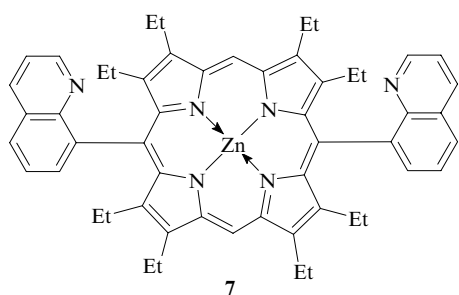
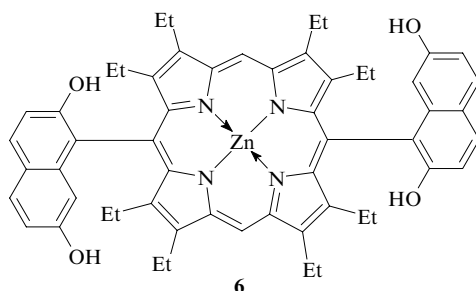
N Zh Mamardashvili Institute of Solution Chemistry, Russian Academy of Sciences, ul. Akademicheskaya 1, 153045 Ivanovo, Russian Federation. Fax (7-493) 233 62 37, tel. (7-493) 233 69 90, e-mail: ngm@isc-ras.ru

Received 21 February 2006

Uspekhi Khimii **75** (8) 820–832 (2006); translated by R L Birnova

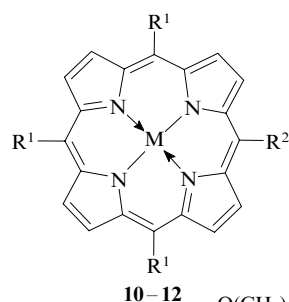
Among ten disaccharides tested, only lactulose is selectively bound to the porphyrin receptor **4**. The position of the hydroxy groups of the carbohydrate matches that of two boronic acid

4



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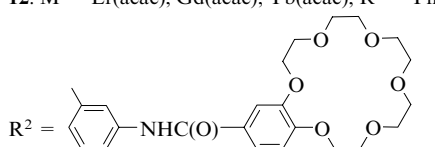
Porphyrin receptors **10** were designed³⁵ for specific binding of amines and amino acid esters. They should be used as esters in non-polar organic solvents and as acids in aqueous media. In organic solvents, the complexation is achieved due to coordination of the amino group of the amino acid by Zn of the porphyrin macrocycle (the enthalpy factor). In aqueous media, competitive binding of solvent molecules to Zn weakens the coordination interactions between host and guest molecules. Under these conditions, dispersion interactions between the long methylene chains of the host and the hydrophobic side substituent of the guest favour the complexation (the enthalpy factor). Dehydration of the interacting surfaces of the host and guest molecules is the principal factor that governs complexation in aqueous media (the entropy factor).



(X = H, Me; $n = 1, 4, 10$);

11: M = Gd(acac), $R^1 = R^2 =$ 

12: M = Er(acac), Gd(acac), Yb(acac); R¹ = Ph,

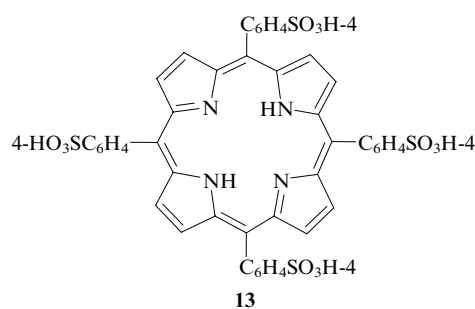


acac is acetylacetonate.

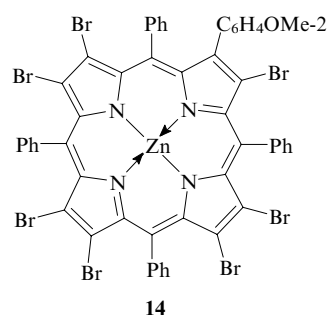
The recognition of optically active zwitter-ionic amino acids was studied in a two-phase system 'organic solvent – water'.³⁶ The amino acids were extracted from the aqueous phase using porphyrins **11**, which formed (1 : 1) complexes with the amino acids. The CD spectra of the resulting complexes manifested two well-resolved signals corresponding to the split Soret band. The magnitude of the molar amplitude of CD (*A*) strongly depended on the nature of the solvent and the substituents in the porphyrin and amino acid molecules, while the sign of the induced CD signals was determined by the chirality of the amino acid. The porphyrin containing di-*tert*-butylphenyl groups manifested the highest sensitivity in aromatic solvents. This method was proposed for determination of absolute configurations of α -amino acids.

Later, the sensitivity of the method was increased through incorporation of a crown-ether fragment into the porphyrin receptor **12**.³⁷ Simultaneous coordination of the CO₂⁻ group of the amino acid in the lanthanide reaction centre of porphyrin, the interaction of the NH₃⁺ group with the crown-ether fragment and the adequate choice of the coordinating metal increase significantly the extraction potential of the receptor and, as a consequence, the magnitude of the molar amplitude *A*.

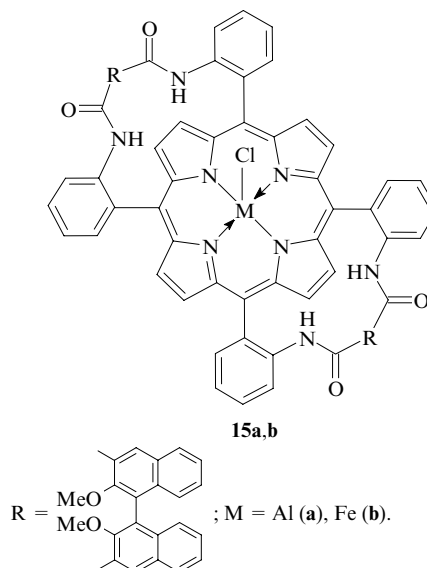
Solid-phase optical detection based on the registration of the hypsochromic shifts in the visible region of the absorption spectrum of porphyrin **13** immobilised as a monolayer on a cellulose film was used for the recognition of amino acids.³⁸ The magnitude of the hypsochromic shift depends on the structure of the amino acid, which makes it possible to quantitatively determine amino acids in solutions.



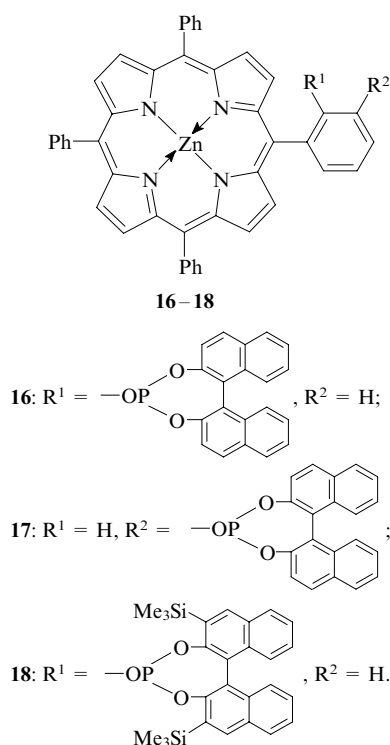
There is an ample body of data on supramolecular systems in which both hosts and guests possess optical activities. Chiral recognition in such systems is based on three-dimensional structural matching of both molecules according to the 'key–lock' principle and intermolecular binding usually involves three centres. Ideally, only one out of two enantiomeric forms of the guest is bound efficiently to the host molecule to form a stable complex, whereas binding of the other enantiomeric form is much weaker. The difference in the binding strength can be established by different spectral methods. For example, two diastereomeric complexes formed by chiral non-planar porphyrin **14** and (*S*)-2-pyrrolidinemethanol owing to coordination and hydrogen bonds could be identified by ¹H NMR spectroscopy.³⁹



A direct correlation was found⁴⁰ between the enantioselectivities of complexation and catalytic oxidation. The chirality of the metal complexes of the 'strapped' porphyrin derivatives **15a,b** studied was due to steric hindrance to rotation of two binaphthyl fragments around the C(1)–C(1') bonds. The aluminium complex **15a** bound chiral epoxides and alcohols. Distinct differences between the electronic absorption spectra of complexes upon binding of enantiomers enabled determination of the complexation constants by spectrophotometric titration. The corresponding iron complex **15b** catalysed, with high efficiency and enantioselectivity, the epoxidation of non-functionalised alkenes. A linear relationship between the changes in the free energies of complexation and catalytic epoxidation suggests that both processes follow similar stereoselective mechanisms.



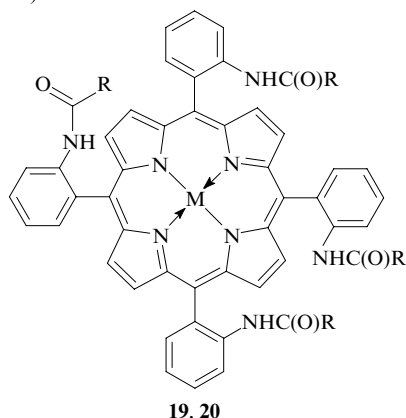
Porphyrins **16–18** possessing optical activities due to the 1,1'-binaphthyl fragments react with various phosphorus-containing chiral and achiral ligands. The complexes formed were used as



supramolecular bidentate templates in the palladium-catalysed asymmetric allylic alkylation of racemic 1,3-diphenylpropen-2-yl acetate with dimethyl malonate as a nucleophile. It was found⁴¹ that the enantioselectivity of alkylation was determined not only by absolute configurations of porphyrin receptors and ligands, but also by structural features of the porphyrins, *e.g.*, bulkiness (the introduction of the SiMe₃ groups into porphyrin **18**) and arrangement of the binaphthyl substituent in the *ortho*- and *meta*-positions of porphyrins **16** and **17**.

5,10,15,20-Tetraphenylporphyrin derivatives **19** containing L-amino acids in the *ortho*-positions of the phenyl substituents formed (1 : 2) complexes with carbohydrates.⁴² The fact that these porphyrins did not exceed tetrakis(decyl)-substituted receptors (**19**, R = NHC₁₀H₂₁-n) in binding capacity suggests the predominant contribution of urea fragments to H-bonding with the OH groups of carbohydrates.

A chiral derivative of ruthenium tetraphenylporphyrin complex **20** with optically active groups on both sides with respect to the porphyrin plane (the $\alpha,\beta,\alpha,\beta$ -isomer) recognises enantiomers of amino acid esters. The binding of valine methyl ester by the ruthenium complex **20** occurred with the highest enantioselectivity and it was the L-enantiomer that was predominantly bound (*ee* 66%).^{43, 44}

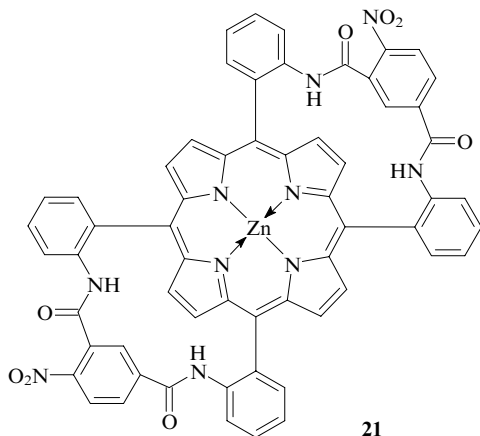


19, 20

19: M = 2H, Zn; R = L-ValOMe, L-ThrOMe, L-TrpOMe, NHC₁₀H₂₁-n;
20: M = RuO₂, Zn; R = C(OMe)(CF₃)Ph.

The zinc complex of the $\alpha,\beta,\alpha,\beta$ -isomer of porphyrin **20** efficiently recognised the *S*-enantiomer of bulky 1-(1-naphthyl)ethylamine; the ratio of the binding constants was $K_S/K_R = 2.4$.⁴⁵

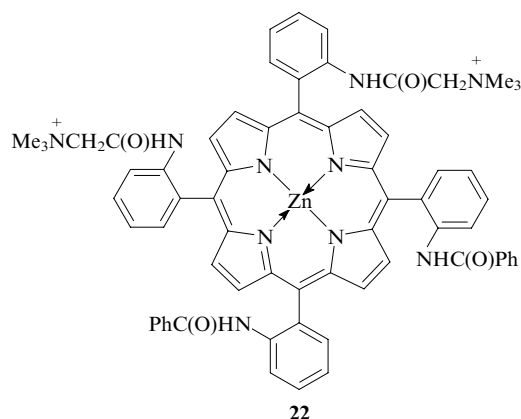
The stereoselectivity of the binding of D-valine methyl ester reached $K_D/K_L = 7.5$ when bridged chiral metalloporphyrin **21** was used. The preferential supramolecular complex was stabilised due to coordination and H-bonding of the carbonyl group of the guest with the amide group in the isophthalalyl fragment of the host.⁴⁶



21

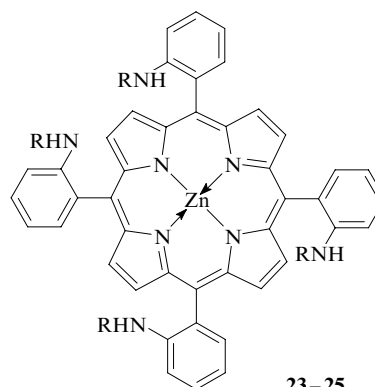
Thermodynamic analysis of the complexation revealed that the conformational freedom of the guest was largely lost as early as in the coordination step. The enthalpy factor that takes into account the formation of hydrogen bonds was suggestive of stabilisation of the complex as a whole.⁴⁶

Both enantiomers of *C*₂-symmetric chiral water-soluble porphyrin **22** were used for enantioselective recognition of a series of amino acids and dipeptides in alkaline aqueous solutions. The stereoselectivity was effected by virtue of coordination of the NH₂ group by the Zn atom, Coulomb attraction between the carboxylate anion and the cationic ammonium group and steric interactions between the side group of the amino acid and the phenyl group of the *ortho*-substituent of porphyrin.⁴⁷



22

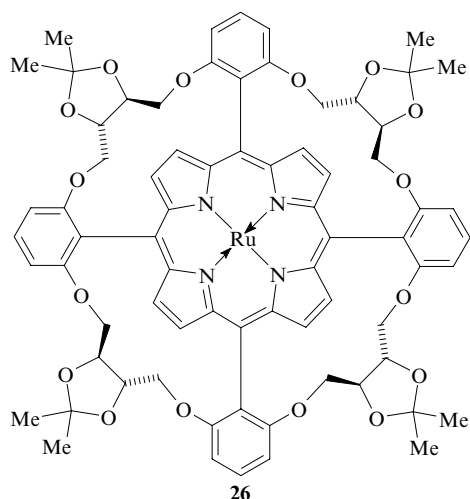
The most efficient recognition of amino acid esters by porphyrins modified by amino acids (complexes **23–25**) has been described.⁴⁸ Thus the enantioselectivity of binding of D-phenylalanine methyl ester reached the value of $K_D/K_L = 21.54$ and showed an exponential dependence on temperature. Diastereomeric complexes exhibited different CD spectra. Thus the CD spectrum of porphyrin **23** weakly bound to L-alanine methyl ester was similar to that of free porphyrin **23** and contained a single negative Cotton effect in the Soret band region. On the other hand, the strong complex with D-alanine methyl ester possessed a split signal owing to exciton interactions between porphyrin and the carbonyl group of the amino acid.



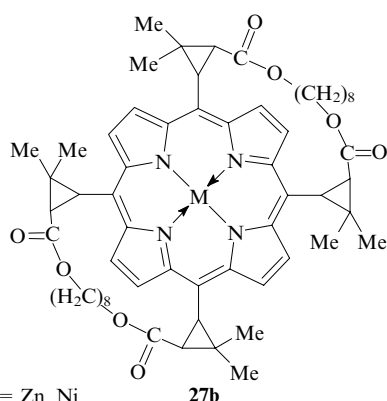
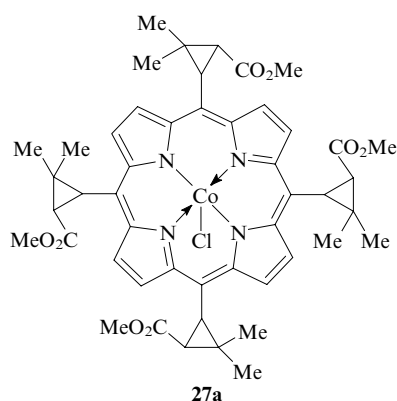
23–25

R = BocAla (**23**), BocPro (**24**), BzGln (**25**); Boc = Bu^tOC(O).

The crucial importance of the three-centre model in chiral recognition was corroborated by low (*ee* 15%) binding stereoselectivity of racemic isocyanides by the Ru porphyrin complex **26**. This receptor was able to coordinate ligands, but had no additional centres for H-bonding.⁴⁹

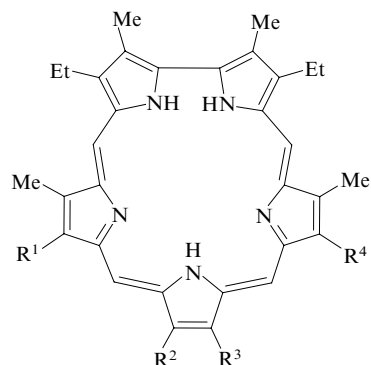


X-Ray diffraction analysis and ^1H NMR spectroscopy of chiral cobalt porphyrin complex **27a** revealed that the combination of one coordination interaction and two hydrogen bonds enabled efficient enantioselective recognition of amino alcohols and amino acid esters.^{50–54} Moreover, cobalt porphyrin complex **27a** can be used for determination of enantiomeric excess in primary amines and aziridines by ^1H NMR spectroscopy.⁵³ A dependence of the conformation of the macrocycle on the nature of the central metal ion was established for metalloporphyrins **27b**; the $\alpha,\alpha,\alpha,\alpha$ -conformation was changed to the $\alpha,\beta,\alpha,\beta$ -conformation upon substitution of Ni for Zn.⁵⁴



M = Zn, Ni.

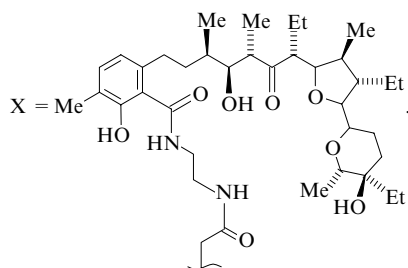
Different chiral porphyrin derivatives are also used for binding of optically active compounds. Thus the lasalocid–sapphyrin conjugates **28–30** were used for the transfer of aromatic amino acids from one aqueous phase to another through an organic layer.⁵⁵ The mechanism of this reaction includes formation of a stable supramolecular ensemble of the host molecule with the zwitterionic form of the amino acid by virtue of electrostatic interaction of the carboxylate anion with protonated sapphyrin and formation of H-bonds between the NH_3^+ group of the amino acid and the ionophore fragment of lasalocid.



28: $\text{R}^1 = \text{R}^4 = \text{Et}$, $\text{R}^2 = \text{Me}$, $\text{R}^3 = \text{CH}_2\text{X}$;

29: $\text{R}^1 = \text{X}$, $\text{R}^2 = \text{R}^3 = \text{Et}$, $\text{R}^4 = \text{CH}_2\text{C}(\text{O})\text{PheO}^-\text{Bu}^t$;

30: $\text{R}^1 = \text{X}$, $\text{R}^2 = \text{R}^3 = \text{Et}$, $\text{R}^4 = \text{CH}_2\text{C}(\text{O})\text{PheOH}$;

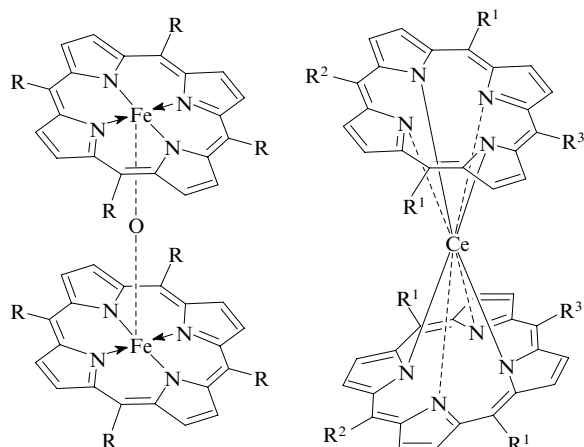


III. 'Host–guest' systems based on dimeric and oligomeric porphyrins

The above-cited examples of host–guest systems based on monomeric porphyrins demonstrate broad potential for their practical application. However, very often efficient functioning of monomeric porphyrin receptors is impossible without a synergetic support by one or several porphyrins. This stimulates the construction of novel chirogenic host–guest ensembles based on dimeric and oligomeric porphyrins. Such systems are classified according to the presence of a chiral fragment and the number of porphyrin macrocycles in the host molecule and the type of the covalent bridge.

First, let us consider the ensembles consisting of achiral or racemic bisporphyrin hosts and optically active guests. An achiral bisporphyrin molecule should possess at least two reaction sites and a flexible covalent bridge in order to adopt a stereospecific three-dimensional conformation upon interaction with chiral guest molecules. Then a supramolecular chiral ensemble is formed.

Double-decker bisporphyrins **31–38** linked 'centre-to-centre' were designed for binding of miscellaneous guest molecules.^{56–61}



31, 32

33–38

31: R = C₆H₄B(OH)₂-3; 32: R = C₆H₄B(OH)₂-4;

33: R¹ = R² = R³ = 4-Py;

34: R¹ = Ph, R² = R³ = 4-Py;

35: R¹ = 3,5-(MeO)₂C₆H₃, R² = R³ = 4-Py;

36: R¹ = 4-MeOC₆H₄, R² = R³ =

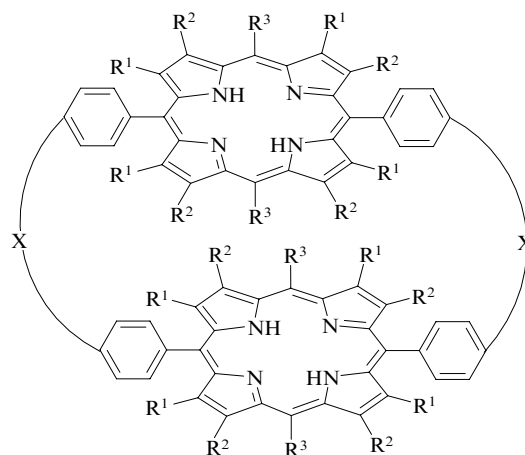
37: R¹ = R² = 4-MeOC₆H₄, R³ =

38: R¹ = 4-MeOC₆H₄, R² = R³ =

The association mechanism involves the interaction of a bidentate guest with two complex-forming groups of adjacent porphyrins, which brings about twist of the porphyrin macrocycles around the central axis to the left or to the right depending on the stereochemistry of the guest molecule. This asymmetric twist results in changes in the interporphyrin exciton interactions and induction of optical activity in the region of absorption of the porphyrin. The induced optical activity retained for 3 days at 0 °C and over one year at –37 °C. The host–guest complexation occurred with a high degree of cooperativity, manifesting a positive allosteric effect; the characteristics of the CD signals strongly depended on the structure of the guest molecule,^{56,57} the nature of the solvent⁶¹ and pH.⁶⁰

Bisporphyrin systems **31**, **32**, **36** and **37** containing boronic acid were successfully employed for the recognition of carbohydrates; the dimers containing pyridyl substituents (**33–35**) were used for the binding of chiral dicarboxylic acids, while cationic bisporphyrin **38** interacted with dianions. Bisporphyrin receptor **35** possessed an ability of memorising chirality. Interestingly, bisporphyrin **36** interacts with glucose oligomers as guests, and the sign of optical activity of the complex changes depending on the number of monosaccharide units.⁵⁹

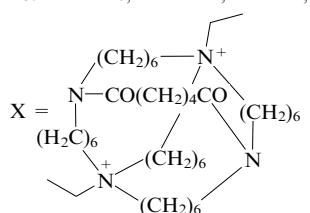
‘Face-to-face’ bisporphyrins **39** and **40** linked by covalent cryptand-containing bridges between the opposite positions of the macrocycles efficiently bind trisaccharides in aqueous solutions, predominantly by encapsulation.⁶² Very weak induction of CD in the region of the Soret band is observed due to the inability of bisporphyrins to change their conformations depending on the stereochemistry of guest molecules because of structural rigidity of the cryptand-containing bridges.



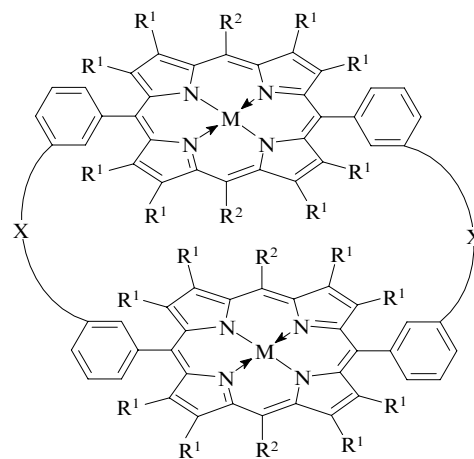
39, 40

39: R¹ = R² = H, R³ = C₆H₄Me-4;

40: R¹ = Me, R² = Prⁿ, R³ = H;



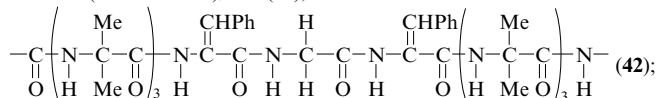
Dimers **41** and **42** containing flexible covalent bridges manifested good structural matching to bidentate pyridyl-anchored chiral peptides of appropriate lengths. As a result, stable inclusion complexes (1:1) with association constants of the order of $2.3 \times 10^6 \text{ M}^{-1}$ are formed. It was found that the helical structure of the guest plays a key role in the transcription of chiral information by inducing strong exciton interactions in the Soret absorption band.⁶³



41–43

M = Zn, R¹ = H, R² = 2,4,6-Me₃C₆H₂;

X = CO(NHMeCO)₉NH (**41**),



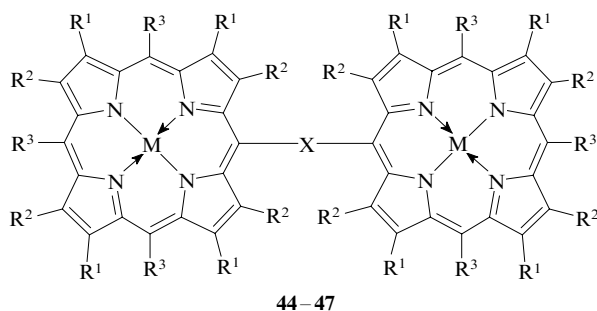
M = 2H, R¹ = Me, R² = 2,6-(MeO)₂C₆H₃,

X = 4-OCH₂C₆H₄CH₂O-4 (**43**).

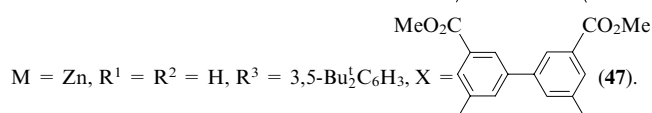
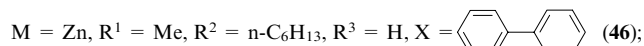
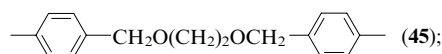
Bisporphyrin **43** with shorter *para*-xylylene bridges was used for the complexation with mandelic acid. This resulted in a significant (more than sevenfold) enhancement of a CD signal ($A = 260 \text{ cm}^{-1} \text{ M}^{-1}$) in comparison with the complex based on monomeric porphyrin. This effect is due to induction of helical chirality upon forced changes in mutual arrangement of both porphyrin rings in the course of formation of the supramolecular ensemble. Increasing concentrations of guest molecules triggered complex changes in the CD spectra manifested as multistep equilibrium. Such systems present interest as candidate chirality sensors for the study of stereochemistry of interacting guest molecules.⁶⁴

Yet another structural type of bisporphyrins is based on combination of two chromophores linked through a single bridge. In this case, the mutual arrangement of the porphyrin macrocycles is less predictable because of lesser rigidity of the system. The complexation with a bidentate guest molecule can favour approach of the porphyrin moieties to each other and their fixation in the 'face-to-face' mode.

Lanthanide-containing bisporphyrins **44** and **45** linked through ether bridges of various lengths provide examples of such systems. These dimers were obtained as potential host molecules for binding cystine polyions.⁶⁵ The selectivity of recognition is largely determined by the size of the optically active guest molecules. Thus ytterbium bisporphyrin complex **44** with a short bridge effectively extracted cystine from aqueous solutions into the organic phase, but not cystathionine, homocystine or methionine. In contrast, bisporphyrin **45** effected preferential extraction of more extended homocystine. The formation of 'tweezers'-like 1:1 complexes was accompanied by the appearance of a complex CD signal in the Soret band region; its intensity was notably increased in comparison with the signal of the monomeric complex.



M = Yb(acac), Gd(acac); $R^1 = R^2 = \text{H}$; $R^3 = \text{Ph}$:

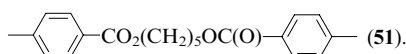
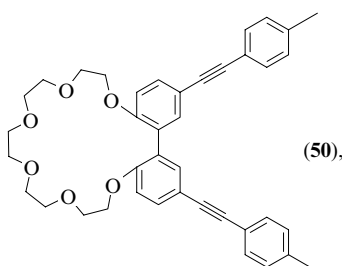
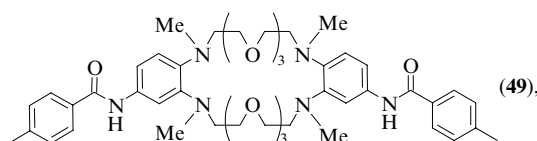
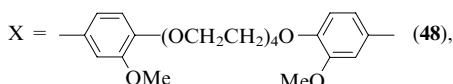
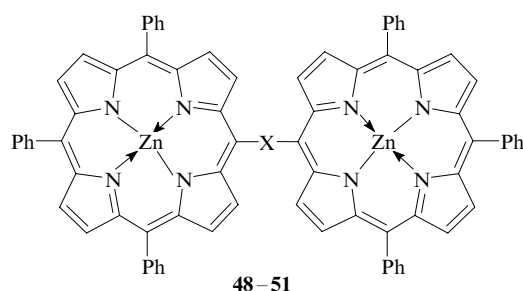


High binding selectivity of chiral diamines by bisporphyrins **46** and **47** linked through rigid bridges was reported.⁶⁶ The matching of the distance between the zinc atoms of the porphyrin macrocycles to the length of the chain linking two NH_2 groups of the guest is a prerequisite for efficient complexation. The highest association constant ($K_a = 2.4 \times 10^6 \text{ M}^{-1}$) was found for the pair dimer **47**-cystine ethyl ester. The induced CD signal strongly depended on the bulkiness of the peripheral substituents in the porphyrin macrocycles and temperature. Thus the molar ampli-

tude A increased 1.5-fold with a decrease in temperature down to -45°C .

The feasibility of control over bisporphyrin conformation increased substantially upon introduction of a crown-ether-type linkage into the host molecule by virtue of specific binding of the crown-ether fragment to alkali metal ions.⁶⁷⁻⁶⁹ Thus the addition of Na^+ ions to the bisporphyrin **48**-*trans*-1,2-diaminocyclohexane system caused a nearly twofold increase in the association constant due to the change in the bisporphyrin geometry and a concomitant significant increase in the molar amplitude A of the induced CD signal.⁶⁷

A similar effect was observed in the interaction of bisporphyrin **49** with *N*-alkyl-1,2-diaminocyclohexane.⁶⁸ However, in this case the formation of a complex with a larger crown-ether cavity required larger K^+ ions. Bisporphyrin **49** recognised the chirality of potassium camphorates and mandelates.



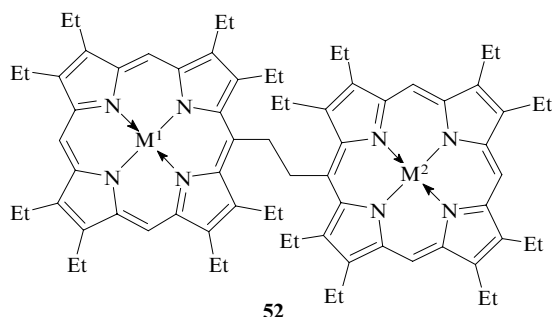
The chirality of porphyrin **50** in a 'tweezers' conformation which is conferred on it by its interaction with an optically active diamine, is retained after replacement of the chiral ligand by an achiral one in the presence of Ba^{2+} ions. The intensity of the CD signal in this particular system decreased only slightly within 24 hours.⁶⁹

The 'tweezers'-like systems discussed above manifest high optical activities due to asymmetric spatial arrangement of two porphyrin chromophores. However, no detailed interpretation of electronic and structural factors responsible for this phenomenon has been given so far. In a series of studies,⁷⁰⁻⁸⁰ attempts were undertaken to solve this problem using flexible bisporphyrin **51** that adopts 'tweezers'-like conformation upon complexation with bidentate ligands.

Presumably,⁷⁰⁻⁸⁰ optical activity observed in the formation of supramolecular systems results from the stereospecific differentiation of the relative bulkiness of substituents at the chiral carbon atom of the guest owing to the ability of bisporphyrin to adopt the sterically least hindered conformation. The factors that influence the geometry of the ensemble, *e.g.*, H-bonding, the presence of

heteroatoms, the nature of the solvent, *etc.*, should also be taken into consideration. The sign of the induced CD signal upon exciton interactions of two chiral tetrapyrrole fragments of bisporphyrin **51** can be used for determination of absolute configurations of bidentate guest molecules. In the case of discrepancies between the predicted and experimental chirality, conformational analysis was carried out using the molecular mechanics method. Some dependences of induced CD signals on the nature of the guest molecule, the solvent and temperature were given.^{70–80}

The complexation of bisporphyrins **52** in which the tetrapyrrole fragments are linked through C₂-bridges was studied in order to get a deeper insight into the mechanism of induction of optical activities of supramolecular systems based on bisporphyrins.^{8, 81–95}



$M^1 = M^2 = \text{Zn, Mg}; M^1 = \text{Zn}, M^2 = 2\text{H}.$

In contrast with the bisporphyrin systems considered above, this host molecule recognises chiralities of both bidentate and monodentate guests due to a limited number of conformations adopted by bisporphyrin with a short covalent bridge. Absorption, CD and ¹H NMR spectra suggest that bisporphyrin **52** interacts with primary amines by a cooperative mechanism to yield stable host–guest complexes (1 : 2) where bisporphyrin is in the *anti*-conformation. The Gibbs free energy for this complexation varies from -6.7 to -8.4 kcal mol⁻¹. The specific mechanism of induction of the optical activity in bisporphyrin **52** upon complexation with chiral monodentate guests stems from the difference in the repulsion forces of two bulkiest substituents at the asymmetric centre of the ligand and the ethyl groups of the neighbouring porphyrin fragment. The mutual repulsion of these groups forces the tetrapyrrole macrocycles to move away from one another and to twist, which results in generation of an intensive CD signal in the Soret band region, which is characteristic of exciton interactions. The correlation between the sign of the signal and induced helicity of the system enables determination of absolute configurations of monodentate guest molecules.

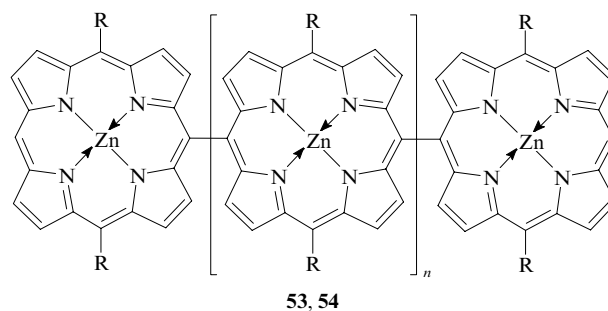
The effects of various factors on induction of chirality have been studied in detail.^{81–95} It was found^{81, 82, 84} that the value of the molar amplitude, *A*, in the CD spectra was proportional to the size of the bulkiest substituent at the asymmetric centre in homologous ligands. The crucial role of the solvent as an active component of the supramolecular system was determined^{89, 90} based on the analysis of solvent–solute interactions in the boundary zones where the difference between the complexation involving competing chiral ligands was small and the guest could be replaced by the solvent molecule. Temperature is yet another factor that governs chirogenic processes. Thus a drop in temperature, which diminished the mobility of the system, was accompanied by a significant increase in the molar amplitude *A*.^{85–87} In this case, chirality could be induced as a result of binding of optically active alcohols despite their low affinities for zinc porphyrins. The ability of chiral alcohols to induce optical activity is significantly enhanced upon substitution of the Mg²⁺ ion for the central Zn²⁺ ion in the porphyrin macrocycle.⁸⁸ Phase transition is yet another important factor that controls optical activities of bisporphyrin complexes **52** with monodentate

amines.⁹⁵ Phase transition in a system caused a significant (1.6–9-fold) increase in the anisotropy factor together with solid-phase ‘switch’ of chirality due to formation of intermolecular aggregates of opposite helicity.

The interaction of bisporphyrin **52** with bidentate guests yielded extremely stable ‘tweezers’-like complexes (1 : 1) with binding constants reaching 10⁷ M⁻¹. In the majority of cases, further increase in the concentration of bidentate guests shifts the equilibrium towards the formation of supramolecular host–guest complexes (1 : 2) where bisporphyrin adopts the *anti*-conformation.^{91–94} An interesting effect, *viz.*, switchover of chirality, which was controlled exclusively by the stoichiometry of the supramolecular system as a result of opposite mutual spatial arrangement of its porphyrin components in 1 : 1 and 1 : 2 complexes, was characteristic of enantiopure 1,2-diphenylethylenediamine used as a guest.

A more detailed rationale for induced optical activity in supramolecular systems based on bisporphyrins was gained with chiral 1,2-diaminocyclohexane as a guest. Based on X-ray data on the structure of bisporphyrin **52**–(*R,R*)-1,2-diaminocyclohexane complex and the Kuhn–Kirkwood mechanism of coupled-oscillator interaction, the intense bisigned CD signal (*A* = -590 cm⁻¹ litre mol⁻¹) was rationalised as a combination of two B_{||}–B_{||} and B_⊥–B_⊥ counter-clockwise electronic homo-interactions, whereas the contribution of the corresponding B_{||}–B_⊥-heterointeractions was insignificant.⁹⁴ Thus, high sensitivity and the ability of bisporphyrin **52** to recognise optical activities of different guest molecules, together with a deep insight into complexation mechanisms, make it a worthy candidate for versatile chirality sensors.

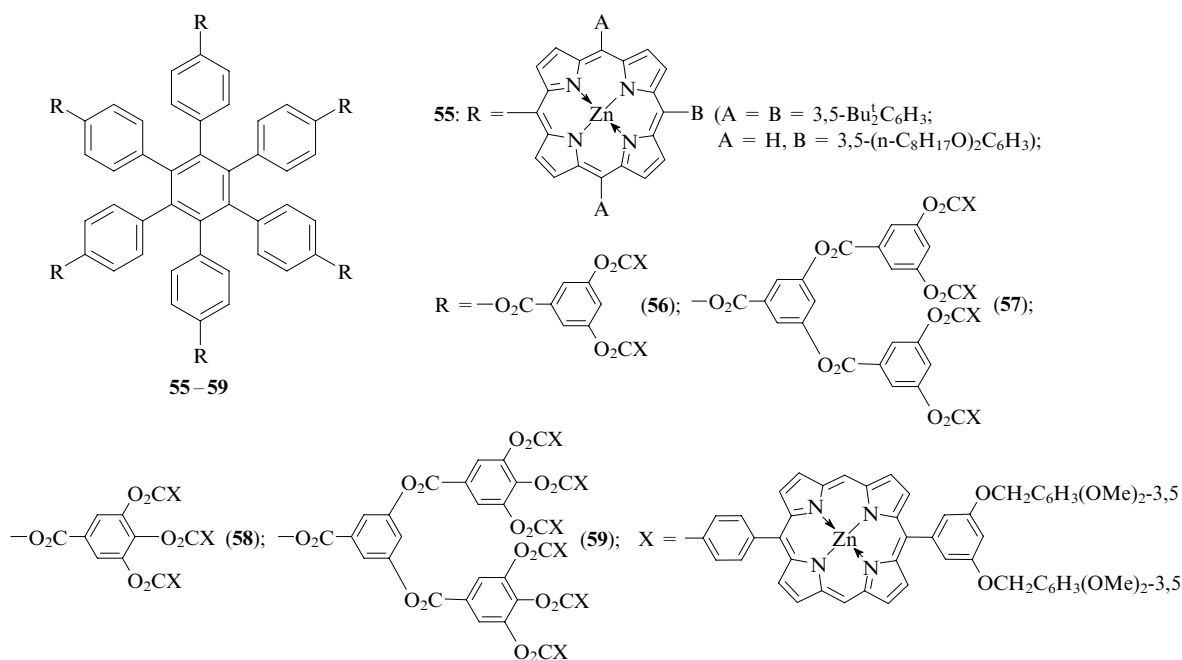
Bisporphyrin **53** with rigidly linked macrocycles was recommended for selective binding of oligosaccharides by a cooperative mechanism.^{60, 96} The fixed distances between the porphyrin fragments correspond closely to the size of maltotetraose, which results in stable host–guest complexes (1 : 2). This is concomitant with the appearance, in the CD spectrum in the region of the Soret band, of a complex chiroptic response consisting of three non-equivalent and asymmetric Cotton effects probably due to superposition of two or more CD signals.



53: $R = \text{—} \langle \text{C}_6\text{H}_4 \rangle \text{—} \text{B} \begin{matrix} \diagup \text{O} \diagdown \\ \diagdown \text{O} \diagup \end{matrix} \text{—}, n = 0;$

54: $R = \text{—} \langle \text{C}_6\text{H}_2(\text{CO}_2\text{H})_2 \rangle \text{—} \text{OC}_{12}\text{H}_{25-n}, n = 0, 1, 2, 6.$

The increase in the number of porphyrin macrocycles in *meso,meso*-linked oligomers **54** brought about significant enhancement of the effect of induced chirality.⁹⁷ In the presence of tetrahydropyrimidinone, these oligomers formed helical structures due to H-bonding of the carboxy groups in the *meso*-aryl substituents of porphyrin and the urea nitrogen atoms. The direction of helix formation was controlled by complexation with chiral diamino-1,1'-binaphthyl derivatives resulting in the appearance of induced CD signals. The intensity of the latter increased with the increase in the number of porphyrin units from



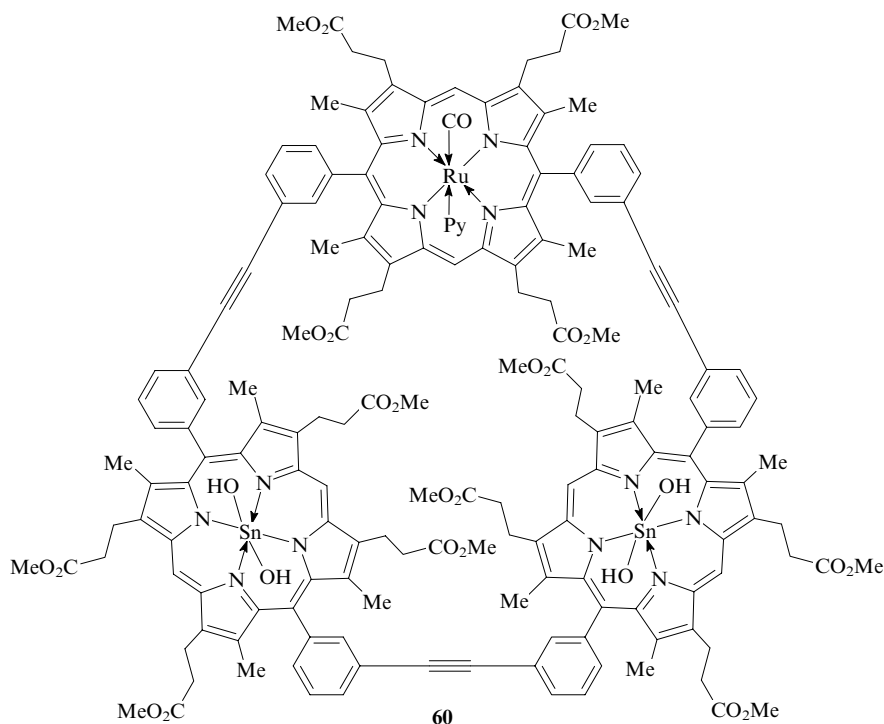
2 to 8. An interesting chirality memory effect was observed for octaporphyrin **54** ($n = 6$): the addition, to a helix formed by octaporphyrin and an optically active guest, of an opposite enantiomer caused a decrease in the induced chirality value, but not its complete cancel or switching the sign.

Yet another type of multiporphyrin systems was investigated.^{98,99} In the presence of enantiomerically pure 1-(1-naphthyl)ethylamines, hexamers **55** manifested intense CD signals in the Soret band region; other chiral amines induced weak Cotton effects.

High stereoselectivity was observed for a series of dendritic porphyrins **56–59** in their complexation with bidentate chiral guests. The induced CD signal strongly depended on the number of porphyrin fragments; the maximum value of A ($2693\text{ cm}^{-1}\text{ M}^{-1}$) was found for dendritic complexes **57**. However, this effect has not been comprehensively investigated yet.

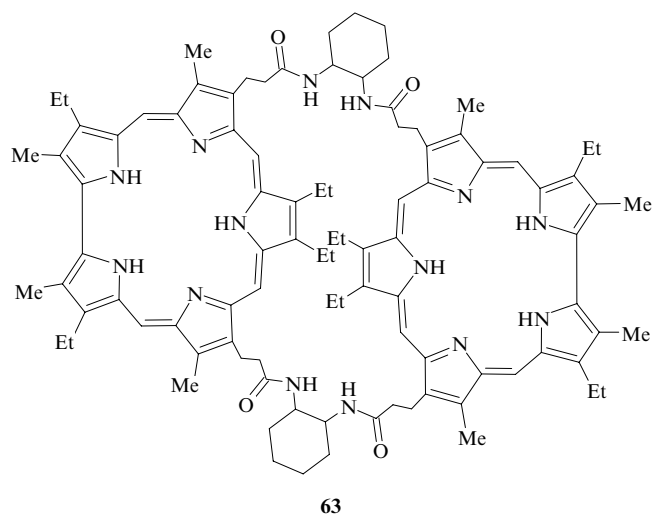
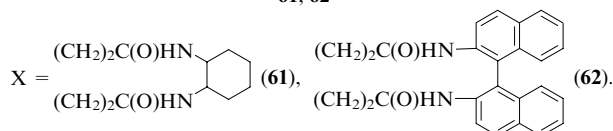
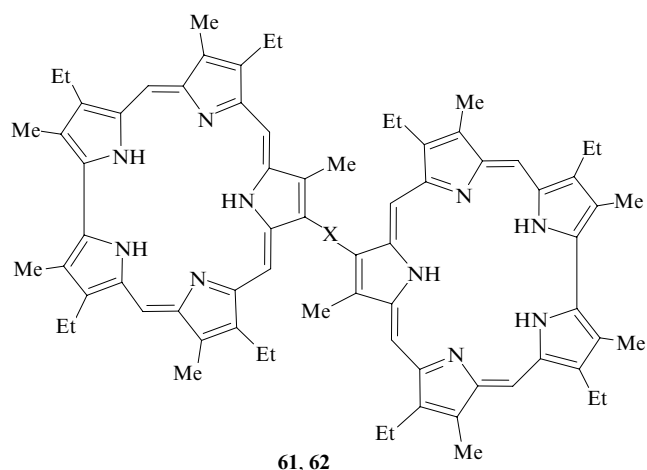
An attempt to develop a supramolecular system for chiral recognition and enantioselective catalysis based on heterometallic trimer **60** was undertaken.¹⁰⁰ In the first step, optically active carboxylic acids bind to tin-containing porphyrin fragments of the trimer **60** in a hexacoordination mode with formation of a host–guest ensemble (1 : 4) with a chiral cavity. However, further attempts to use this ensemble for separation of a racemic mixture of chiral substituted pyridines with subsequent catalytic asymmetric epoxidation were unsuccessful, apparently due to the loss of rigidity of the chiral cavity.

Host–guest systems in which both components possess optical activities can find wide application. Thus a series of chiral sapphyrin dimers **61–63** were used for the recognition of dicarboxylate anions by virtue of Coulomb attraction and formation of hydrogen bonds.¹⁰¹ Dimers **61** and **62** formed stable complexes with *N*-benzyloxycarbonylaspartic and *N*-benzyloxycarbonylglu-



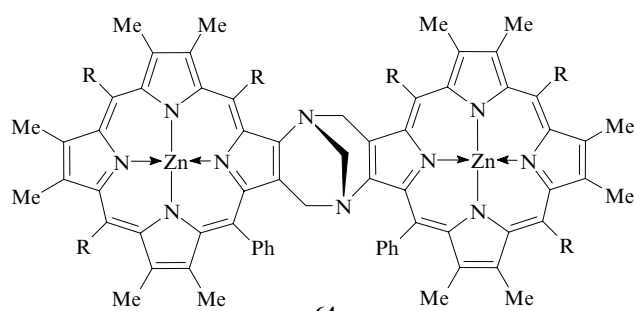
tamic acids ($K_a \sim 10^4 - 10^5 \text{ M}^{-1}$), the binding of glutamic acid being more preferable.

Despite its low affinity for the guest molecules considered above, the cyclic dimer **63** also possesses the ability for chiral recognition. Presumably, this is due to high structural matching of the host and guest molecules as a result of rigid fixation of saphyrin fragments by two covalent bridges. The detailed recognition mechanism demands additional investigation.



63

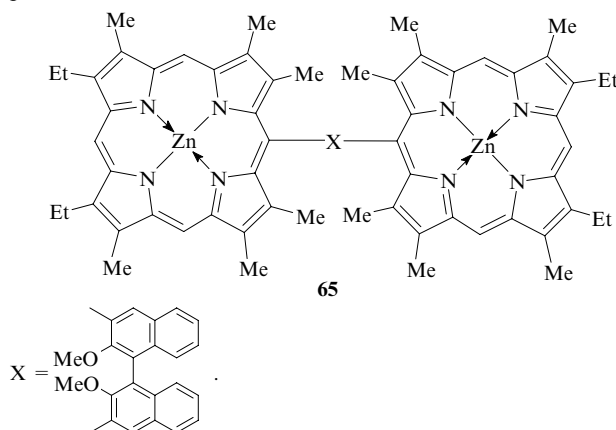
Bisporphyrin **64** with spatially fixed macrocycles was used for enantioselective binding of histidine and lysine esters (*ee* 80%–86% and 48%, respectively). The complexation was achieved through two-site interaction between two nitrogen atoms of the guest and two zinc ions of the host; this yielded ‘tweezers’-like structures.¹⁰²



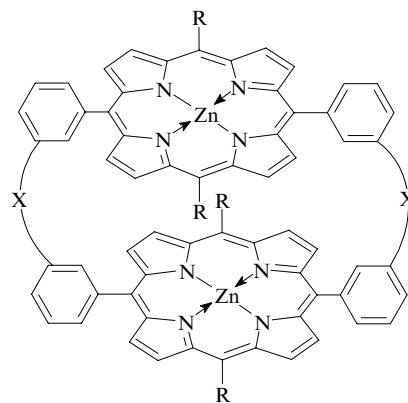
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$R = 3,5\text{-Bu}_2\text{C}_6\text{H}_3$.

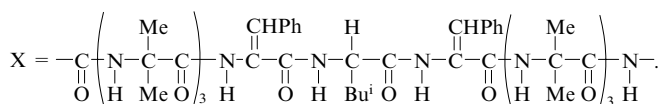
Bisporphyrin **65** rigidly bridged by a 1,1'-binaphthyl fragment was used for chiral recognition of various amino acid derivatives.⁶⁶ This host molecule manifested especially high affinity for lysine derivatives due to formation of ‘tweezers’-like complexes. The stereoselectivity of binding is determined by steric repulsion of two methoxy groups of the bridge and the amide group of the amino acid derivative in the less favourable diastereomeric complex.



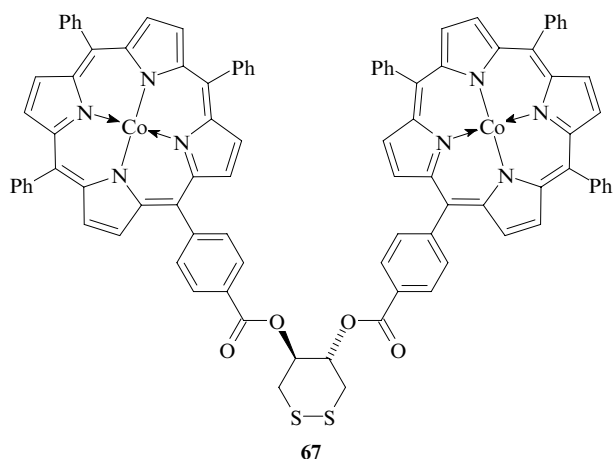
Chiral dimeric porphyrin **66** was used for stereoselective separation (*ee* 80%) of bidentate ligands of various lengths. Guest molecules contained an optically active leucine unit and two terminal pyridine fragments enabling two-site binding.¹⁰³ The formation of the preferential ‘tweezers’-like complex was accompanied by a significant increase in the CD signal intensity in the Soret band region. The observed effect is due to stabilisation of the twisted conformation of the host molecule as a result of its binding to the helical guest molecule.



66



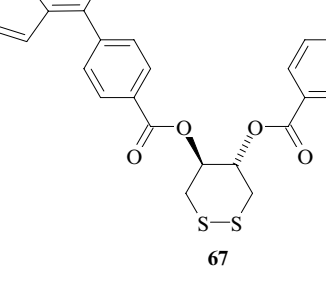
On the contrary, the intensity of a negative single signal in the CD spectrum of bisporphyrin **67** decreased dramatically in the presence of limonene.¹⁰⁴ This was accompanied by a hypsochromic shift the magnitude of which depended on the configuration of the enantiomer bound.



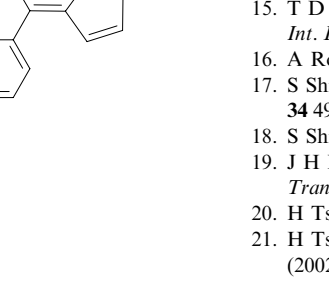
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References

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A similar decrease in the signal intensity in the CD spectrum of chiral bischlorin **68** was observed upon its interaction with optically active ligands.

The effect observed is also due to conformational changes in the host molecule. The significant differences between the chiroptical responses of the complexes with enantiomers suggests possible application of bischlorin **68** for chiral recognition.¹⁰⁵

* * *

The published data considered in this review suggest that optically active supramolecular systems based on porphyrins and their derivatives present indubitable interest for both determination of absolute configurations of different organic molecules and in-depth studies of transcription of optical activity. Recent progress in this area is an important prerequisite to the development of advanced molecular technologies, such as chiral nanotechnology, design of 'smart' molecular tools to memorise chirality and optical activity sensors.

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A new class of compounds with unusual magnetic behaviour: quasi-one-dimensional complex oxides of the $A_{3n+3m}A'_nB_{3m+n}O_{9m+6n}$ family

G V Bazuev

Contents

I. Introduction	749
II. Commensurate and incommensurate oxides	750
III. Low-dimensional platinum group metal oxides	752
IV. Low-dimensional d and p element oxides	754
V. Specific features of the formation of $A_{3n+3m}A'_nB_{3m+n}O_{9m+6n}$ oxides	757
VI. Magnetic properties	757

Abstract. The results of investigations into the conditions of synthesis, structure and magnetic properties of quasi-one-dimensional perovskite-like complex oxides of the $A_{3n+3m}A'_nB_{3m+n}O_{9m+6n}$ family ($A = \text{Ca, Sr, Ba}$; $A' = \text{Cu, Ni, Co, Zn, Mg}$; B are platinum metals, Mn and other d and p elements) are generalised. It is shown that the low-dimensional structure of the compounds is determined by the presence of isolated chains consisting of octahedra occupied by the B cations and trigonal prisms with the A' -cations which alternate in various ratios. The reasons for the formation of incommensurate compounds and the methods for the refinement of their structures are considered. It is demonstrated that the presence of transition metals and the quasi-one-dimensional structure are responsible for the high anisotropy of the magnetic properties of the $A_{3n+3m}A'_nB_{3m+n}O_{9m+6n}$ oxides and, in particular, for the preservation of the intrachain exchange interactions to relatively high temperatures and the low temperatures of three-dimensional magnetic ordering. The bibliography includes 127 references.

I. Introduction

Over the recent years, compounds with low-dimensional crystal structures, in particular, two-dimensional layered and one-dimensional chain compounds manifesting strongly anisotropic physical properties have attracted much attention from specialists in inorganic and solid state chemistry and solid state physics. Among quasi-one-dimensional compounds with chain structures, complex platinum metal oxides, which effectively served as a basis for the emergence of this class of low-dimensional oxides, are of particular interest. Presently, a series of oxides with the general formula $A_{3n+3m}A'_nB_{3m+n}O_{9m+6n}$ based on such metals as Pt, Ir, Ru, Rh, *etc.* have been synthesised.^{1,2} According to structural attributes, the Sr_4PtO_6 oxide³ (that belongs to the K_4CdCl_6 structural type⁴), where both A and A' cationic sites are occupied by Sr can be regarded as the first representative of this family. The values of m and n for this compound are 0 and 1, respectively.

G V Bazuev Institute of Solid State Chemistry, Urals Branch of the Russian Academy of Sciences, ul. Pervomayskaya 91, 620219 Ekaterinburg, Russian Federation. Fax (7-343) 374 44 95, tel. (7-343) 374 49 43, e-mail: bazuev@ihim.uran.ru

Later in the 1990s, other oxides with the common formula $A_3A'BO_6$, where $A = \text{Ca, Sr, Ba}$; $A' = \text{Cu, Ni, Zn, etc.}$; B are platinum group elements, were synthesised.^{5–9} Noteworthy, it was complex oxide $\text{Sr}_3\text{CuPtO}_6$ that was the first reported compound from this series.^{5,6} This new phase characterised by a distorted Sr_4PtO_6 structure with the Cu atoms substituting the Sr atoms in the positions A' formed spontaneously upon an attempted growth of single crystals of strontium cuprate, a high-temperature superconductor, in a platinum crucible. More recently, oxides with formulas $A_4A'B_2O_9$ ($m = 1$ and $n = 3$), $A_6A'B_4O_{15}$ ($m = 1$ and $n = 1$) and $A_9A'_2B_5O_{21}$ ($m = 1$ and $n = 2$) and other compounds have been prepared.^{10–12} A brief analysis of the conditions of synthesis and description of the structures of compounds from this class synthesised prior to 2000 can be found elsewhere.¹³

In structural inorganic chemistry, the above oxides are typically considered as perovskite-related, since complex oxides with the common formula ABO_3 can formally be regarded as a particular case of the formula $A_{3n+3m}A'_nB_{3m+n}O_{9m+6n}$ (for $m = 1$ and $n = 0$). The perovskite structure is usually described in one of two ways. On the one hand, the perovskite structure can be represented as a spatial network of polyhedra, *viz.*, BO_6 octahedra, which can be picked out based on the mutual arrangement of the metal and oxygen atoms constituting the compound. This polyhedral representation is especially pictorial and convenient for the analysis of various structural distortions of perovskites related to the rotation or tilting of the octahedra. The ideal cubic perovskite structure in the polyhedral representation is depicted in Fig. 1a.

On the other hand, a description of the perovskite structure can be based on the concept of cubic and hexagonal close packings of the atoms A and O constituting an ABO_3 perovskite. Strictly speaking, only the cubic close packing refers to the perovskite structure. The hexagonal close packing is typical of crystal structures of some other compounds with the same stoichiometry (*e.g.*, BaNiO_3 ,¹⁴ see Fig. 1b) or with several structural modifications [including BaMnO_3 (Refs 15 and 16)]. For some of ABO_3 oxides (in particular, for BaTiO_3)¹⁷ both perovskite and hexagonal modifications are known. Taking these factors into account, the hexagonal perovskite structure can be represented as a stack of closely packed AO_3 layers along the c axis (Fig. 2) with the B atoms occupying the octahedral cavities formed by the oxygen anions. The A cations are close in size to the O^{2-} oxygen anions, whereas the B cations are characterised by a smaller radius. According to the stoichiometry, the number of the octahedra is equal to the number of the A atoms. Chains (columns) composed

Received 25 January 2006

Uspekhi Khimii 75 (9) 835–850 (2006); translated by Ya V Zubavichus

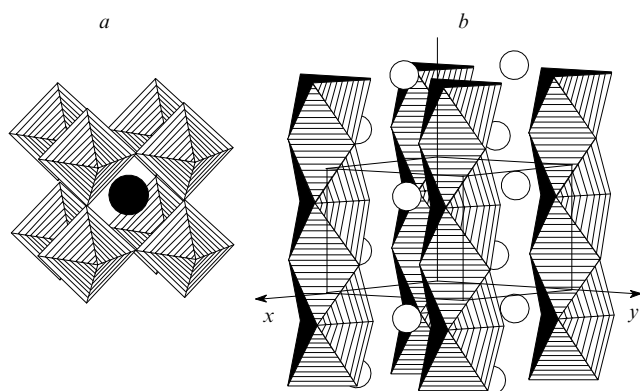


Figure 1. The cubic (a) and hexagonal (b) structures of an ABO_3 perovskite.

of face-sharing octahedra are characteristic of the crystal structure of the 2H polytype of an ABO_3 perovskite (see. Fig. 1 b).

An analysis of the structure of complex oxides belonging to the $A_{3n+3m}A'_nB_{3m+n}O_{9m+6n}$ family taking into account the stacking sequence of closely packed AO_3 layers (see Fig. 2 a) reveals its close relation to the hexagonal perovskite structure. For this purpose, it is convenient to triple the perovskite formula unit to $A_3B_3O_9$ and represent the composition of a layer with the hexagonal close packing as A_3O_9 . Then the structure of a compound belonging to the family $A_{3n+3m}A'_nB_{3m+n}O_{9m+6n}$ can be considered as a stack of layers with stoichiometries A_3O_9 and $A_3A'O_6$ along the c axis. The $A_3A'O_6$ layers can formally be generated from the A_3O_9 layers by replacing three oxygen atoms with an A' atom. The ratio between the number of $A_3A'O_6$ and A_3O_9 layers is determined by the n/m ratio in the formula $A_{3n+3m}A'_nB_{3m+n}O_{9m+6n}$. The presence of the $A_3A'O_6$ layers in the oxide structures gives rise to a new type of coordination, additional to the octahedral one, *viz.*, trigonal prismatic (Fig. 2 b). The unit cell parameter a for these compounds relates to the respective parameter of the hexagonal perovskite lattice as $a = \sqrt{3}a_p \approx 10 \text{ \AA}$, whereas the parameter c depends on m and n . A change in the composition of the oxides from ABO_3 to $A_{3n+3m}A'_nB_{3m+n}O_{9m+6n}$ gives rise to the emergence of chains composed of alternating octahedra and trigonal prisms going along the c axis. This structure is typical, for instance, of Sr_4PtO_6 , where one out of four Sr atoms occupies a trigonal prismatic site (Fig. 3). In the $A_3A'BO_6$ oxides, the octahedra are occupied by the B cations, whereas the trigonal prisms are occupied by the A' cations. Evidently, the ratio between the number of prisms and octahedra in the structure is determined by the ratio of stoichiometric coefficients of the A' and B atoms in the formula. For instance, an $A_4A'B_2O_9$ oxide includes one prism per two octahedra and thus contains chains composed of dimers of octahedra

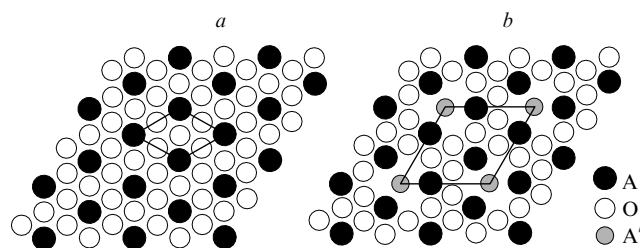


Figure 2. Compositions of alternating layers in oxides of the $A_{3n+3m}A'_nB_{3m+n}O_{9m+6n}$ family for two ultimate stoichiometries. (a) A_3O_9 ($n = 0, m = 1$), (b) $A_3A'O_6$ ($n = 1, m = 0$). The unit cells in the ab plane are shown.

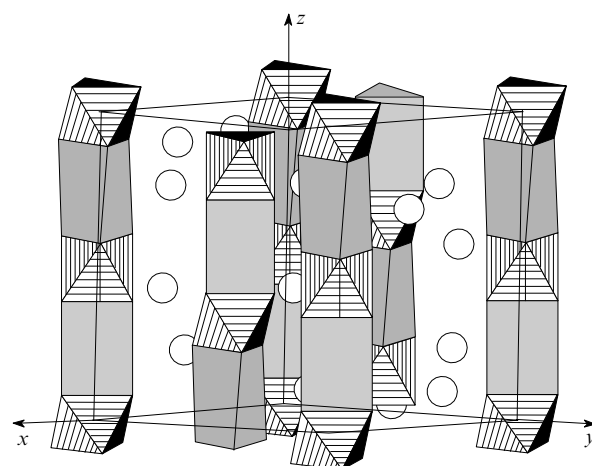


Figure 3. The crystal structure of Sr_4PtO_6 .

The octahedra are occupied by the Pt atoms, the trigonal prisms are occupied by the Sr atoms; open circles denote the Sr atoms that separate the Sr – Pt-chains.

separated by a trigonal prism. In the structure of an $A_9A'_2B_5O_{21}$ oxide, the chains are formed by dimers and trimers of the BO_6 octahedra separated by an $A'O_6$ prism (Fig. 4).¹⁸ The octahedra are connected to each other and to the prisms through face-sharing, which gives rise to rather short metal – metal distances. In these structures, the chains are isolated from each other by the A cations (most frequently, alkaline-earth metals).

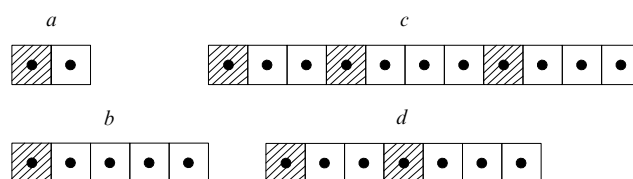


Figure 4. A schematic representation of the chain composition for some oxides of the $A_{3n+3m}A'_nB_{3m+n}O_{9m+6n}$ family.¹⁸ (a) $A_3A'MnO_6$, (b) $A_6A'Mn_4O_{15}$, (c) $A_{14}A'_3Mn_8O_{11}$, (d) $A_9A'_2Mn_5O_{21}$. Shaded squares denote trigonal prisms, plain squares denote octahedra.

II. Commensurate and incommensurate oxides

Following the synthesis of some representatives of the $A_{3n+3m}A'_nB_{3m+n}O_{9m+6n}$ family as polycrystalline powders, the frequent formation of incommensurate structures was discovered.^{10, 11, 19} The incommensurability of the oxides is caused by such factors as their quasi-one-dimensional structure, different composition of the $[A]_\infty$ and $[(A',B)O_3]_\infty$ chains and relatively easily occurring inversion of cations over the polyhedral sites in the chains. The crystal structure of a compound is regarded as incommensurately modulated along the c axis provided that the ratio between the translation periods of the two chains is irrational.

Crystal structures of these compounds can be considered as a composite of two interacting subsystems characterised by identical unit cell parameters a and b but different parameters c , *i.e.*, c_1 and c_2 . The first subsystem includes the $[(A',B)O_3]_\infty$ chains with the parameter $c_1 \approx c_{\text{hex.per.}}/2$, which defines the mean distance between the cations within the polyhedral chains. The second subsystem is composed of the $[A]_\infty$ chains with the parameter $c_2 = c_{\text{hex.per.}}$, which defines the mean distance between alternating

A_3O_9 and $A_3A'O_6$ planes. Therefore, the ratio of the translation parameters c_1 and c_2 corresponding to the two mean sublattices is directly related to the stoichiometry. If the c_1/c_2 ratio (the so called γ -component of the modulation vector) is rational, the structure is regarded as commensurate; but if the ratio is irrational, the translation vector along the c axis becomes formally infinite and thus the structure should be regarded as incommensurate.

Therefore, for a commensurate unit cell, $pc_1 = qc_2$, i.e., $c_1/c_2 = q/p$ (q and p are integers). A unit cell of an oxide of the $A_{3n+3m}A'_nB_{3m+n}O_{9m+6n}$ family consists of $2p$ A_3O_9 and/or $A_3A'O_6$ layers and q polyhedra.¹² {Within this model, the c_1 parameter refers to the $[A]_\infty$ -subsystem and the c_2 parameter refers to the $[(A',B)O_3]_\infty$ subsystem.} Each A_3O_9 layer occupies one octahedral site within the chain. Upon the introduction of an $A_3A'O_9$ layer, a prismatic site is generated, which is twice as large as the octahedral site.

Let us consider two ultimate compositions of oxides from the $A_{3n+3m}A'_nB_{3m+n}O_{9m+6n}$ family, viz., ABO_3 ($n = 0, m = 1$) and $A_3A'BO_6$ ($n = 1, m = 0$). A unit cell of a 2H-perovskite ABO_3 contains two A_3O_9 layers and two transition metal cations, thus $p = 1, q = 2, c_1/c_2 = 2$. Meanwhile, the structure of an $A_3A'BO_6$ oxide includes 6 layers (3 A_3O_9 layers and 3 $A_3A'O_6$ layers) and 4 cations per unit cell, i.e., $p = 3, q = 4, c_1/c_2 = 4/3$. These two limiting cases demonstrate that $(4p/3) \leq q \leq 2p$. For commensurate oxides with the stoichiometry $A_4A'B_2O_9$, $p = 2, q = 3$ and $c_1/c_2 = 3/2$, whereas $p = 3, q = 5$ and $c_1/c_2 = 5/3$ for the $A_6A'B_4O_{15}$ oxides. As has been shown by Blake *et al.*,¹² an analysis of stacking sequences of the $A_3A'O_6$ and A_3O_9 layers based on the parameters p and q allows one to predict possible stoichiometries of compounds from the $A_{3n+3m}A'_nB_{3m+n}O_{9m+6n}$ ($m = 1$) $\equiv$ ($A_3A'O_6$) $_n$ (A_3O_9) family and, furthermore, establish criteria for their commensurability.

One compound can have both commensurate and incommensurate modifications. (However it should be kept in mind that these modifications would correspond to different, although quite similar, compositions.) The literature data on the conditions of formation of commensurate and incommensurate phases are somewhat self-contradicting. For instance, $Sr_4CuIr_2O_9$ phases with commensurate and incommensurate structures were prepared by the calcination of reactants in air at the same temperature of 1120 °C for 5 h and 4 days, respectively.¹⁰ A complex oxide Sr_3ZnRhO_6 as a commensurate phase was synthesised from Sr carbonate, Zn oxide and Rh metal by the calcination in a Pt crucible in air first at 800 °C for 10 h and then at 1150 °C for 3 days.²⁰ Meanwhile, the thermal decomposition of the respective metal nitrates at 450 °C for 24 h followed by the calcination at 1150 °C for 3 days yielded the incommensurate phase. The authors speculated that it is a prolonged thermal treatment that is responsible for the formation of incommensurate phases. The transition from the commensurate to the incommensurate phase is realised in a narrow temperature range. As has been suggested,²¹ the transition is irreversible. Information on the chemical composition of the commensurate and incommensurate phases is also ambiguous. According to results by Battle *et al.*,¹⁰ compositions of the two phases of $Sr_4CuIr_2O_9$ are indistinguishable within the error limit, whereas the incommensurate phase of $Sr_3ZnRhO_{6+\delta}$ was found to be richer in oxygen than its commensurate modification. Layland and zur Loye reported²⁰ that the Sr_3MRhO_6 oxide is extremely sensitive to fine details of the synthesis conditions (such as changes in the oxygen partial pressure, heating rate, temperature, duration, etc.), as evidenced by the emergence of the incommensurate phase. It is of note that the c_1/c_2 ratio can vary continuously during the thermal treatment. Moore and Battle argued²² that the composition of the starting load for the synthesis of $Sr_4CuMn_2O_9$ in the commensurate modification should be changed from the stoichiometric 4 : 1 : 2 (Sr : Cu : Mn) to 4 : 1.04 : 1.92.

It may well be suggested that any compound (either with a commensurate or incommensurate structure) is characterised by unique composition and intrinsic structural peculiarities. The

formation of incommensurate structures can be due to the insertion of oxygen into trigonal prisms giving rise to two octahedra instead of a prism, generation of vacancies and changes in the chain length (i.e., the c_1 parameter).

In principle, usual three-dimensional space groups can be used for the interpretation of incommensurate structures, but this requires the postulation of superstructures characterised by extremely large unit cells, which complicates their analysis. In particular, a structural description of an incommensurate phase of the $Sr_{1.3244}Cu_{0.3244}Mn_{0.6756}O_3$ oxide would require a c parameter as large as 191.92 Å.²¹

In practice, it is much more convenient to describe such crystal structures within the so-called superspace formalism with space groups of a higher dimensionality.^{2,19} For this purpose, additional coordinates associated with a shift of the modulation wave with respect to the parent structure by a vector d are introduced. The dimensionality of this new space is given by $3 + d$, where d is the number of linearly independent modulation vectors q . In the reciprocal space, the modulation vector q is defined as:

$$q = \alpha a^* + \beta b^* + \gamma c^*,$$

where α, β and γ are components of the vector q ; a^*, b^* and c^* are the reciprocal unit cell parameters of the unmodified phase.

In the case of $A_{3n+3m}A'_nB_{3m+n}O_{9m+6n}$ oxides, the incommensurability can occur only in one direction, viz., along the c axis, thus $q = \gamma c^*$ and the structure is described in the space of dimensionality $(3 + 1)$.

Four basis vectors are required to index all diffraction lines of a modulated phase

$$H = ha_1^* + kb_1^* + lc_1^* + mc_2^*,$$

where H is the diffraction vector in the reciprocal space. The 'principal' reflections ($hkl0$) with $l \neq 0$ and ($hk0m$) with $m \neq 0$ can be interpreted neglecting the modulation as Bragg reflections corresponding to the $[(A',B)O_3]$ and $[A]$ subsystems, respectively. In such a case, the diffraction pattern manifests no satellite reflections ($hklm$) with $l \neq 0$ and $m \neq 0$. If the two subsystems are mutually ordered, the satellite reflections appear imposed on the main set of principal reflections.

Sometimes, differences in the chemical composition of commensurate and incommensurate phases are so small that they cannot be determined by analytical techniques. To overcome this problem, a model was elaborated within the superspace formalism, which makes it possible to accurately determine the stoichiometry of an $A_{3n+3m}A'_nB_{3m+n}O_{9m+6n}$ oxide based on its X-ray diffraction parameters. For this purpose, the formula of a compound should be rewritten as $A_{1+x}A'_xB_{1-x}O_3$ [$x = n/(3m + 2n)$], since x can be directly related to the γ -component of the modulation vector^{2,19}

$$\gamma = \frac{c_1}{c_2} = \frac{c_2^*}{c_1^*} = \frac{1+x}{2}.$$

The γ value can vary from 0.5 to 0.75, which corresponds to variations in x over a range of $0 \leq x \leq 0.5$. Within this model, x can change continuously, which corresponds to various combinations of octahedra and trigonal prisms in the chain and gives rise to the infinite number of possible unique structures and chemical compositions. Oxides with stoichiometries from ABO_3 to $A_3A'BO_6$ fall into this range. As has been mentioned above, the ratio between the number of prisms and octahedra in the chain is determined by the ratio between the number of atoms A' and B

$$\frac{N_{\text{prism}}}{N_{\text{oct}}} = \frac{x}{1-x}.$$

Therefore, if the c_1/c_2 ratio is known, the value of x can be determined from the above expression with a high accuracy, which is equivalent to the precise knowledge of stoichiometry for an $A_{3n+3m}A'_nB_{3m+n}O_{9m+6n}$ oxide. This implies that a compound

$A_{1+x}A'_xB_{1-x}O_3$ can be considered as incommensurate or commensurate provided that x is irrational or rational, respectively.

Atomic density modulation functions for compounds of this family can be described within the superspace formalism with sawtooth functions of occupancies and modulations of shifts along the c axis. The major advantage of the use of sawtooth shift modulation functions is the significant decrease in the number of independent variables describing the structure. By varying the parameters, compounds with any stoichiometries (or with any values of x), including ultimate ones, such as 2H-perovskite ABO_3 ($x = 0$) or $A_3A'BO_6$ ($x = 0.5$), can be represented.

In a structural study of an incommensurate phase of $Sr_{1+x}Cu_xMn_{1-x}O_3$ ($x = 1/3$),²¹ the Bragg peaks observed in the experimental diffraction pattern were initially indexed based on two sublattices: $[(Cu, Mn)O_3]$ in the space group $R\bar{3}m$ and $[Sr]$ in the space group $P3c1$ (Fig. 5) with similar a parameters and different c parameters, i.e., c_1 and c_2 . The c_1/c_2 ratio was found to be 0.6625, which clearly indicated the incommensurability of the phase (a ratio 0.666 and $x = 0.3250$ are expected for the respective commensurate oxide with a similar composition). The refinement in the superspace group $R\bar{3}m(00\gamma)0s$ yielded the precise stoichiometry ($x = 0.3244$) and unit cell parameters $a = 9.5933(7)$ Å, $c_1 = 2.5933(3)$ Å and $\gamma = 0.6622(1)$. The stoichiometry determined differ from $Sr_4CuMn_2O_9$ by an increased Mn/Cu ratio and a larger number of octahedral sites in the chains going along the c axis. The elementary unit of the chain includes 11 combinations (1 TP + 2 O) and one combination (1 TP + 3 O), where TP means trigonal prism and O means octahedron.

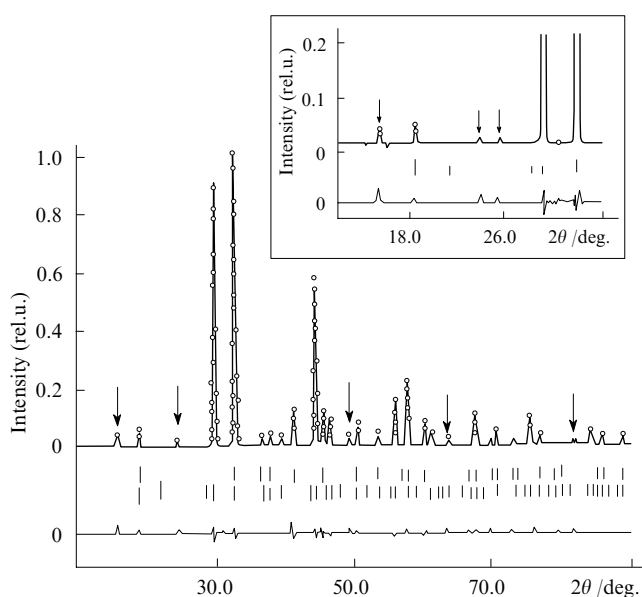


Figure 5. The Rietveld refinement of the powder pattern for a composite oxide, $Sr_{1.3244}Cu_{0.3244}Mn_{0.6756}O_3$: experimental data (dots), best-fit and difference.²¹

The positions of reflections indexed for two independent sublattices in 3D-space groups are marked with dashes; non-indexable reflections are marked with arrows.

The results reported by Abakumov *et al.*²³ and by Mironov *et al.*²⁴ can be cited as an illustrative example on the structure determination of a quasi-one-dimensional oxide, $Sr_{1.32}Mn_{0.83}Cu_{0.17}O_3$, using a combination of techniques, including electron diffraction, high-resolution electron microscopy and X-ray diffraction coupled with the crystal structure refinement in the $(3+1)D$ -space. The experimentally found value of γ for this compound was 0.6616(1), which corresponds to $x = 0.3232$ in $A_{1+x}A'_xB_{1-x}O_3$. This value is close to the ratio $p'/q' = 1/3$,

where p' is the number of prisms in the chain and the number of octahedra is $q' - p'$ (see †). Taking into account that $x = p'/q'$, this may be rewritten as

$$\frac{N_{\text{prism}}}{N_{\text{oct}}} = \frac{x}{1-x} = \frac{p'}{q'-p'}.$$

Based on this expression, the sequence of octahedra and prisms in the chain was determined. According to the Farey's rule,² a sequence with the most uniform distribution of trigonal prisms is realised in the chain of polyhedra. Therefore, the ratio p'/q' for $x = 0.3232$ should be 32/99. This implies that the chain of polyhedra going along the c axis contains 99 polyhedra representing dimers and trimers of octahedra separated by single trigonal prisms. The overall parameter c appears close to 515 Å, which makes a traditional description of the structure in the 3D-approximation impossible. In contrast to the $Sr_{1.3244}Mn_{0.6756}Cu_{0.3244}O_3$ phase discussed above,²¹ the trigonal prismatic sites in $Sr_{1.32}Mn_{0.83}Cu_{0.17}O_3$ are occupied by the Cu and Mn cations $[Sr_{1.323}(Cu_{0.174}Mn_{0.149})_{\text{prism}}(Mn_{0.677})_{\text{oct}}O_3]$ (Ref. 23).

The X-ray diffraction pattern of $Sr_3ZnRhO_{6.34}$ can be indexed²⁰ assuming two sublattices with $a = 9.6378(5)$ Å and $c = 2.7012(2)$ Å in the space group $R\bar{3}m$ and with $a = 5.5640(9)$ Å and $c = 3.9539(7)$ Å in the space group $P31c$. For this phase, the ratio $c_1/c_2 = 0.6832$ is significantly smaller than the ideal value 3/4 expected for the commensurate phase Sr_3ZnRhO_6 . On the other hand, this value is close to 2/3 typical of structures comprising two octahedra and one trigonal prism along the c axis. Such a structure corresponds to the composition $A_4A'B_2O_9$. The increased oxygen content in the incommensurate phase can indicate the transformation of trigonal prisms into octahedra upon the respective synthesis conditions. Stitzer *et al.*¹³ noted that it should be possible to detect such a transition using the thermogravimetric analysis, although no experimental evidence of the process has been reported so far. Presently, the conditions of synthesis favouring the formation of the above oxides with either commensurate or incommensurate structures remain unclear.

III. Low-dimensional platinum group metal oxides

1. $A_3A'BO_6$ oxides

Platinum metals form an extended series of quasi-one-dimensional oxides with the common stoichiometry $A_3A'BO_6$. Oxides with other compositions have also been reported. Selected examples of these compounds are listed in Table 1. A systematic analysis indicates that the platinum group metals in the quasi-one-dimensional $A_3A'BO_6$ oxides can be in the tri- (Rh), tetra- (Rh, Pt, Ir or Ru) and pentavalent (Ru, Ir or Rh) states. It is of note that complex Rh^{5+} oxides from this family (e.g., Sr_3NaRhO_6 and Sr_3LiRhO_6) were the first examples of rhodium oxides in the formal oxidation state 5+ (see Ref. 53). These compounds were synthesised at 600 °C by the crystallisation of a melt of RhO_2 , $Sr(OH)_2$ and alkali metal hydroxides at ambient pressure. These compounds manifest low stability in air. Upon their storage in a humid atmosphere, Rh^{5+} undergoes partial reduction to Rh^{4+} .

The A' sites can be occupied by alkali metals, 3d elements (most typically, bivalent), Cd, Mg and rare-earth elements. The vast majority of $A_3A'BO_3$ oxides ($B = Pt, Ir, Rh, Ru$) are isostructural to Sr_4PtO_6 . The Sr_4PtO_6 oxide is crystallised in the rhombohedral space group $R\bar{3}c$ with $a = 9.740(2)$ Å and $c = 11.900(2)$ Å (in the hexagonal setting). A similar structure is also typical of Ca_4PtO_6 (Refs 25 and 26) and Ba_4PtO_6 (Ref. 30). The unit cell parameters of these oxides are somewhat modified as compared to the aforementioned values of the Sr^{2+} compound according to the ionic radii of Ca^{2+} and Ba^{2+} .

† The parameters p' and q' relate to the aforementioned parameters p and q through the following expressions: $p' = 2p - q$, $q' = q$.

Table 1. Chemical compositions of oxides of the $A_{3n+3m}A'_nB_{3m+n}O_{9m+6n}$ family (B is a platinum group metal).

<i>m</i>	<i>n</i>	Gross formula	Compound
1	0	ABO ₃	BaNiO ₃ (Ref. 14)
0	1	A ₃ A'BO ₆	Ca ₄ PtO ₆ , ^{25,26} Ca ₄ IrO ₆ , ²⁷ Ca ₄ PdO ₆ , ²⁸ Sr ₄ PtO ₆ , ³ Sr ₄ IrO ₆ , ²⁷ Sr ₄ PdO ₆ , ²⁸ Sr ₄ RhO ₆ , ²⁹ Ba ₄ PtO ₆ , ³⁰ Ca _{3.5} Cu _{0.5} PtO ₆ , ³¹ Sr ₃ A'PtO ₆ (A' = Cu, ^{5,6} Ni, ³² Co, ³³ Zn, Cd, ³⁴ Mg ³⁵), (Na,La ₂)NaPtO ₆ , ³⁶ Ca ₃ A'IrO ₆ (A' = Na, ³⁷ Co, ³⁸ Cu, ³⁹ Ni, ⁴⁰ Zn, ⁴¹ Mg ⁴¹), Sr ₃ A'IrO ₆ (A = Li, Na, Ca, Co, Ni, Zn Cu, Cd, Mg), ^{7,42–45} Ba ₃ NaIrO ₆ , ⁴⁶ A ₃ A'RuO ₆ (A = Ca, Sr, Ba; A' = Li, Na), ^{9,35,45–47} Co, ³⁸ Cu ⁴⁸), Ca ₃ A'RhO ₆ (A' = Co, Fe), ⁴⁹ Sr ₃ A'RhO ₆ (A' = Zn, ²⁰ Ni, Cu, ⁵⁰ Sc, In, Sm–Yb, Y ^{51,52}), Sr ₃ ARhO ₆ (A = Li, Na) ⁵³ Sr ₄ Ru ₂ O ₉ , ⁵⁴ A ₄ A'Ir ₂ O ₉ (A = Sr, Ba; A' = Cu, Zn) ¹⁰
1	3	A ₄ A'B ₂ O ₉	Ba ₆ A'Ir ₄ O ₁₅ (A' = Cu, Zn), ¹¹ Sr ₆ Rh ₅ O ₁₅ (Ref. 55)
2	3	A ₅ A'B ₃ O ₁₂	Ba ₈ CoRh ₆ O ₂₁ (Ref. 56)
1	1	A ₆ A'B ₄ O ₁₅	Ba ₉ Cu ₂ Ir ₅ O ₂₁ , ¹² Ba ₉ Rh ₈ O ₂₁ (Ref. 57)
5	3	A ₈ A'B ₆ O ₂₁	Ba ₁₂ Rh _{9.25} Ir _{1.75} O ₃₃ (Ref. 58)
1	2	A ₉ A'B ₅ O ₂₁	Ba ₁₄ Cu ₃ Ir ₈ O ₃₃ (Ref. 12)
3	1	A ₁₂ A'B ₂ O ₃₃	Ba ₁₆ Cu ₃ Ir ₁₀ O ₃₉ (Ref. 12)
5	9	A ₁₄ A'B ₈ O ₃₃	
7	9	A ₁₆ A'B ₁₀ O ₃₉	

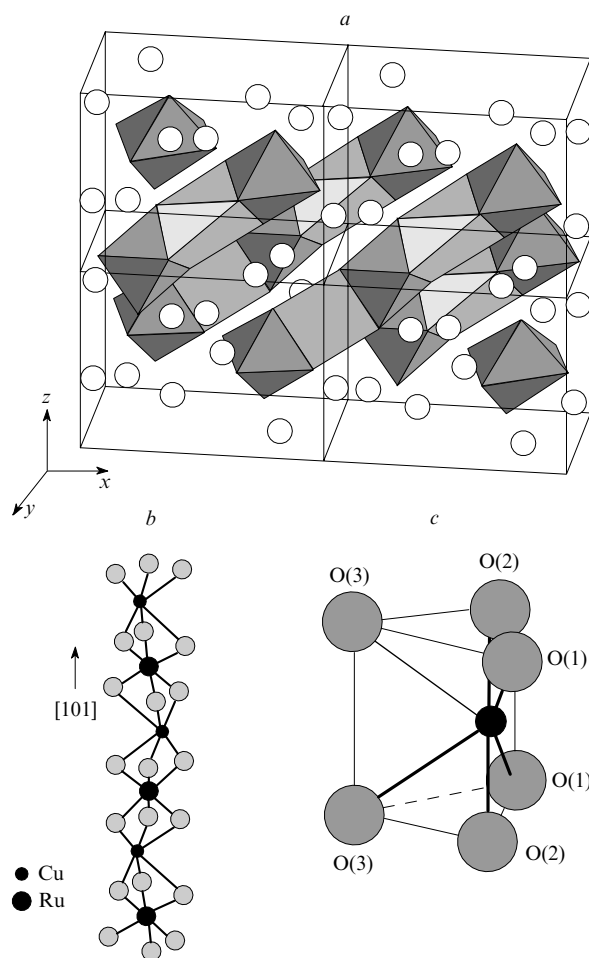
Oxides containing divalent copper in the A' sites (in particular, Sr₃CuPtO₆, Sr₃CuIrO₆, Ca₃CuIrO₆ and Ca₃CuRhO₆) are characterised by slightly different structures due to the Jahn–Teller nature of the Cu²⁺ cation. The change is due to a shift of the Cu²⁺ cation from the centre of the trigonal prism towards one of its rectangular faces. As a result, the symmetry lowers from rhombohedral to monoclinic (space group *C2/c*). The crystal structure of a monoclinic modification of the Ca_{3.1}Cu_{0.9}RuO₆ oxide is shown in Fig. 6. Interestingly, the presence of calcium cations in the trigonal prismatic sites does not increase the symmetry of the phase and both the Ca²⁺ and Cu²⁺ ions in the prismatic sites are actually located in one of the faces adopting the planar square coordination.

The A sites in the A₃A'BO₆ oxides are preferably occupied by alkaline-earth metals. The only exception to this rule is represented by the (Na,La₂)NaPtO₆ oxide, where La and Na jointly occupy the A sites. A half of Na⁺ cations in this structure occupy the trigonal prismatic sites.

2. Oxides with other stoichiometries

A number of platinum group metal oxides corresponding to other *n* and *m* have been synthesised, which are characterised by a larger ratio of the number of octahedral sites to that of prismatic sites than in A₃A'BO₆ (see Table 1). Among them, Sr₄Ru₂O₉ is worth mentioning, since a quasi-one-dimensional structure with empty trigonal prisms is known for this compound.

An increase in the fraction of octahedra in the chain gives rise to an increase in *c*. For instance, *c* is 35.0564 Å for Ba₁₆Cu₃Ir₁₀O₃₉. Such oxides are characteristic of two metals, *viz.*, Ir and Rh, with one exception represented by Ba₄Pt_{1.7}Cu_{1.1}O_x. This phase was obtained in an attempted growth of single crystals of ErBa₂Cu₃O₇, a high-temperature superconductor, in a platinum crucible.⁵⁹ The structural studies of these objects are complicated by the necessity to refine a large number of positional parameters. Nevertheless, the structure of

**Figure 6.** The crystal structure of Ca_{3.1}Cu_{0.9}RuO₆.⁴⁸

The orientation of chains of polyhedra in the monoclinic unit cell (*a*), the arrangement of atoms within a chain (*b*) and the expanded view of a trigonal prismatic site (*c*) are shown.

Ba₁₆Cu₃Ir₁₀O₃₉ with 54 independent atoms in a unit cell[‡] was successfully refined based on the neutron diffraction data.¹²

As a rule, only small plate-, needle- or rod-like single crystals of A_{3n+3m}A'_nB_{3m+n}O_{9m+6n} oxides (A = Ca, Sr, Ba; A' = Cu, Ni, Co, Zn, Mg; B is a platinum group metal, Mn, *etc.*) can be grown. The vast majority of single crystals was grown from various fluxes composed of metal carbonates, hydroxides, halides or their eutectic mixtures. Alkaline-metal carbonates, metals, simple or pre-prepared complex oxides with a specific composition were used as reactants. The syntheses were conducted in aluminium, platinum, silver or nickel crucibles in air or in sealed ampoules (as in the case of Sr₃NaIrO₆, see Ref. 43). In particular, single crystals of Ba₈CoRh₆O₂₁ were grown⁵⁶ from a potassium carbonate flux in an alumina crucible starting from Rh, BaCO₃ and Co₃O₄ powders. The loaded crucible was heated in air from room temperature to the reaction temperature of 1050 °C at a rate of 600 °C h^{−1}, kept at this temperature for 12 h and cooled down to 875 °C at a rate of 12 °C h^{−1}. Then the furnace was switched off and the crucible with the reaction product was left inside the furnace to slowly cool down. The flux was removed by washing with water, and the crystals were withdrawn from the crucible. Single crystals of Sr₁₄Cu₃Mn₈O₃₃ were synthesised in a similar way (the annealing at 1200 °C for 48 h followed by cooling down to 880 °C at a rate of 6 °C h^{−1}).²¹

[‡] To our knowledge, this is the most complex structure among this class of oxides solved and refined from powder diffraction data.

Relatively large single crystals were obtained using the method of crystal growth from salt melts. This enabled high-precision structural elucidations and verification of the magnetic anisotropy of these compounds. Studies of single crystals of the $\text{Ba}_8\text{CoRh}_6\text{O}_{21}$ oxide have shown⁵⁶ that its structure is built up of six successive RhO_6 polyhedra and a distorted CoO_6 trigonal prism. The cobalt–oxygen (2.184–2.197 Å) and rhodium–oxygen (1.905–2.055 Å) distances lie in the typical range of distances formed by these cations in similar oxides. According to calculations of the valence force sums, the Rh and Co ions in the chain are in the tetra- and divalent states, respectively, although the combination $\text{Co}^{3+}-\text{Rh}^{3+}-5\text{Rh}^{4+}$ also cannot be ruled out. With this respect, it has to be noted that the valence state combination $(\text{A}')^{2+}-\text{Rh}^{4+}$ has been postulated for $\text{Ca}_3\text{A}'\text{RhO}_6$

(A = Co and Fe) based on analysis of the structural and magnetic data.⁴⁹

IV. Low-dimensional d and p element oxides

Quasi-one-dimensional complex oxides of the family $\text{A}_{3n+3m}\text{A}'_n\text{B}_{3m+n}\text{O}_{9m+6n}$ with 3d elements occupying the B sites include cobalt and nickel compounds with the common formulas $\text{Ca}_3\text{Co}_2\text{O}_6$ ($m=0, n=1$),⁶⁰ $\text{Sr}_4\text{Ni}_3\text{O}_9$ ($m=1, n=3$),^{61,62} $\text{Ba}_6\text{Ni}_5\text{O}_{15}$ (Ref. 63) and $\text{Sr}_6\text{Co}_5\text{O}_{16}$ ($m=1, n=1$);⁶⁴ manganese compounds with the formulas $\text{Ca}_3\text{A}'\text{MnO}_6$ and $\text{Ba}_6\text{A}'\text{Mn}_4\text{O}_{15}$ ($\text{A}' = \text{Zn, Co, Cu}$)^{65–72} and some other examples, are listed in Table 2.

Table 2. The chemical compositions of oxides of the $\text{A}_{3n+3m}\text{A}'_n\text{B}_{3m+n}\text{O}_{9m+6n}$ family (B = Co, Ni, Mn and other 3d or p elements).

<i>m</i>	<i>n</i>	Formula		Compound	Ref.
		gross	<i>x</i> in $\text{A}_1+x\text{A}'_x\text{B}_{1-x}\text{O}_3$		
1	0	ABO_3	0	BaMnO_3	15, 16
0	1	$\text{A}_3\text{A}'\text{BO}_6$	0.5	$\text{Ca}_3\text{Co}_2\text{O}_6$	60
				$\text{Ca}_3\text{NiMnO}_6$	65, 67–70
				$\text{Ca}_3\text{ZnMnO}_6$	65, 67, 70
				$\text{Ca}_3\text{CoMnO}_6$	71
				$\text{Ca}_3\text{CuMnO}_6$	65, 71, 72
				$\text{Ca}_3\text{ZnCoO}_3$	67
				$\text{Sr}_3\text{A}'\text{CrO}_6$ ($\text{A}' = \text{Sc, In, Lu, Yb–Ho, Y}$)	73
				$\text{Sr}_3\text{A}'\text{NiO}_6$ ($\text{A}' = \text{Sc, In, Tm, Yb, Lu}$)	74
				$\text{Sr}_3\text{PbNiO}_6$	75
				Ba_3NaBO_6 (B = Nb, Ta)	76
				A_3NaSbO_6 (A = Sr, Ba), A_3LiSbO_6 (A = Ca, Sr, Ba)	77
				A_3NaBiO_6 (A = Ba, Sr), $\text{Sr}_3\text{LiBiO}_6$	78
1	3	$\text{A}_4\text{A}'\text{B}_2\text{O}_9$	0.333	$\text{Sr}_4\text{Ni}_3\text{O}_9$	61, 62
				$\text{Sr}_4\text{Cr}_3\text{O}_9$	79
				$(\text{Sr}_{0.5}\text{Ca}_{0.5})_4\text{Co}_3\text{O}_9$	80
				$\text{Ca}_4\text{CuMn}_2\text{O}_9$	81, 82
				$\text{Sr}_4\text{CuMn}_2\text{O}_9$	21, 22, 81–83
				$\text{Sr}_4\text{NiMn}_2\text{O}_9$	82, 84–86
				$\text{Sr}_4\text{Ni}_{3-x}\text{Mn}_x\text{O}_9$	87
				$\text{Sr}_4\text{CoMn}_2\text{O}_9$	82, 88
				$\text{Sr}_4\text{ZnMn}_2\text{O}_9$	22, 89, 90
				$\text{Sr}_4\text{MgMn}_2\text{O}_9$	89
2	3	$\text{A}_5\text{A}'\text{B}_3\text{O}_{12}$	0.25	$\text{Sr}_5\text{Co}_4\text{O}_{12}$	80
				$\text{Ba}_5\text{PdMn}_3\text{O}_{12}$	91
				$\text{Ba}_5\text{ZnMn}_3\text{O}_{12}$	90
				$(\text{Sr}_{0.75}\text{Ba}_{0.25})_5\text{NiMn}_3\text{O}_{12}$	92
1	1	$\text{A}_6\text{A}'\text{B}_4\text{O}_{15}$	0.2	$(\text{Ba}_{0.25}\text{Sr}_{0.75})_6\text{Co}_5\text{O}_{15}$	80
				$\text{Ba}_6\text{Ni}_5\text{O}_{15}$	63
				$\text{Sr}_6\text{Co}_5\text{O}_{15}$	64
				$\text{Ba}_6\text{A}'\text{Mn}_4\text{O}_{15}$ ($\text{A}' = \text{Cu, Zn}$)	66
				$\text{Ba}_6\text{A}'\text{Mn}_4\text{O}_{15}$ ($\text{A}' = \text{Ni, Mg, Pd}$)	91, 93
4	3	$\text{A}_7\text{A}'\text{B}_5\text{O}_{18}$	0.16667	$(\text{Ba}_{0.5}\text{Sr}_{0.5})_7\text{Co}_6\text{O}_{18}$	94
				$\text{Ba}_7\text{A}'\text{Mn}_5\text{O}_{18}$ ($\text{A}' = \text{Pd, Mg}$)	91, 95
5	3	$\text{A}_8\text{A}'\text{B}_6\text{O}_{21}$	0.1429	$\text{Ba}_8\text{Co}_7\text{O}_{21}$	94
				$\text{Ba}_8\text{MgMn}_6\text{O}_{21}$	95
2	1	$\text{A}_9\text{A}'\text{B}_7\text{O}_{24}$	0.125	$\text{Ba}_9\text{Co}_8\text{O}_{24}$	94
				$\text{Ba}_9\text{MgMn}_7\text{O}_{24}$	96
1	2	$\text{A}_9\text{A}'_2\text{B}_5\text{O}_{21}$	0.2857	$\text{Sr}_9\text{Ni}_2\text{Mn}_5\text{O}_{21}$	92
				$\text{Sr}_9\text{Co}_2\text{Mn}_5\text{O}_{21}$	97, 98
7	3	$\text{A}_{10}\text{A}'\text{B}_8\text{O}_{27}$	0.1111	$\text{Ba}_{10}\text{Co}_9\text{O}_{27}$	99
3	1	$\text{A}_{12}\text{A}'\text{B}_{10}\text{O}_{33}$	0.09091	$\text{Ba}_{12}\text{Co}_{11}\text{O}_{33}$	100
5	9	$\text{A}_{14}\text{A}'_3\text{B}_8\text{O}_{33}$	0.2727	$\text{Sr}_{14}\text{Co}_{11}\text{O}_{33}$	101
				$\text{Sr}_{14}\text{Co}_3\text{Mn}_8\text{O}_{33}$	98
				$\text{Sr}_{14}\text{Cu}_3\text{Mn}_8\text{O}_{33}$	21

The structures of Co and Ni complex oxides are similar to those of the platinum metal-based compounds discussed above. Typically, octahedra and trigonal prisms forming the chains going along the *c* axis contain the same d element in different oxidation states.

In contrast to the Co and Ni compounds, quasi-one-dimensional manganese oxides were obtained only in a combination with other elements occupying the trigonal prismatic sites. Such compounds can be synthesised under normal conditions in air. The manganese atoms occupy the octahedral sites, whereas the A' sites can be occupied by such metals as Zn, Co, Ni, Cu or Mg, as in the case of platinum metal complex oxides.

1. $A_3A'MnO_6$ oxides

Manganese-containing oxides belonging to the $A_3A'MnO_6$ family were synthesised only with calcium. Ni, Co, Zn and Cu can act as A'. Attempted syntheses of $Sr_3A'MnO_6$ ($A' = Co, Ni$) oxides afforded a $Sr_3NiMnO_{6.36}$ phase, which appeared similar in terms of both stoichiometry and structure to $A_4A'B_2O_9$ compounds ($n = 3, m = 1$). A transition from the initial composition of $Sr_3NiMnO_{6.36}$ to $A_4A'B_2O_9$ has resulted⁸⁴ in a modified formula, viz., $Sr_4(Sr_{0.20}Ni_{1.40}Mn_{1.40})O_{8.88}$.

The crystal structure of $Ca_3A'MnO_6$ with $A' = Ni, Co$ or Zn was refined in the space group $R\bar{3}c$ in the hexagonal setting (the Sr_4PtO_6 structural type). A similar structure was earlier confirmed for $Ca_3Co_2O_6$.⁶⁰ In this oxide, Co^{3+} cations in the octahedral and trigonal prismatic sites adopt the low-spin (LS) and high-spin (HS) states, respectively. An investigation of the formation of $Ca_3Co_{1-x}Mn_{1-x}O_6$ solid solutions gave rise to two new isostructural oxides, Ca_3CoMnO_6 and $Ca_3Co_{1.25}Mn_{0.75}O_6$.⁷¹ The unit cell parameters of both Ca_3CoMnO_6 and $Ca_3Co_{1.25}Mn_{0.75}O_6$ are significantly larger than those of $Ca_3Co_2O_6$ due to the larger ionic radius of manganese as compared to cobalt.

The presence of cationic combinations $(A')^{2+} - Mn^{4+}$ in the $Ca_3A'MnO_6$ oxides ($A' = Ni, Co$ or Zn) was suggested based on the analysis of interatomic distances and magnetic susceptibility measurements. The trigonal prismatic sites in these oxides are occupied by the Co, Ni or Zn ions. (In the case of Ca_3NiMnO_6 , 8% of the Mn atoms are substituted with Ni;^{69,70} this explains the presence of admixing nickel oxide NiO in the samples studied.)

The Co–O (2.140 Å) and Ni–O (2.137 Å) interatomic distances, as determined in structural studies of these phases, are close to typical values observed in other oxides with the respective metals in the divalent state. The A'–Mn interatomic distances in the chains are 2.645 Å, 2.650 Å and 2.658 Å for Co, Ni and Zn phases, respectively. So short A'–Mn distances are explained by the fact that the octahedra containing the Mn^{4+} cations are combined with the trigonal prisms with the $(A')^{2+}$ cations into the infinite chains by face-sharing. Despite the presence of short Mn–A' contacts, no direct metal–metal bonds are formed, and all these oxides are insulators, according to the measurements of their specific resistivity.

In contrast to the manganese-based $Ca_3A'MnO_6$ oxides with $A' = Ni, Co$ or Zn discussed above, the crystal structure of a Ca_3CuMnO_6 oxide was refined in the triclinic space group $P\bar{1}$. According to the combined structure refinement against neutron and X-ray diffraction data, this triclinic unit cell can be derived from a C-centred monoclinic cell of Sr_3CuPtO_6 (the $C2/c$ space group). Nevertheless, in contrast to the structure of Sr_3CuPtO_6 , there are two independent positions of both Cu and Mn atoms in the unit cell of Ca_3CuMnO_6 . According to the refinement of partial occupancies of these atomic positions, 90% of the Cu(1) sites are occupied by the copper atoms, whereas 10% of them are occupied by the manganese atoms. The Cu(2) sites are exclusively occupied by copper. Both types of copper atoms are in the trigonal prismatic cavities. However, detailed analysis of the copper–oxygen interatomic distances has revealed that the coordination numbers of both types of copper atoms are better described as (4+2). Assuming the planar square coordination environment (the coordination number of 4), the mean copper–oxygen dis-

tances are 2.122 Å and 2.026 Å for the Cu(1) and Cu(2) sites, respectively.

Such a coordination environment is a manifestation of the Jahn–Teller effect typical of the divalent copper cations. Due to the substitution of 10% of the copper atoms in the Cu(1) sites with Mn, the mean cation–anion distances increase (2.122 Å for the coordination number of 4) and the atoms shift towards the centre of the trigonal prism. Taking into account two more remote oxygen atoms (*i.e.*, for the coordination number of 4+2), the mean Cu(1)–O distance is 2.201 Å. Meanwhile, the Cu(2) atoms are located virtually in the centre of a lateral face of the trigonal prism. Two types of manganese atoms [*i.e.*, Mn(1) and Mn(2)] are located inside the octahedra and the mean manganese–oxygen distances are 1.929 Å and 1.904 Å, respectively. A unit cell of Ca_3CuMnO_6 contains six crystallographically independent types of the calcium atoms, which occupy distorted square antiprismatic sites (the coordination number of 8). The mean Ca–O distances lie in the range from 2.425 Å to 2.513 Å. The octahedra accommodating the Mn(1) and Mn(2) atoms are combined with the trigonal prisms with the Cu(1) and Cu(2) atoms through face-sharing (Fig. 7) to form isolated zigzag chains composed of alternating copper and manganese atoms in a sequence: ... Mn(1)Cu(1)–Mn(2)Cu(2)Mn(1) ..., *etc.* The chains are isolated from each other with columns of distorted square antiprisms of oxygen atoms accommodating the calcium ions.

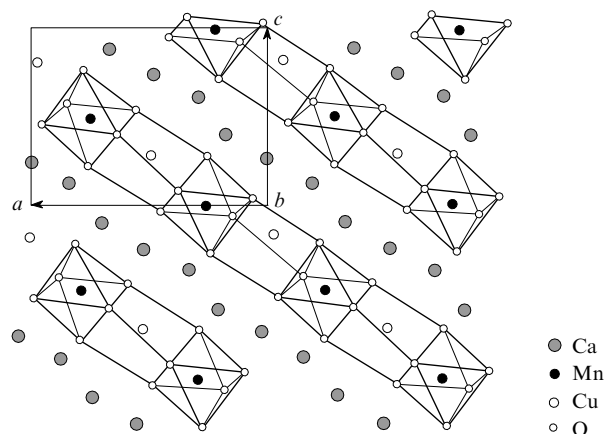


Figure 7. A projection of the crystal structure of Ca_3CuMnO_6 to the (010) plane.

A unit cell and isolated chains of the MnO_6 octahedra (two types) and CuO_6 trigonal prisms (two types) are shown.

It is of note that a minor modification of the Ca_3CuMnO_6 oxide afforded another compound, $Ca_{3.1}Cu_{0.9}MnO_6$.¹⁰² Its crystal structure at 302 K was refined in the rhombohedral space group $R\bar{3}c$, as for other $Ca_3A'MnO_6$ ($A' = Co, Ni, Zn$) oxides. However a new triclinic phase appears in the sample in addition to the rhombohedral one upon cooling to 294 K, which further becomes the dominant phase at 288 K. Similar phase transitions occurring at different temperatures were also detected for other compounds containing the Jahn–Teller Cu^{2+} ions in the A' sites, such as $Sr_3Cu_{1-x}M_xIrO_6$ ($M = Ni, Zn; 0 \leq x \leq 0.5$) and $Ca_{3.1}Cu_{0.9}RuO_6$.¹⁰² In particular, a disordered rhombohedral structure of $Ca_{3.1}Cu_{0.9}RuO_6$ converts into an ordered monoclinic phase upon cooling to below 623 K.

2. Oxides with other stoichiometries

Some more complex oxides belonging to the family $A_{3n+3m}A'_nMn_{3m+n}O_{9m+6n}$ (with larger *n* and *m* and with a higher fraction of the octahedral sites in the chains) are also given in Table 2. Due to the similarity of ionic radii of manganese and other 3d elements, these phases possess specific structures and

manifest particular magnetic properties thus attracting a lot of attention from researchers. In particular, Melkorezova and Bazuev⁸⁷ demonstrated the existence of solid solutions with the common stoichiometry $\text{Sr}_4\text{Ni}_{3-x}\text{Mn}_x\text{O}_9$ in addition to the individual $\text{Sr}_4\text{NiMn}_2\text{O}_9$ oxide. These solid solutions were synthesised by the citrate method, which usually affords commensurate phases. However it was found that $\text{Sr}_4\text{Ni}_3\text{O}_9$ samples prepared in this way contained some amounts of NiO and SrO . The solid solutions $\text{Sr}_4\text{Ni}_{3-x}\text{Mn}_x\text{O}_9$ reveal a complex pattern of changes in the unit cell parameters (Fig. 8). The a parameter linearly increases with an increase in the Mn content, whereas c first decreases but then starts to increase passing a minimum at $x = 1.5$. The unit cell volume increases non-monotonically with an increase in x (*viz.*, with an inflexion at $x = 1.5$). Two oppositely directed factors affect the value of c as a function of the solid solution composition. The first factor is a gradual replacement of smaller Ni^{4+} cations with larger Mn^{4+} cations in the B sites. The second factor is a shortening of the Ni–Mn interatomic distances due to a shift of a part of the Ni^{2+} cations in the A' sites towards the faces of trigonal prisms. The experimental dependence of c on the composition indicates that the effects of the shift of Ni from the centres of prisms towards their faces prevail in the initial stages of the formation of the solid solutions (below $x = 1.5$), whereas the effects of manganese substitution for nickel starts to dominate in the late stages ($x > 1.5$).

Quarez *et al.*¹⁰³ reported the synthesis of a new representative of the $\text{A}_{3n+3m}\text{A}'_n\text{B}_{3m+n}\text{O}_{9m+6n}$ family, $\text{Ba}_4\text{NaMn}_2\text{O}_9$ ($n = 3$, $m = 1$), which is characterised by a quasi-one-dimensional structure with $a = 10.006(2)$ Å and $c = 8.210(3)$ Å (the $P321$ space group). This compound was prepared as single crystals electro-

chemically in NaOH melt. All attempts at the solid-state synthesis of this phase under various experimental conditions failed. In the $\text{Ba}_4\text{NaMn}_2\text{O}_9$ oxide, the sodium and manganese cations occupy the trigonal prismatic and octahedral sites, respectively. The authors argue that this compound represents the first example of manganese in the mean oxidation state of $4.5+$. It has to be noted, however, that the mixed-valence state of manganese in this compound was confirmed through neither magnetic nor spectroscopic measurements. No experimental evidence on an ordered arrangement of the Mn^{4+} and Mn^{5+} ions in the available crystallographic sites was given.

A similar hexagonal phase was also detected in the Sr-Li-Mn-O system. It was synthesised by the solid-state method from manganese oxide and lithium and strontium carbonates.¹⁰⁴ The X-ray diffraction pattern of this phase was satisfactory indexed in the $P321$ space group with $a = 9.42(1)$ Å and $c = 7.85(1)$ Å, similarly to the respective diffraction patterns of $\text{Sr}_4\text{Ni}_3\text{O}_9$ (Ref. 61) and $\text{Sr}_{12}\text{Ni}_{7.5}\text{O}_{27}$.¹⁰⁵ However this phase cannot exactly correspond to the composition of $\text{Sr}_4\text{LiMn}_2\text{O}_9$, since a $\text{Sr}_7\text{Mn}_4\text{O}_{15}$ impurity is always formed in addition to the hexagonal product when the exact stoichiometric load is taken for the solid-state synthesis.¹⁰⁶

A few strontium-based incommensurate oxides, *viz.*, $\text{Sr}_{14}\text{A}'_3\text{Mn}_8\text{O}_{33}$ [$A' = \text{Cu}$ (Ref. 21) or Co (Ref. 98)] and $\text{Sr}_9\text{A}'_2\text{Mn}_5\text{O}_{21}$ [$A' = \text{Ni}$ (Ref. 92) or Co (Refs 97 and 98)], have been synthesised, whereas no Ca- or Ba-containing analogues have been reported. The idealised crystal structures of $\text{Sr}_{14}\text{Co}_3\text{Mn}_8\text{O}_{33}$ and $\text{Sr}_9\text{Co}_2\text{Mn}_5\text{O}_{21}$ are shown in Fig. 9.

Apart from Mn, Co and Ni, some other 3d transition metals form quasi-one-dimensional oxides. In particular, syntheses of chromium-containing oxides with the composition Sr_3MCrO_6 ($M = \text{Sc}$, In , Lu-Ho , Y) in sealed quartz ampules at 1050°C were reported.⁷³ The Cr^{3+} cations in these compounds occupy the octahedral sites, whereas the trigonal prismatic sites are occupied by rare-earth elements. Probably, the $\text{Sr}_4\text{Cr}_3\text{O}_9$ oxide with a chain-like structure synthesised as single crystals (the $C_3^1-P_3$ space group, $z = 3$)⁷⁹ also belongs to this family. In this structure, the Cr^{3+} and Cr^{4+} cations occupy the octahedral and trigonal prismatic sites, respectively. A series of quasi-one-dimensional $\text{Sr}_3\text{LnNiO}_6$ oxides ($\text{Ln} = \text{Sc}$, In , Lu-Er) have been reported.⁷⁴ In these phases, the Ln^{3+} cations in the stable oxidation state stabilise nickel in the oxidation state $3+$. Colourless crystals of Ba_3NaBO_6 ($B = \text{Nb}$, Ta) with a trigonal structure have been synthesised by Wehrum and Hoppe.⁷⁶

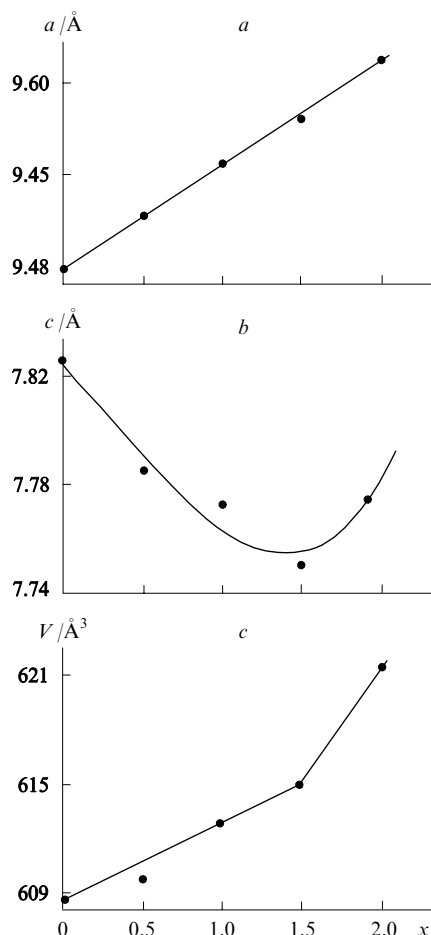


Figure 8. The unit cell parameters a (a), c (b) and volume V (c) for $\text{Sr}_4\text{Ni}_{3-x}\text{Mn}_x\text{O}_9$ solid solutions as a function of composition (x).

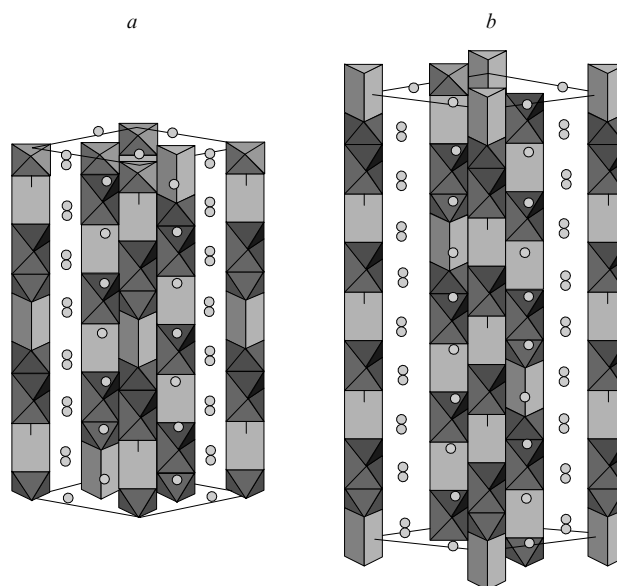


Figure 9. A polyhedral representation of the idealised crystal structures of $\text{Sr}_{14}\text{Co}_3\text{Mn}_8\text{O}_{33}$ (a) and $\text{Sr}_9\text{Co}_2\text{Mn}_5\text{O}_{21}$ (b).⁹⁸

Some low-dimensional $A_3A'BO_6$ oxides containing p elements, in particular, Pb (Ref. 75), Sb (Ref. 77) and Bi (Ref. 78) were synthesised (see Table 2). In these oxides, antimony and bismuth have an oxidation state of +5 and occupy the octahedral B sites in the chains. In contrast, the Pb^{4+} ions occupy the trigonal prismatic sites in the Sr_3PbNiO_6 oxide.

V. Specific features of the formation of $A_{3n+3m}A'_nB_{3m+n}O_{9m+6n}$ oxides

Oxides with the stoichiometry $A_3A'BO_6$ constitute the most numerous group of compounds within the family. The A sites in the oxides of this group are occupied by divalent alkaline-earth metals, *i.e.*, Ca, Sr or Ba (among them, strontium compounds are most widespread). The cationic pairs $A'B$ can correspond to various combinations of the oxidation states, *i.e.*, $(A')^+ - B^{5+}$, $(A')^{2+} - B^{4+}$, $(A')^{3+} - B^{3+}$ and $(A')^{4+} - B^{2+}$ (see⁸). In an analysis of reasons governing the distribution of cations over the two available sites it should be taken into account that the trigonal prismatic A' sites are characterised by a significantly larger size than the octahedral B sites. The B cations tend to occupy the octahedral sites since they typically have a higher charge and, respectively, a smaller ionic radius in the $A'B$ pair. The Sr_3LiBiO_6 oxide represents an exception to this rule, since it is the Li^+ cations that occupy the octahedral sites in this compound.[†] The authors suggested⁷⁸ that the trigonal prismatic sites are too large to accommodate the Li^+ cations. It is of note that this oxide is crystallised in a triclinic lattice, unlike the vast majority of the $A_3A'BO_6$ compounds.

Sr_3PbNiO_6 is another exception to the above rule. In this oxide, the highly charged Pb^{4+} ions ($r = 0.775$ Å) occupy the trigonal prismatic sites, whereas the smaller Ni^{2+} cations ($r = 0.69$ Å) appear in the octahedral B sites. Smith *et al.*,⁷⁵ who synthesised the Sr_3PbNiO_6 phase for the first time, utilised the term 'inverse' to describe its structure by analogy with the normal and inverse spinels. The presence of the Ni^{2+} ions in the octahedral sites of the Sr_3PbNiO_6 oxides is very surprising since nickel occupies the trigonal prismatic sites in all other known $A_3A'BO_6$ oxides.

The presence of large Ba^{2+} cations ($r = 1.42$ Å for the coordination number of 8)¹⁰⁷ in the A sites of $A_3A'BO_6$ oxides conforms to the general trend that only large alkali metal cations occupy the A' sites in the $Ba_3A'BO_6$ oxides, where $A' = Li, Na$; $B = Ir, Ru, Sb, Bi, Nb, Ta$). It might be suggested that a Ba_3MnBO_6 oxide containing the Mn^{2+} ions with the largest ionic radius among divalent 3d elements should exist. However this can be realised only with large tetravalent cations as B. The existence of complex oxides with the common formula A_4PtO_6 ($A = Ca, Sr, Ba$) with the A^{2+} cations in the trigonal prismatic A' sites, which are characterised by similar structures, probably means that there is no limitation on the maximum radius of an A' cation for the cationic pair $(A')^{2+} - B^{4+}$.

It has to be noted that only Ca^{2+} ions ($r = 1.12$ Å), which have the smallest ionic radius in the series $Ca^{2+} - Sr^{2+} - Ba^{2+}$, are capable of forming $A_3A'MnO_6$ oxides with the small Mn^{4+} ions in the B sites.

The influence of the size factor on the stability of the oxides has been analysed in detail for the cationic pair $(A')^{3+} - B^{3+}$. In a series of compounds with the common formula Sr_3LnRhO_6 [$r(Rh^{3+}) = 0.665$ Å], only phases with $Ln = Sc, In, Yb - Sm$ appear stable.^{51,52} For the Sr_3LnCrO_6 series [$r(Cr^{3+}) = 0.615$ Å], stable compounds were obtained with $Ln = Sc, In, Lu - Ho$ and Y .⁷³ Among Sr_3LnNiO_6 oxides (the ionic radius of the Ni^{3+} cation in the low-spin state is 0.56 Å), the

phases with $Ln = Sc, In, Lu - Er$ and Y are stable.⁷⁴ It is evident that the size of the trigonal prismatic cavities is insufficient to accommodate rare-earth metal cations larger than Ho^{3+} and Y^{3+} in the latter case. The above example demonstrates that a contraction of the octahedral site due to the introduction of smaller ions instead of larger ones results in the respective contraction of the trigonal prismatic sites and *vice versa*. Exactly due to this reason, the trigonal prismatic cavity appears quite appropriate for the Li^+ cations in Sr_3LiSbO_6 but too loose in Sr_3LiBiO_6 . The ionic radii of the alkaline-earth metal cations in the A (see above) and A' sites produce analogous effects. In particular, the Mg^{2+} cation can be introduced in an A_3MgBO_6 oxide only provided that $A = Sr$ (with the exception of Ca_3MgIrO_6).⁴¹

Let us now consider the specific features of the formation of the $A_{3n+3m}A'_nB_{3m+n}O_{9m+6n}$ oxides and the influence exerted on this process by the size of cations. Manganese-containing oxides with the stoichiometry $A_3A'MnO_6$ exist only for $A = Ca$. Meanwhile, stable $A_4A'Mn_2O_9$ oxides are known only for Sr (with the single exception of $Ca_4CuMn_2O_9$). Barium forms groups of oxides belonging to the family starting from the composition $A_5A'Mn_3O_{12}$. As has been discussed above, the n/m ratio determines the ratio between the numbers of the $[A_3A'O_6]$ and $[A_3O_9]$ layers stacked along the c axis. In the $A_3A'MnO_6$ oxides ($n = 1, m = 0$), all the $[A_3O_9]$ layers are replaced with $[A_3A'O_6]$. In the $A_4A'Mn_2O_9$ oxides, three $[A_3A'O_6]$ layers occur per $[A_3O_9]$ layer. Therefore, the distance between neighbouring A_3O_9 layers should increase with an increase in the number of octahedra in the chains; this is achieved by an increase in the ionic radius of the A^{2+} cation upon the replacement of Ca with Sr and Ba. In other words, a higher fraction of octahedra in the chains requires a larger cation in the A site.

The cationic compositions of the $A_3A'BO_6$ oxides is similar to the compounds from the Ruddlesden–Popper family (*i.e.*, $A_3B_2O_7$ or $A_{n+1}B_nO_{3n+1}$ with $n = 2$). Taking into account that some of the Ruddlesden–Popper oxides contain two different cations in the B sites [*e.g.*, $Sr_3FeCoO_{7-\delta}$,¹⁰⁸ $Sr_3Fe_{2-x}Mn_xO_{7-\delta}$ (Ref. 109)] and the oxygen deficiency δ can be as large as 1, it might be expected that they undergo structural transitions into quasi-one-dimensional structures. Indeed, a transition from the Ruddlesden–Popper structure to a quasi-one-dimensional structure of the $A_3A'BO_6$ type was observed in $Sr_3ScCoO_{6+\delta}$.¹¹⁰ The former phase, $Sr_3ScCoO_{6.08}$, was synthesised at 1250 °C, whereas the latter, at 1100 °C. However the quasi-one-dimensional Sr_3ScCoO_6 complex oxide undergoes amorphisation and probably decomposition upon storage in air.

VI. Magnetic properties

The presence of transition metals and the quasi-one-dimensional character determines the specific magnetic properties of the oxides under consideration. The relation of magnetic properties to the structure is governed to a large extent by a high degree of mutual isolation of the $[A'B_nO]_\infty$ chains. According to magnetic studies of single crystals of these compounds, the low-dimensional character of their structures gives rise to a pronounced anisotropy of their magnetic properties. These systems typically undergo magnetic ordering at low temperatures. Notwithstanding, some compounds from the $A_{3n+3m}A'_nB_{3m+n}O_{9m+6n}$ family are characterised by relatively high temperatures of the magnetic ordering, despite their quasi-one-dimensional structures. In particular, $Ca_3A'RuO_6$ oxides ($A' = Li, Na$) manifest a collinear magnetic structure with the Néel temperature of $T_N \approx 100$ K.⁹ So high value of T_N implies a three-dimensional antiferromagnetic ordering. $Sr_3A'BO_6$ complex oxides manifest the whole spectrum of magnetic properties (Table 3): they reveal either 1D-antiferromagnetism or ferromagnetism. Furthermore, ferromagnetic interactions inside the chain and antiferromagnetic interchain interactions are typical of these phases. The disordered quantum spin chain paramagnetism has been discovered for the first time in a compound from this family,

§ It is of note that strontium forms compounds with all possible cationic pairs, whereas barium-containing oxides are known mainly for the $(A')^+ - B^{5+}$ cationic pairs.

† The Li^+ and Bi^{5+} cations are characterised by identical ionic radii (0.76 Å).¹⁰⁷

Table 3. The magnetic properties of $\text{Sr}_3\text{A}'\text{BO}_6$ oxides ($\text{A}' = \text{Ni, Cu, Zn, Co}$; $\text{B} = \text{Ir, Pt}$).

Compound	Properties
$\text{Sr}_3\text{NiIrO}_6$	antiferromagnetism
$\text{Sr}_3\text{CuIrO}_6$	ferromagnetism
$\text{Sr}_3\text{ZnIrO}_6$	antiferromagnetism
$\text{Sr}_3\text{NiPtO}_6$	"
$\text{Sr}_3\text{CuPtO}_6$	"
$\text{Sr}_3\text{CoPtO}_6$	disordered spin chain paramagnetism
$\text{Sr}_3\text{ZnPtO}_6$	diamagnetism
$\text{Sr}_3\text{CuIr}_{0.5}\text{Pt}_{0.5}\text{O}_6$	disordered spin chain paramagnetism

$\text{Sr}_3\text{CuPt}_{0.5}\text{Ir}_{0.5}\text{O}_6$ (see Ref. 8). The $\text{Ca}_3\text{Co}_2\text{O}_6$ oxide undergoes the ferrimagnetic ordering at $T < 25$ K (Ref. 111) due to the ferromagnetic and antiferromagnetic exchange interactions between the cobalt cations located within the same chain and in neighbouring chains, respectively.

For the analysis of magnetic properties it would be convenient to subdivide the $\text{A}_3\text{A}'\text{BO}_6$ compounds into two groups: in the first group, magnetic cations occupy exclusively the octahedral sites and in the second group, the magnetic cations occupy both the octahedral and trigonal prismatic sites. In the former case, the distance between magnetic cations located in different chains is only slightly larger than that within the same chain. Usually, changes in the magnetic susceptibility (χ) for such compounds are interpreted within the one-dimensional Ising model. The interactions between the magnetic cations typically give rise to the antiferromagnetic correlations with maxima in $\chi = f(T)$ curves. Normally, no long-range magnetic ordering is observed in these compounds.

On the other hand, $\text{A}_3\text{A}'\text{BO}_6$ compounds with magnetic ions occupying both the A' and B sites often manifest a complex magnetic behaviour due to an interplay between the intrachain and interchain magnetic interactions. In particular, a magnetic structure was revealed for $\text{Ca}_3\text{Co}_2\text{O}_6$ in a low-temperature neutron diffraction study. Meanwhile, no magnetic reflections were observed in other isostructural compounds (such as $\text{Sr}_3\text{NiIrO}_6$).⁷ Taking into account that the basal plane in the crystal structure of $\text{Sr}_3\text{NiIrO}_6$ is described by a 2D hexagonal lattice (*i.e.*, each chain is surrounded by six neighbouring chains), it might be assumed that the lack of the magnetic ordering is caused by either a disorder in the distribution of the transition metal atoms over the crystallographic sites or a specific geometric structure of the crystal (the geometric frustration).

The magnetic properties of $\text{A}_3\text{A}'\text{BO}_6$ oxides ($\text{B} = \text{Pt, Ir, Rh, Ru}$) are strongly dependent on the electronic configuration of metals occupying both the A' and B sites. Many of these compounds are similar in terms of their structures but their magnetic properties are manifold. In the $\text{Sr}_3\text{A}'\text{PtO}_6$ oxides ($\text{A}' = \text{Cu, Co, Ni, Zn}$), the platinum atoms occupying the octahedral sites are in the low-spin (diamagnetic) state. As a consequence, the $\text{Sr}_3\text{ZnPtO}_6$ oxide with the diamagnetic Zn^{2+} cation behaves as a diamagnetic. In contrast, according to the magnetic susceptibility measurements, the Ni^{2+} cations in the $\text{Sr}_3\text{NiPtO}_6$ oxide manifest a strong one-ion magnetic anisotropy, which induces the local antiferromagnetic ordering at $T < 25$ K.³² Furthermore, $\text{Sr}_3\text{CoPtO}_6$ reveals the disordered spin chain paramagnetism. According to the magnetic susceptibility and heat capacity measurements, the behaviour of $\text{Sr}_3\text{CuPtO}_6$ (Refs 32 and 112) is well described by theoretical models for classical spin chain compounds with $S = 1/2$. It is ferromagnetism that is typical of such compounds (see Table 3).

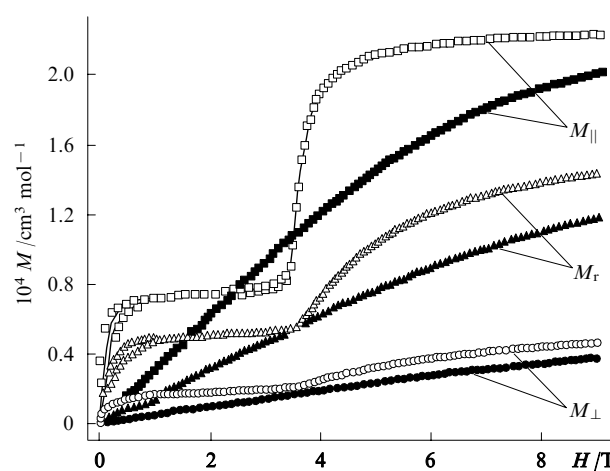
The iridium-based $\text{Sr}_3\text{A}'\text{IrO}_6$ oxides are characterised by a more complex pattern of magnetic behaviour due to the replacement of the diamagnetic Pt^{4+} cations in the octahedral sites with the low-spin $\text{Ir}^{4+}(\text{d}^5)$ cations having an unpaired electron. The magnetic susceptibility of $\text{Sr}_3\text{ZnIrO}_6$ above the antiferromagnetic

transition (25 K) is well described by the Heisenberg linear chain model. The magnetic properties of $\text{Sr}_3\text{NiIrO}_6$ evolve in a complicated manner as a function of temperature, which is due to an interplay between the ferromagnetic interchain and antiferromagnetic intrachain exchange interactions. The first preliminary conclusion⁷ on the ferromagnetic behaviour of $\text{Sr}_3\text{CuIrO}_6$ was corrected in more recent studies. Actually,¹¹³ below the magnetic transition temperature in the zero field, this compound behaves as a spin glass, but it converts into the ferromagnetic state already in a weak magnetic field (~ 200 Oe). Similarly, detailed investigations^{114,115} into the magnetic properties of $\text{Sr}_3\text{Cu}_{1-x}\text{Zn}_x\text{IrO}_6$ and $\text{Sr}_3\text{CuPt}_x\text{Ir}_{1-x}\text{O}_6$ solid solutions reveal a more complex character of the magnetic interactions both in the individual quasi-one-dimensional oxides and solid solutions than that reported initially.

The $\text{Ca}_3\text{CuIrO}_6$ and $\text{Ca}_3\text{CuRhO}_6$ oxides undergo the magnetic ordering¹¹⁶ at ~ 15 K, but the nature of these magnetic transitions is rather complex. As for Co-based oxides, $\text{Ca}_3\text{CoIrO}_6$ undergoes the frustrated magnetic ordering below 30 K.^{38,117} Meanwhile, the $\text{Ca}_3\text{CoRuO}_6$ oxide behaves as a normal antiferromagnetic with $T_N = 55$ K.³⁸

When polycrystalline samples are studied, no saturation magnetisation can be achieved even in very strong magnetic fields, which is a specific feature of the magnetic properties of quasi-one-dimensional oxides. Therefore, accurate values of the saturation magnetisation and, consequently, ferromagnetic moments can only be determined for single crystals by performing careful measurements along specific crystallographic directions. The ferromagnetic moment of $\text{Ca}_3\text{Co}_2\text{O}_6$ was measured for a polycrystalline sample mixed with epoxy resin magnetised in a field of 80 kOe.¹¹¹ As a result of this treatment, the sample had a strong preferred orientation along the c axis and manifested highly anisotropic magnetic properties (Fig. 10). The character of the observed dependence of magnetisation M on the applied magnetic field strength H indicates that the ferromagnetic chains ($T_{C1} = 26$ K) interact antiferromagnetically ($T_{C2} = 13$ K). In weak fields, this system occurs in the partially disordered antiferromagnetic (PDA) state at $10 \leq T \leq 25$ K but converts into the ferrimagnetic state at $T < 10$ K. In the PDA state, one third of the chains are magnetically disordered while two third of the chains are ferromagnetic and interact with each other antiferromagnetically.

Smith and co-workers⁵⁶ observed a strong anisotropy of the magnetic susceptibility χ of single-crystalline $\text{Ba}_8\text{CoRh}_6\text{O}_{21}$ ori-

**Figure 10.** The magnetisation curves of $\text{Ca}_3\text{Co}_2\text{O}_6$ measured in a magnetostatic field of a strength $0 \leq H \leq 9$ T at 12 K (open symbols) and 35 K (closed symbols).¹¹¹

$M_{||}$, $M_{\perp}$ are the magnetisation values measured for the sample oriented with its c axis parallel and perpendicular to the applied magnetic field, respectively; M_r is the magnetisation for an unoriented samples.

ented with the crystallographic c axis either parallel or perpendicular to the applied magnetic field. The anisotropy is preserved up to room temperature. The rhodium cations in the $A_3A'RhO_6$ oxides can be tri-, tetra- or pentavalent, depending on the oxidation state of an element in the A' sites. The magnetic properties of the Sr_3LnRhO_6 compounds were interpreted⁵² assuming expected values of the magnetic moments for the Ln^{3+} cations and the low-spin state for the Rh^{3+} cations ($t_{2g}^6e_g^0$, $S = 0$). The cobalt and iron cations in Ca_3CoRhO_6 and Ca_3FeRhO_6 are divalent, while rhodium is tetravalent, according to measurements of χ .⁴⁹ Presumably, the temperature dependence of the magnetic properties of Ca_3CoRhO_6 is similar to that of Sr_3NiIrO_6 and Ca_3CoIrO_6 . The magnetic susceptibility measured in the zero-field cooling (ZFC) mode drops down at 35 K, whereas it remains virtually constant upon cooling in a magnetic field (*i.e.*, in the FC mode). According to the results reported by Niitaka *et al.*,⁴⁹ this compound is characterised by the antiferromagnetic interchain exchange interactions coupled with the ferromagnetic intrachain interactions. Neutron diffraction studies¹¹⁸ showed that this compound occurs at $T < 90$ K in the partially disordered antiferromagnetic state (1/3 of the chains are magnetically disordered, while 2/3 of the chains are ordered ferromagnetically and interact with each other antiferromagnetically). According to recent results by Niitaka *et al.*¹¹⁸ (in contrast to earlier data⁴⁹ on the magnetic susceptibility), both transition metals in the Ca_3CoRhO_6 oxide are trivalent. This conclusion is supported by an analysis of the oxidation states of cations in $Ca_3Co_2O_6$ and Ca_3CoRhO_6 based on theoretical electron band structure calculations.¹¹⁹ Despite the pronounced similarity between these two compounds in terms of both their structures and magnetic properties, the antiferromagnetic interchain interactions therein are substantially different, as evidenced by measurements of the specific heat capacity.¹²⁰ Studies of related rhodium oxides with the Co atoms substituted with Fe and Zn revealed that the Ca_3FeRhO_6 oxide undergoes a three-dimensional antiferromagnetic transition at 12 K, while Sr_3ZnRhO_6 experiences an inhomogeneous magnetic ordering below ~ 15 K.¹²¹ The antiferromagnetic interactions at $T < 10$ K were also observed¹²² for Sr_4RhO_6 and Sr_3CaRhO_6 . Mwamuka *et al.*¹²³ elucidated the magnetic behaviour of $Sr_4Fe_{0.73}Rh_{2.27}O_9$. Unfortunately, the experimental data on χ obtained were insufficient to unambiguously establish the oxidation states of Fe and Rh in this compound. A maximum in the $\chi = f(T)$ curve at 8 K points to a probable antiferromagnetic ordering.

Manganese-based complex oxides also exhibit diverse magnetic properties. The antiferromagnetic ordering in Ca_3ZnMnO_6 and Ca_3NiMnO_6 was established by means of neutron diffraction.⁶⁷ It is of note that the Ca_3ZnMnO_6 oxide, where a half of cationic positions in the chains (*viz.*, trigonal prismatic sites) are occupied by the diamagnetic Zn^{2+} ions, is characterised by a significantly lower Néel temperature ($T_N = 25$ K) than $Ca_3A'RuO_6$ ($A' = Li, Na$). The Ca_3NiMnO_6 oxide containing magnetic cations in both the octahedral and trigonal prismatic sites is an antiferromagnetic with $T_N = 20$ K (according to Ref. 67) or 18 K (according to Ref. 69). The $\chi = f(T)$ curve for this oxide obeys the Curie–Weiss law only above 300 K, which is probably due to the preservation of the local magnetic ordering up to high temperatures. In contrast to the ferro(ferri)magnetic $Ca_3Co_2O_6$ compound, its Mn-analogue, Ca_3CoMnO_6 , reveals the long-range antiferromagnetic ordering ($T_N = 13$ K).^{71, 124} It has to be however noted that only short-range magnetic ordering was revealed in Ca_3CoMnO_6 at 4.2 K using neutron diffraction:⁷¹ only broad weak reflexes were observed in the diffraction pattern instead of distinct magnetic reflections. Furthermore, the heat capacity *vs.* temperature curve for this phase has a kink at 13 K, which is indicative of magnetic correlations extending to a part of the crystal rather than to the whole crystal.¹²⁴ Probably, this is a reason for the absence of magnetic reflections in the neutron powder diffraction pattern of this compound. The magnetic properties of $Ca_3Co_{1.25}Mn_{0.75}O_6$ are similar to those of

Ca_3CoMnO_6 except for a higher T_N (18 K). For these phases, both the ferromagnetic ordering and spin glass state can be decisively ruled out. These oxides undergo spin-reorientation transitions at $T \leq 5$ K, as evidenced by the hysteresis loops in their magnetisation curves.

According to the measurements of the magnetic susceptibility and heat capacity,^{71, 125} the triclinic Ca_3CuMnO_6 oxide undergoes the antiferromagnetic ordering at $T < 6$ K. This compound manifests strict long-range magnetic order and is not liable to the magnetic structure frustration, despite the positional disorder of the Cu^{2+} and Mn^{4+} cations and the presence of several types of these cations, which are characterised by different Cu–O and Mn–O bond lengths. The heat capacity *vs.* temperature curve reveals two distinct λ -peaks at 5.2 K and 3.6 K. The experimental data^{69–72} on the magnetic susceptibility of $Ca_3A'MnO_6$ are shown in Fig. 11.

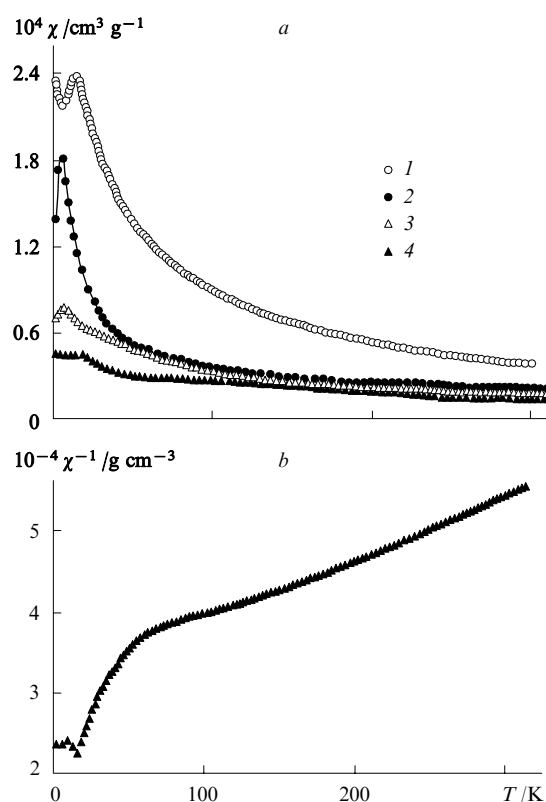


Figure 11. The temperature dependences of magnetic susceptibility (a) and the Curie–Weiss plots (b) for a series of $Ca_3A'MnO_6$ oxides. $A' = \text{Co}$ (1), Cu (2), Zn (3), Ni (4).

The magnetic susceptibility of $Sr_4ZnMn_2O_9$ and $Sr_4MgMn_2O_9$ as a function of temperature is shown in Fig. 12.⁸⁹ It is clearly seen that the magnetic susceptibility of these oxides reveals a complex temperature dependence at $T < 250$ K and does not obey the Curie–Weiss law. The apparent magnetic moments approach the purely spin value of the Mn^{4+} ions at a high temperature. The $\chi(T)$ curves exhibit a broad maximum at 100–150 K, which is more pronounced in the case of $Sr_4ZnMn_2O_9$. These experimental data on $\chi(T)$ for $Sr_4ZnMn_2O_9$ and $Sr_4MgMn_2O_9$ were analysed within a model of the isotropic exchange interactions between the Mn^{4+} – Mn^{4+} dimers. The dramatic increase in the magnetic susceptibility at low temperature obeys the Curie–Weiss law, which indicates that not all the Mn^{4+} ions in $Sr_4ZnMn_2O_9$ and $Sr_4MgMn_2O_9$ are combined into dimers.

Similar conclusions were derived for $Sr_4NiMn_2O_9$ (Refs 84–86) and $Sr_4CuMn_2O_9$ (Refs 20, 22 and 81). Each

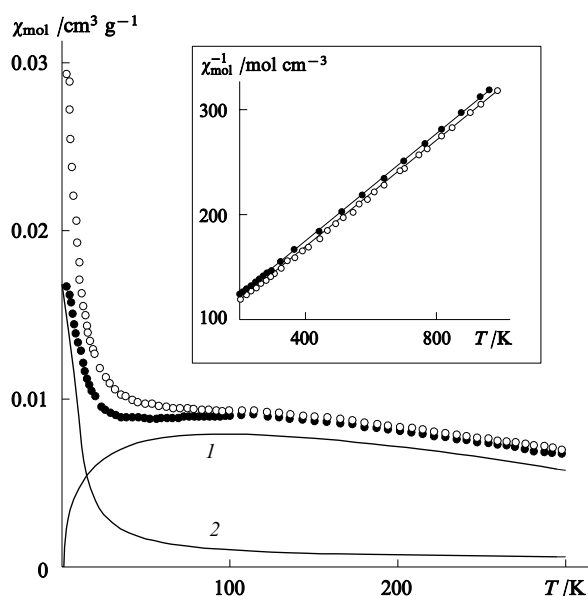


Figure 12. The temperature dependences of magnetic susceptibility for $\text{Sr}_4\text{MgMn}_2\text{O}_9$ (open circles) and $\text{Sr}_4\text{ZnMn}_2\text{O}_9$ (closed circles).⁸⁴ The curves 1 and 2 show the contributions of the dimeric and paramagnetic components. The Curie–Weiss plot for the compound showing the linearity in the temperature range of 300–950 K is given in the inset.

Mn^{4+} ion in the chains present in the crystal structures of the $\text{A}_4\text{A}'\text{Mn}_2\text{O}_9$ oxides is involved in the exchange interactions with a neighbouring Mn^{4+} cation and a divalent cation (Zn, Mg, Ni or Cu). It is the exchange interactions between the Mn^{4+} ions that dominate the magnetic susceptibility of these phases at $T < 250$ K, although nickel and copper have their own unpaired electrons in the d shells (in contrast to zinc and magnesium). The contribution from the exchange interactions between the Mn^{4+} and Ni^{2+} (Cu^{2+}) ions is negligibly small.

Among the $\text{A}_4\text{A}'\text{Mn}_2\text{O}_9$ oxides, $\text{Sr}_4\text{CoMn}_2\text{O}_9$ is worthy of a special note. The temperature dependence of inversed magnetic susceptibility for this compound at $T > 150$ K obeys the Curie–Weiss law⁸²

$$\chi = \frac{C}{T - \Theta}.$$

The paramagnetic moment experimentally measured in this temperature range ($6.61 \mu_B$) is close to the theoretical value calculated for the cationic combination $\text{Co}^{2+} - 2\text{Mn}^{4+}$ ($6.71 \mu_B$). The negative value of Θ (-120 K) indicates that the antiferromagnetic interactions dominate. This oxide exhibits a spontaneous magnetisation at $T < 12$ K. In order to analyse the origin of this low-temperature magnetism, real and imaginary parts of the dynamical magnetic susceptibility were measured in the frequency range from 0.1 Hz to 10 kHz. It was found that the $\text{Sr}_4\text{CoMn}_2\text{O}_9$ oxide is characterised by a partially disordered magnetic structure close to that typical of spin glasses and different from that of $\text{Sr}_4\text{NiMn}_2\text{O}_9$, where pairs of the Mn^{4+} ions interact antiferromagnetically along the chains. Similar magnetic properties were observed in $\text{Sr}_{14}\text{Co}_3\text{Mn}_8\text{O}_{33}$ (Ref. 98) and $\text{Sr}_9\text{Co}_2\text{Mn}_5\text{O}_{21}$ (Refs 97 and 98). The temperature dependence of the magnetic susceptibility plotted in the coordinates $1/\chi = f(T)$ for some of the $\text{A}_4\text{A}'\text{Mn}_2\text{O}_9$ oxides discussed above are shown in Fig. 13. A step observed for $\text{Ca}_4\text{CuMn}_2\text{O}_9$ at 123 K is attributed to the presence of the perovskite CaMnO_3 phase, manifesting a weak ferromagnetism at $T < 123$ K, in the sample studied.

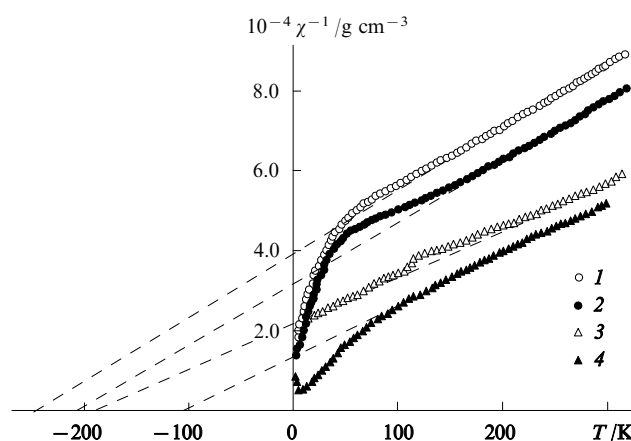


Figure 13. The Curie–Weiss plots for $\text{Sr}_4\text{NiMn}_2\text{O}_9$ (1), $\text{Sr}_4\text{CuMn}_2\text{O}_9$ (2), $\text{Ca}_4\text{CuMn}_2\text{O}_9$ (3) and $\text{Sr}_4\text{CoMn}_2\text{O}_9$ (4).⁸²

In the case of $\text{Ba}_6\text{ZnMn}_4\text{O}_{15}$, the magnetic susceptibility as a function of temperature deviates from the Curie–Weiss law in a temperature range of 4.2–300 K,⁶⁶ which is manifested in a drastic increase in χ at $T < 16$ K and a broad local maximum in the $\chi = f(T)$ curve at 45 K. It was suggested that the short-range antiferromagnetic interactions between the Mn^{4+} cations giving rise to the one-dimensional alignment of magnetic moments in the face-sharing octahedra is preserved up to 300 K. The increase in χ at $T < 16$ K is due to the contribution of the Mn^{4+} cations with uncompensated (owing to the structural disorder) magnetic moments into the total magnetic susceptibility.

The temperature dependence of the magnetic susceptibility for $\text{Ba}_6\text{CuMn}_4\text{O}_{15}$ was interpreted⁶⁶ as a joint effect of the paramagnetism of the Cu^{2+} ions in the trigonal prismatic sites and the ordering of the Mn^{4+} cations (that gives rise to a broad maximum at 90 K). The neutron diffraction patterns of $\text{Ba}_6\text{CuMn}_4\text{O}_{15}$ and $\text{Ba}_6\text{ZnMn}_4\text{O}_{15}$ measured at 1.7 K revealed magnetic reflections attributable to the appearance of the long-range magnetic order of the ions in the octahedral sites. The magnetic behaviour of these oxides was simulated using an unusual magnetic structure, in which the antiferromagnetic superexchange interactions in a strongly frustrated crystal structure gives rise to a rotation of spins in neighbouring chains by 120° .

The magnetic properties of the $\text{Ba}_6\text{A}'\text{Mn}_4\text{O}_{15}$ oxides ($\text{A}' = \text{Mg}, \text{Ni}$)⁹⁴ differ significantly from those of their zinc and copper analogues.⁶⁶ In particular, the $\chi = f(T)$ curve for the $\text{Ba}_6\text{MgMn}_4\text{O}_{15}$ oxide reveals no broad maxima at intermediate temperatures. This compound follows the Curie–Weiss law at $T > 125$ K. Since the magnetic susceptibilities of $\text{Ba}_6\text{ZnMn}_4\text{O}_{15}$ and $\text{Ba}_6\text{MgMn}_4\text{O}_{15}$ are governed exclusively by the exchange interactions between the Mn^{4+} cations, the differences between these two phases should be attributed to different distributions of the Mn^{4+} cations over the octahedral and trigonal prismatic sites therein. The experimentally determined value of the Curie constant for $\text{Ba}_6\text{NiMn}_4\text{O}_{15}$ appeared smaller than the respective theoretical value calculated as a joint contribution from the nickel and manganese cations. This discrepancy can be explained assuming that a part of the Ni^{2+} cations adopt the planar square coordination. This fraction should amount to $\sim 28\%$ to reconcile the experimental and theoretical values of the Curie constant.

The experimental data on the magnetic susceptibility and magnetisation of $\text{Ba}_9\text{MgMn}_7\text{O}_{24}$ (Ref. 96) are close to the respective results for $\text{Ba}_5\text{PdMn}_3\text{O}_{12}$, $\text{Ba}_6\text{PdMn}_4\text{O}_{15}$ and $\text{Ba}_7\text{PdMn}_5\text{O}_{18}$.⁹¹ In particular, a deviation of the $1/\chi = f(T)$ curve from the Curie–Weiss law is observed at $T < 225$ K owing to the magnetic ordering of the Mn^{4+} cations in the quasi-one-dimensional chains $-\text{MgO}_6-(\text{MnO}_6)_7-\text{MgO}_6-(\text{MnO}_6)_7-$ composed of trigonal prisms accommodating the Mg^{2+} cations and octahedra occupied by Mn^{4+} . Additionally, a

specific character of the magnetic susceptibility as a function of the applied magnetic field strength at 2 K suggests a low ferromagnetic moment.

It would be interesting to compare the magnetic properties of oxides from the $A_{3n+3m}A'_nMn_{3m+n}O_{9m+6n}$ family with those of $BaMnO_3$, the ultimate representative of the family.¹⁶ The magnetic susceptibility of $BaMnO_3$ and many quasi-one-dimensional oxides of the family deviates from the Curie–Weiss law in a temperature range from 4.2 K to 300 K. Furthermore, at temperatures $T < 215$ K, the magnetic susceptibilities χ measured in a magnetic field and in the zero field are different; the reason for this discrepancy remains unclear. The transition from a paramagnetic into a magnetically ordered state occurs at 59 K. Probably, this transition for $BaMnO_3$ and other $A_{3n+3m}A'_nMn_{3m+n}O_{9m+6n}$ oxides differs from ordinary transitions from a paramagnetic into an antiferromagnetic state. It should rather be considered as a transition from a 1D-magnetically ordered state into a 3D-ordered one. Within the chains, the spins of neighbouring Mn^{4+} cations interact antiferromagnetically and lie in the plane perpendicular to [001]. The comparative analysis of the magnetic properties of $BaMnO_3$ and other known $A_{3n+3m}A'_nMn_{3m+n}O_{9m+6n}$ oxides with $A' = Zn^{2+}$, Mg^{2+} demonstrates their essential similarity. This implies that in the case of compounds with diamagnetic cations in the trigonal prismatic sites, the interchain magnetic exchange prevails over the intrachain interactions. But when a second magnetic cation is introduced into the $[A'Mn_nO]_\infty$ chains, the pattern of magnetic behaviour becomes more complex. Jordan *et al.*⁹⁸ pointed out that the magnetic properties of the quasi-one-dimensional phases, such as $Sr_3NiRhO_{6+\delta}$, $Sr_3CuRhO_{6+\delta}$, $Sr_4NiMn_2O_9$ and $Ca_3Co_{1+x}Mn_{1-x}O_6$, are extremely sensitive to the positional disorder within the chains and structural transitions.

Interesting results were obtained in a study of $Ca_3A'MnO_6$ ($A' = Zn, Cu, Ni, Co$), solid solutions $Ca_3Zn_{1-x}Cu_xMnO_6$ ($0 \leq x < 0.75$) isostructural to the hexagonal K_4CdCl_6 phase, $Ca_3Zn_{0.25}Cu_{0.75}MnO_6$ (with a triclinic lattice similar to that of Ca_3CuMnO_6) and $Ca_4A'Mn_2O_9$ by means of ESR.^{126,127} The ESR spectra of the $Ca_3A'MnO_6$ oxides ($A' = Zn, Cu$) revealed intense signals of the Mn^{4+} cations, although there were no features attributable to Cu^{2+} . Furthermore, the integral spectral intensity and g-factors were temperature dependent. The lack of ESR signal from the copper ions in the spectra of Ca_3CuMnO_6 and solid solutions $Ca_3Zn_{1-x}Cu_xMnO_6$ ($0 \leq x < 1$) can be due to the planar square coordination of the Cu ions in these compounds. A weak signal emerging in the spectrum of the quasi-one-dimensional Ca_3CuMnO_6 oxide following its annealing at 470 K can indicate¹⁰² a change in the coordination type of the Cu^{2+} ions. Therefore, it might be suggested that the compound undergoes a structural phase transition at $T > RT$.

The ESR spectra of $Ca_3A'MnO_6$ ($A' = Ni, Co$) revealed no signals of the Mn^{4+} ions. The intensities of the observed lines (which are 4 orders of magnitude smaller than in the case of the oxides with $A' = Zn, Cu$) with $g = 2.11$ and widths $\Delta H \sim 590$ G are virtually independent of temperature in the range of 77–490 K.

According to the analysis of the ESR features of the Mn^{4+} cations in the spectrum of Ca_3CuMnO_6 , a weak antiferromagnetic ordering exists already at 300 K. Taking into account the absence of ESR signals of Mn^{4+} in the spectra and the lack of the magnetic order in $Ca_3A'MnO_6$ with $A' = Ni$ or Co , it might be suggested that relatively strong exchange interactions are realised between the nickel (cobalt) and manganese cations, which give rise to a redistribution of the electron density and a change in the charge state of the A' cations from $2+$ to $3+$ and, respectively, of the manganese cations from $4+$ to $3+$, in contrast to structural data that are indicative of the cationic combinations $(A')^{2+} - Mn^{4+}$.

The ESR spectra of the $Sr_4A'Mn_2O_9$ oxides ($A' = Zn, Cu, Ni$) also reveal distinct signals of Mn^{4+} and no signals of Cu^{2+} and Ni^{2+} .

* * *

An analysis of the available information concerning quasi-one-dimensional oxides of the $A_{3n+3m}A'_nB_{3m+n}O_{9m+6n}$ family indicates that the number of theoretically predicted compounds belonging to the family presently significantly exceeds the number of actually synthesised and characterised compounds. This is equally true for platinum metal- and manganese-based complex oxides. Most probably, the major reason for this is a similar chemical composition of possible phases, which impedes the purposeful search for conditions of their synthesis. For instance, Bazuev *et al.*⁸¹ studied the $Ca - Cu - Mn - O$ system and obtained two compounds, Ca_3CuMnO_6 and $Ca_4CuMn_2O_9$. The latter phase contained admixtures of CuO (according to powder X-ray diffraction data) and $CaMnO_3$ (according to magnetic measurements). This compound is incommensurate. The ratio $c_1/c_2 = 0.6891$ is significantly larger than the value 0.666 typical of phases with this stoichiometry but rather close to the value of 0.6923 expected for a commensurate phase with the composition $A_{18}A'_5Mn_8O_{39}$ ($m = 1, n = 5$). Hopefully, the experimental conditions required to stabilise both these phases, *i.e.*, $Ca_4CuMn_2O_9$ and $Ca_{18}Cu_5Mn_8O_{39}$ will be found in the future.

The vast majority of quasi-one-dimensional oxides known to date have been synthesised using solid-state reactions, therefore, more efforts should be put forth for the search for conditions of solid-state syntheses affording single crystals of desired size and quality.

Although magnetic parameters are reported in virtually any study dealing with the synthesis of new oxides of the $A_{3n+3m}A'_nB_{3m+n}O_{9m+6n}$ family, the general trends in the magnetic behaviour of quasi-one-dimensional compounds have not been elucidated in sufficient details. This relates to complex correlations between the structure of these compounds (including such features as short metal–metal distances within the chains and a substantial separation of neighbouring chains), electronic configuration of the d elements in the A' and B sites and their properties. The nature of low-temperature magnetic phases has not been determined to date. The interrelations between changes in the chemical composition of the compounds at the course of their synthesis and their magnetic behaviour are yet to be established.

For the compounds containing several (most frequently, two) transition metal cations in the $[(A'B)O_3]_\infty$ chains, the determination of valency combinations $A' - B$ becomes a challenge. As follows from the above discussion, even accurate structural data are insufficient in some cases to rationalise the results of magnetic measurements. This problem is especially severe for cobalt-containing compounds. Presumably, the involvement of theoretical methods for the electron structure calculation will help to overcome this problem.

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^a — *Dokl. Chem. (Engl. Transl.)*^b — *Russ. J. Inorg. Chem. (Engl. Transl.)*^c — *Bull. Russ. Acad. Sci., Phys. (Engl. Transl.)*^d — *Russ. J. Phys. Chem. (Engl. Transl.)*

Energetics of bimolecular nucleophilic reactions in solution

V M Vlasov

Contents

I. Introduction	765
II. S _N 2 reactions	765
III. S _N Ar reactions	769
IV. S _N V and Ad _N reactions	774
V. Reactions at the carbonyl carbon	779
VI. Reactions of carbocations with nucleophiles	785
VII. Miscellaneous reactions	788
VIII. The role of the enthalpy–entropy compensation effect	792
IX. Relationship between the mechanisms of bimolecular nucleophilic reactions and activation parameters	792

Abstract. Published data on the activation parameters of bimolecular nucleophilic reactions in solution are generalised and described systematically. The factors that influence the relation between the activation parameters in these reactions are discussed. The relationships between the mechanisms of bimolecular nucleophilic substitution and addition reactions and their activation parameters are considered, and the role of the enthalpy–entropy compensation effect is analysed. The bibliography includes 229 references.

I. Introduction

Bimolecular nucleophilic reactions (BNR) provide the basis for the synthesis of various classes of organic compounds. These include S_N2, S_NAr, S_NV and Ad_N reactions, reactions at the carbonyl carbon atom, reactions of carbocations with anions, *etc.*¹ There is a substantial body of data on the kinetics and mechanisms of these reactions (see, for examples, Refs 2–6). However, after the publication of the monograph by Leffler and Grunwald,⁶ no generalisations of the changes in the enthalpy of activation ($\Delta H^\ddagger$), the entropy of activation ($\Delta S^\ddagger$) and the activation free energy ($\Delta G^\ddagger$) for bimolecular nucleophilic reactions were made although the number of studies on kinetics and mechanisms of these reactions is being increased steadily. It was demonstrated⁶ that the enthalpy and entropy of activation depend much more substantially on the reaction mechanism than the activation free energy. Hence, analysis of the main factors responsible for the ratio between the enthalpy and entropy contributions to the energy barrier for the reaction is of great importance. The present review is devoted to systematisation and analysis of the data on the energetics of the main types of bimolecular nucleophilic reactions in solution. Particular atten-

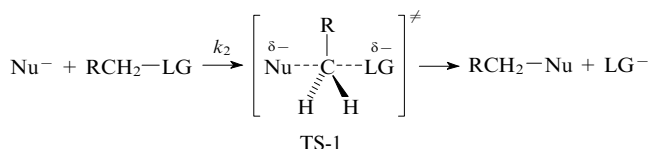
tion is given to the relationship between the reaction mechanisms and the activation parameters. In some cases, a comparison with the data for gas-phase reactions is performed. Of special interest are bimolecular nucleophilic reactions, that proceed by similar mechanisms and at nearly the same rates but are substantially different in the activation parameters.

In the present review, the enthalpy–entropy compensation effect, which is widely discussed in the literature, is considered from the viewpoint of factors responsible for changes in the activation parameters of bimolecular nucleophilic reactions in solution. Based on the published data, the difference between the compensation and isokinetic effects or their equality are noted.

Emphasis is given to typical bimolecular reactions of organic chemistry. For bimolecular reactions of inorganic compounds, only selected data for ligand substitution reactions of complex compounds are considered.

II. S_N2 reactions

S_N2 reactions in solution are characterised by negative entropies of activation $\Delta S^\ddagger$ because the transition states (TS) are well organised.^{7–10} The values of $\Delta S^\ddagger$ depend on the nature of the substrate and nucleophile and the reaction conditions.^{8–12} For example, the entropy of activation of S_N2 reactions at the saturated carbon atom involving anionic nucleophiles in proton-donor and polar aprotic solvents vary in the range from –2.3 to –83.1 J mol^{–1} K^{–1} (Table 1).



Nu is a nucleophile and LG is a leaving group.

It should be noted that negative $\Delta S^\ddagger$ for both fast and slow reactions vary in a narrow range (for example, see entries 3, 6, 14, 25, 27 and 33 in Table 1). Apparently, the structural features of TS-1 play the decisive role in the determination of $\Delta S^\ddagger$. An increase in the entropy of activation (smaller negative $\Delta S^\ddagger$) corresponds to the less organised and earlier TS-1 on the S_N2 reaction coordinate characterised by a lower degree of formation

V M Vlasov 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 (7-383) 330 97 52, tel. (7-383) 330 88 33,
e-mail: vmvlasov@nioch.nsc.ru

Received 1 February 2006

Uspekhi Khimii 75 (9) 851–883 (2006); translated by T N Safonova

Table 1. Rate constants and activation parameters for S_N2 reactions at the saturated carbon atom of RCH₂LG with anionic nucleophiles.

Substrate RCH ₂ LG	Entry	Nucleophile	Solvent	Temper- ature /°C	k_2 /litre mol ⁻¹ s ⁻¹	$\Delta H^\ddagger$	$-\Delta S^\ddagger$	$\Delta G^\ddagger$	Ref.
MeCl	1	KSCN	MeOH	71.1	2.51×10^{-4}	93.3	44.0	108.8	13
	2	KSCN	DMF	71.1	0.266×10^{-2}	77.8	69.0	102.2	13
MeI	3	KSCN	MeOH	60.1	1.46×10^{-2}	77.1	49.2	92.5	13
	4	PhONa	MeOH	59.2	2.66×10^{-3}	89.9	24.5	98.1	14
	5	4-NO ₂ C ₆ H ₄ ONMe ₄	MeCN	30	0.854×10^{-2}	61.8	80.8	86.3	15
	6	2,4-(NO ₂) ₂ C ₆ H ₃ ONMe ₄	MeCN	30	3.18×10^{-5}	76.2	79.7	100.3	15
	7	4-NO ₂ C ₆ H ₄ CO ₂ NMe ₄	MeCN	30	4.57×10^{-2}	66.6	51.0	82.0	15
	8	3,5-(NO ₂) ₂ C ₆ H ₃ CO ₂ NMe ₄	MeCN	30	1.25×10^{-2}	63.1	73.5	85.4	15
	9	2-ClC ₆ H ₄ CO ₂ NMe ₄	MeCN	30	8.08×10^{-2}	68.9	38.7	80.6	15
	10	Me ₄ NBr	MeCN	30	25.8×10^{-2}	69.1	28.4	77.7	15
	11	tetramethylammonium 1,3-dimethylbarbiturate	MeCN	30	2.98×10^{-2}	60.5	74.7	83.1	15
	12	tetramethylammonium 3,4,5,6-tetrachlorophthal- imide ^a	MeCN	30	13.7×10^{-2}	59.1	66.6	79.3	15
EtI	13	4-NO ₂ C ₆ H ₄ ONMe ₄	MeCN	30	0.279×10^{-2}	68.7	67.3	89.1	15
	14	2,4-(NO ₂) ₂ C ₆ H ₃ ONMe ₄	MeCN	30	1.33×10^{-5}	77.4	83.1	102.6	15
	15	4-NO ₂ C ₆ H ₄ CO ₂ NMe ₄	MeCN	30	1.07×10^{-2}	68.0	58.3	85.7	15, 16
	16	3,5-(NO ₂) ₂ C ₆ H ₃ CO ₂ NMe ₄	MeCN	30	0.29×10^{-2}	68.8	66.7	89.0	15
	17	2-ClC ₆ H ₄ CO ₂ NMe ₄	MeCN	30	1.51×10^{-2}	70.6	47.0	84.8	15
	18	Me ₄ NBr	MeCN	30	1.08×10^{-2}	77.4	27.2	85.6	15
	19	tetramethylammonium 1,3-dimethylbarbiturate	MeCN	30	0.18×10^{-2}	68.2	72.5	90.2	15, 17
	20	tetramethylammonium 3,4,5,6-tetrachlorophthal- imide ^a	MeCN	30	0.615×10^{-2}	66.8	67.0	87.1	15, 18
	21	tetramethylammonium 3,4,5,6-tetrachlorophthal- imide ^a	MeCN – MeOH ^b	30	0.184×10^{-4}	89.5	40.5	101.8	18
	22	tetramethylammonium succinimide ^a	MeCN	30	1.65×10^{-1}	58.4	67.4	78.8	19
	23	tetramethylammonium succinimide ^a	MeCN – MeOH ^b	30	0.474×10^{-4}	92.4	23.0	99.4	19
	24	Et ₂ HCCO ₂ NMe ₄	MeCN	30	3.56×10^{-1}	60.8	53.1	76.9	20
	25	Et ₂ HCCO ₂ NMe ₄	MeCN – MeOH ^b	30	0.28×10^{-5}	100.8	18.8	106.5	20
	26	Et ₂ HCCO ₂ NMe ₄	MeCN – MeOH ^c	30	6.24×10^{-4}	92.2	2.3	92.9	20
Bu ⁿ Br	27	PhSNa	DMF	–21	0.53	49.8	51.0	62.7	21
PhCH ₂ Cl	28	NaN ₃	MeOH	75	6.3×10^{-3}	81.5	59.4	102.1	21
	29	MeONa	MeOH	70	3.23×10^{-3}	82.3	47.4	98.6	22
n-C ₆ H ₁₃ OTs	30	NaN ₃	DMSO	30	4.83×10^{-3}	77.8	32.6	87.6	23
	31	KSCN	DMSO	30	0.165×10^{-4}	83.6	51.8	99.3	23
	32	Bu ₄ ⁿ NCl	DMSO	30	1.67×10^{-3}	84.4	18.4	90.0	23
AlkO – – SO ₂ Ar ^d	33	n-C ₁₆ H ₃₃ PBu ₃ ⁿ Cl	cyclo-C ₆ H ₁₂	30	1.0607	59.8	43.9	73.1	24
	34	n-C ₁₆ H ₃₃ PBu ₃ ⁿ Br	cyclo-C ₆ H ₁₂	30	0.6123	63.1	41.0	75.5	24
	35	n-C ₁₆ H ₃₃ PBu ₃ ⁿ I	cyclo-C ₆ H ₁₂	30	0.3073	66.9	33.9	77.1	24

Note. Hereinafter, in the tables $\Delta H^\ddagger$ and $\Delta G^\ddagger$ are given in kJ mol⁻¹; $\Delta S^\ddagger$, in J mol⁻¹ K⁻¹.

^a Names are given according to IUPAC nomenclature; ^b 1 M MeOH; ^c 0.1 M MeOH; ^d Alk = n-C₈H₁₇, Ar = 4-NO₂C₆H₄.

and longer Nu – C bond (entries 3 and 4, 8 and 9, 16 and 17, 21 and 23, 31 and 32 in Table 1).^{3, 25}

Gas-phase ion-molecular S_N2 reactions are also characterised by low $\Delta S^\ddagger$ indicative of a high degree of organisation of the transition state.^{7, 10, 26, 27} For example, $\Delta S^\ddagger$ for the gas-phase reactions of alkyl bromides with chloride ions at high pressure varies in the range from – 83.6 to – 100.7 J mol⁻¹ K⁻¹ (Refs 26 and 27); $\Delta S^\ddagger$ for the reactions of substituted benzyl chlorides with phenolate and benzenethiolate anions, in the range from – 160 to – 170 J mol⁻¹ K⁻¹ (calculations by the PM3 method).⁷

The enthalpy of activation for ion-molecular S_N2 reactions varies in a broad range and is generally smaller for faster reactions (for example, entries 1 and 2, 3 and 4, 5 and 6, 13 and 14, 22 and 23, 24 and 25, 27 and 28, 30 and 31 in Table 1). The enthalpies for faster reactions slightly increase only in the case of a sharp increase in the entropy (entries 31 and 32 in Table 1). The rates of all these reactions are controlled by the enthalpy of activation because $\Delta H^\ddagger \gg T\Delta S^\ddagger$ in all cases (see Table 1).¹⁰ This type of reactions is characterised by the isokinetic relationship with the isokinetic temperature $\beta = 6103$ K,¹⁰ which is substantially higher than the experimental temperature range. However, the isokinetic relation-

ship with a lower isokinetic temperature ($\beta = 1130$ K) is observed for S_N2 reactions at the sp^3 -hybridised carbon atom involving the thiosulfate ion in aqueous organic media, which is evidence for another (apparently, catalytic) reaction pathway in these media.¹¹

The activation parameters for the reactions of ethyl iodide with anionic nucleophiles substantially depend also on the composition of the solvent (entries 20 and 21, 22 and 23, 24 and 25, 26 in Table 1).^{16–20} There is no linear correlation between the parameters $\Delta H^\ddagger$ and $\Delta S^\ddagger$ for the reaction of each nucleophile with EtI in MeCN–MeOH with variation of percentage of MeOH. It should be noted that linear relationships between $\Delta H^\ddagger$ and $\Delta S^\ddagger$ were obtained considering the thermodynamic parameters of the passage from one solvent to another as well as the number of alcohol molecules involved in hydrogen bonding with anionic species.^{16–20}

The enthalpy of activation for the reactions of MeI is always lower than that for the analogous reaction with EtI due to a decrease in the steric hindrance in the transition state, as exemplified by the reactions of MeI and EtI with structurally different anionic nucleophiles (entries 5–20 in Table 1); the correlations between $\Delta H^\ddagger(\text{MeI})$ and $\Delta H^\ddagger(\text{EtI})$ for series of related nucleophiles have been revealed.¹⁵ An analogous influence of the structure of the substrate was found for gas-phase S_N2 reactions.^{26,27} The corresponding calculations for the gas phase and solutions were carried out.²⁸

Based on a comparison of the changes in the entropy of activation for the reactions of MeI and EtI with nucleophiles containing one reaction centre (for example, entries 5 and 13, 10 and 18, 12 and 20 in Table 1) in MeCN, it was concluded that partial desolvation of the nucleophilic centre in the formation of the transition state is the major factor responsible for the relative reactivities of alkyl iodides.¹⁵

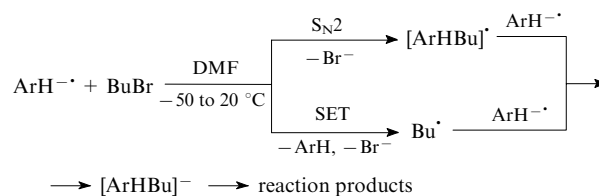
The values of $\Delta G^\ddagger$ for the ion-molecular S_N2 reactions are rather high (see Table 1) due primarily to a contribution of the desolvation energies of the nucleophile and TS-1.^{3,22,24} Quantum-chemical calculations, which were performed with consideration of the solvent effect on the activation free energies for S_N2 reactions, agree well with experimental values.^{28–31} For example, the calculated $\Delta G^\ddagger$ for the reactions of MeCl with Cl^- in DMSO, MeOH and H_2O are 133.7, 145.9 and 147.5 kJ mol^{-1} , respectively.²⁸ For the reaction of EtCl with CN^- in DMSO, the calculated $\Delta G^\ddagger$ is equal to 100.7 kJ mol^{-1} (Ref. 29), whereas the experimental $\Delta G^\ddagger$ is equal to 94.5 kJ mol^{-1} .³⁰

For the reactions of *trans*- γ -derivatives of allyl chlorides $\text{YCH}=\text{CHCH}_2\text{Cl}$ with Cl^- and LiCl, the calculated energy barriers correlate with the substituent constants σ_p to give the reaction constants $\rho = -8.3$ and $\rho = +18.8$, respectively.³¹ An analogous substituent effect in the $\rho\sigma$ correlations is observed for ion and ion-pair reactions in solution as well. It was demonstrated that the ionic structure of the transition state is stabilised by double-bond polarisation rather than by the conjugation effect. At the same time, a substantial charge delocalisation is observed for the ion-pair structure of the transition state.³¹

The calculated activation barriers for the gas-phase S_N2 reactions $\text{F}^- + \text{MeX}$ ($\text{X} = \text{F}, \text{Cl}, \text{CN}, \text{OH}, \text{SH}, \text{NH}_2$ and PH_2) give the following series of the nucleofugic ability of the substituent X (the activation barriers in kJ mol^{-1} are given in parentheses): $\text{Cl} (-51.0) > \text{F} (-3.3) > \text{SH} (11.7) > \text{CN} (56.8) > \text{OH} (67.3) > \text{PH}_2 (82.3) > \text{NH}_2 (137.1)$.³² It should also be noted that the experimental and calculated rate constants for the gas-phase reaction $\text{MeBr} + \text{Cl}^-$ agree well with each other in a broad temperature range.³³

The enthalpy-controlled S_N2 reactions of aromatic radical anions with alkyl bromides in DMF in the temperature range from -50 to 20°C are characterised by low enthalpies of activation (29.3 – 34.3 kJ mol^{-1}) and essentially negative entropies of activation (-79.8 to -54.3 $\text{J mol}^{-1} \text{K}^{-1}$).⁹ Interestingly, the increase in the temperature leads to a switch of the S_N2 -reaction mechanism to the single-electron transfer (SET) mechanism,

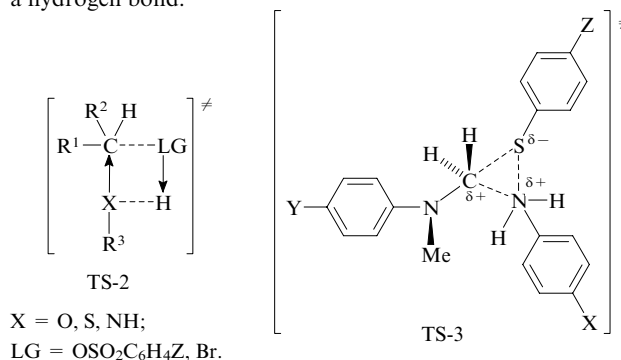
which is accompanied by an increase in $\Delta H^\ddagger$ and $\Delta S^\ddagger$ to 47.6 – 56.8 kJ mol^{-1} and 20.9 $\text{J mol}^{-1} \text{K}^{-1}$, respectively.⁹



ArH is anthracene, Bu = Bu^n , Bu^s , Bu^t .

The same features were observed for the reactions of alkyl chlorides with NO^- .³⁴

Generally, S_N2 reactions at the saturated carbon atom with neutral O-, S- and N-nucleophiles proceed slowly and are characterised by very low $\Delta H^\ddagger$ and $\Delta S^\ddagger$ (Table 2) compared to the parameters for analogous reactions with charged nucleophiles (see Table 1). A noticeable decrease in $\Delta H^\ddagger$ and $\Delta S^\ddagger$ is attributed to the structural features of the transition states. The frontal attack of the nucleophile on the substrate gives rise to the four-membered transition state TS-2 involving a hydrogen bond^{35,40–42} or the three-membered transition state TS-3 without the involvement of a hydrogen bond.⁸



Cyclic TS-2 and TS-3 are late states characterised by a higher degree of the bond formation and cleavage.^{8,42}

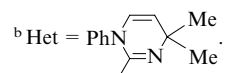
It should be noted that S_N2 reactions at the saturated carbon atom with neutral nucleophiles can be controlled by both the enthalpy and entropy (Table 2). For example, methanolysis of 1-phenylethyl 4-nitro-benzenesulfonate (Table 2, entries 1 and 2) in a mixture of protic and aprotic solvents is controlled by the enthalpy unlike the entropy-controlled reaction in a protic solvent. However, an analogous change in the nature of the solvent in the reactions of ethyl α -bromoacetate with HetSH (Table 2, entries 3 and 4) and aminolysis of allyl bromide (Table 2, entries 7–10) leads to the opposite change in the control. Evidently, higher stabilisation of TS-2 for faster reactions in both protic and aprotic media leads to a decrease in both $\Delta H^\ddagger$ and $\Delta S^\ddagger$, resulting in the entropy control of the reaction (Table 2, entries 1, 4–7 and 9).

In the reactions of ethyl α -bromoacetate with HetSH in various protic and aprotic solvents (Table 2, entries 3 and 4), the enthalpy–entropy compensation effect with the compensation temperature $\beta = 292$ K (below the limit of the experimental temperature range) is observed.³⁶ However, the change in the energetics of the reaction of ethyl α -bromoacetate with thiol in methanol under changes in the nature of the substituent in S-nucleophiles is described by the compensation relation with $\beta = 338$ K (above the limit of the experimental temperature range).³⁶ At the same time, aminolysis of allyl bromide in an aprotic solvent (Table 2, entries 7 and 9) is characterised by the compensation relation with $\beta = 220$ K (much lower than the limit of the experimental temperature range), whereas no linear relationship between $\Delta H^\ddagger$ and $\Delta S^\ddagger$ is observed for this reaction in methanol.³⁷

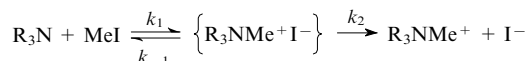
Table 2. Rate constants and activation parameters for S_N2 reactions at the saturated carbon atom of R¹R²CHLG with neutral nucleophiles.

Substrate R ¹ R ² CHLG			Entry	Nucleophile	Temperature /°C	Solvent	<i>k</i> ₂ /litre mol ⁻¹ s ⁻¹ (see ^a)	$\Delta H^\ddagger$	$-\Delta S^\ddagger$	$\Delta G^\ddagger$	Ref.
R ¹	R ²	LG									
Ph	Me	4-NO ₂ C ₆ H ₄ SO ₃	1	MeOH	25	MeOH	2.89×10^{-4}	41.8	216.9	106.5	35
Ph	Me	4-NO ₂ C ₆ H ₄ SO ₃	2	MeOH	25	MeOH–MeCN (1 : 1)	0.658×10^{-4}	58.1	178.9	111.4	35
CO ₂ Et	H	Br	3	HetSH ^b	45	MeOH	19.4×10^{-3}	60.1	91.2	88.3	36
CO ₂ Et	H	Br	4	HetSH ^b	45	Me ₂ CO	44.3×10^{-3}	31.2	171.4	85.7	36
PhNMe	H	4-NO ₂ C ₆ H ₄ S	5	4-MeOC ₆ H ₄ NH ₂	45	MeOH	4.07×10^{-1}	19.2	192.3	80.4	8
PhNMe	H	4-MeC ₆ H ₄ S	6	4-MeOC ₆ H ₄ NH ₂	45	MeOH	1.95×10^{-3}	21.7	229.9	94.8	8
CH ₂ =CH	H	Br	7	4-MeOC ₆ H ₄ NH ₂	30	DMF	8.1×10^{-3}	43.1	133.8	83.6	37
CH ₂ =CH	H	Br	8	4-MeOC ₆ H ₄ NH ₂	30	MeOH	1.69×10^{-3}	64.3	87.8	90.9	37
CH ₂ =CH	H	Br	9	PhNH ₂	30	DMF	3.3×10^{-3}	42.9	152.1	89.0	37
CH ₂ =CH	H	Br	10	PhNH ₂	30	MeOH	0.91×10^{-3}	62.0	100.3	92.4	37
Me	H	I	11	Et ₃ N	25	MeOH	4.08×10^{-5}	75.0	97	103.9	38, 39
Me	H	I	12	Et ₃ N	25	Bu ⁿ OH	1.73×10^{-5}	78.6	92	106.0	38, 39
Me	H	I	13	Et ₃ P	25	MeOH	14.95×10^{-5}	48.6	155	94.8	39
Me	H	I	14	Et ₃ P	25	Bu ⁿ OH	6.172×10^{-5}	64.5	110	97.3	39

^a In entries 1 and 2, the pseudo-first-order rate constant k_1 /s⁻¹; in entries 3–10, the rate constant of the formation of the transition state TS-2 or TS-3 as the rate-determining step in the nucleophilic attack of the substrate; in entries 11–14, the rate constant of decomposition of ion pairs (see the reaction equation).



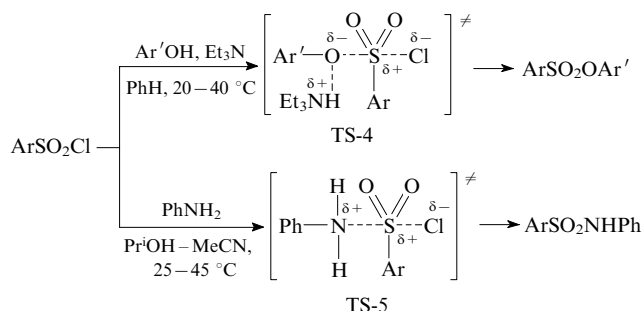
Studies of the quaternisation reactions of aliphatic amines with MeI in an aqueous solution revealed an isokinetic relationship with a negative isokinetic temperature. This fact provides evidence for a stepwise reaction mechanism involving the reversible formation of the ion pair in the first step followed by its dissociation to form free ions.¹²



The quaternisation reactions $Et_3N + EtI$ in solutions of alcohols (entries 11 and 12 in Table 2) correspond to the isokinetic relationship with the positive isokinetic temperature $\beta = 730$ K (higher than the experimental temperature range).^{38, 39} The use of Et_3P as a nucleophile in the latter reaction (entries 13 and 14 in Table 2) leads to a decrease in the isokinetic temperature to 347 K. Therefore, a substantially lower degree of desolvation of Et_3P compared to Et_3N is required, and the positive isokinetic temperatures for both reactions in alcoholic solutions confirm the concerted mechanism.³⁹

A comparison of the energetics of reactions at the saturated carbon atom with charged and neutral nucleophiles demonstrated that these reactions are characterised by very close activation free energies $\Delta G^\ddagger$ in spite of the difference in the structure of transition states (TS-1 and TS-2 or TS-3). Therefore, these differences are reflected primarily in the changes in the activation parameters $\Delta H^\ddagger$ and $\Delta S^\ddagger$.⁶

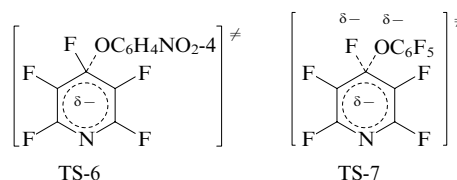
The substitution reactions at the sulfur atom of the sulfo group with anionic and neutral nucleophiles that proceed by a concerted mechanism *via* the trigonal-bipyramidal transition states TS-4 and TS-5 have very low enthalpies ($\Delta H^\ddagger = 8-40$ kJ mol⁻¹) and entropies of activation ($\Delta S^\ddagger$ from -220 to -277 J mol⁻¹ K⁻¹) if the reactivity is entropy-controlled.^{43, 44}



Evidently, these transition states, which are formally similar to the trigonal-bipyramidal transition state TS-1 in S_N2 reactions, are much more organised. It should also be noted that the reaction of benzenesulfonyl chloride with phenols in the presence of Et_3N is characterised by the compensation relation with $\beta = 171$ K (calculated using the experimental data⁴³), which is substantially lower than the limit of the experimental temperature range.⁴³

III. S_NAr reactions

The energetics of bimolecular S_NAr reactions depends on the nature of the leaving group and the nucleophile.⁴⁵ The reactivity in these processes is generally controlled by the enthalpy.⁴⁶⁻⁵¹ Table 3 gives the rate constants for the rate-determining step of the formation of the transition state TS-6 or TS-7 and the activation parameters for S_NAr reactions of various substituted arenes ArLG with charged hard and soft nucleophiles in protic and aprotic solvents. As can be seen from these data, $\Delta S^\ddagger$ varies from -250 to 255 J mol⁻¹ K⁻¹ and $\Delta H^\ddagger$ varies from 3.8 to 232 kJ mol⁻¹. The very low enthalpies of activation correspond to very low (large negative) entropies of activation (entries 14, 39, 41 and 42 in Table 3). In these cases, the reactivity is entropy-controlled. However, other S_NAr reactions listed in Table 3 are



entropy-controlled regardless of the electrophilicity of the substrate and the nature of the nucleophile, the leaving group, and the solvent. Transition states in the reactions of 2,2'-dinitrodiphenyl ether (entry 14 in Table 3) and halogen-substituted pyridines (entries 39 and 41 in Table 3) with sodium phenolate derivatives are well organised due to desolvation of the nucleophile in the formation of the transition state and weak solvation of the delocalised transition state, for example, of TS-6, approaching the σ complex.^{21, 49, 51, 59} By contrast, the entropy control of the reaction of 4-pentafluorophenoxy-2,3,5,6-tetrafluoropyridine with KF (entry 42 in Table 3) is most likely associated with the change from the S_NAr reaction mechanism to the concerted mechanism *via* the transition state TS-7.^{58, 60, 61} The more ordered (compared to TS-6) transition state TS-7 is typical of bimolecular concerted reactions with very low $\Delta S^\ddagger$.⁶²

The switch from the entropy control of the reaction to the enthalpy control can be achieved by varying the nucleophile. An increase in the negative charge delocalisation in a nucleophile leads to a decrease in its desolvation energy. Examples are provided by the reactions of 2-chloro-5-nitropyridine with sodium 4-methoxy- and 4-nitrophenolate in methanol (entries 39 and 40 in Table 3). The use of nucleophiles with a more delocalised charge (electron-withdrawing NO₂ group) instead of nucleophiles with a less delocalised charge (electron-donating MeO group) allows one to change the character of control of the reaction.⁵¹

Analysis of the activation parameters for the S_NAr reactions given in Table 3 revealed a number of compensation relations and isokinetic relationships (Fig. 1).⁶³⁻⁶⁵ Straight line I in Fig. 1 relates primarily to fast reactions (entries 10, 12, 27-31 and 33-37 in Table 3) with rate constants $k_2 > 1 \times 10^{-4}$ litre mol⁻¹ s⁻¹ and only the reaction of 4-nitrobenzonitrile with CsF in DMSO (entry 15 in Table 3) is slow [$k_2(80^\circ C) = 1.58 \times 10^{-7}$ litre mol⁻¹ s⁻¹] due to a substantial increase in the entropy contribution as a result of the formation of the late transition state and, consequently, a slight change in the

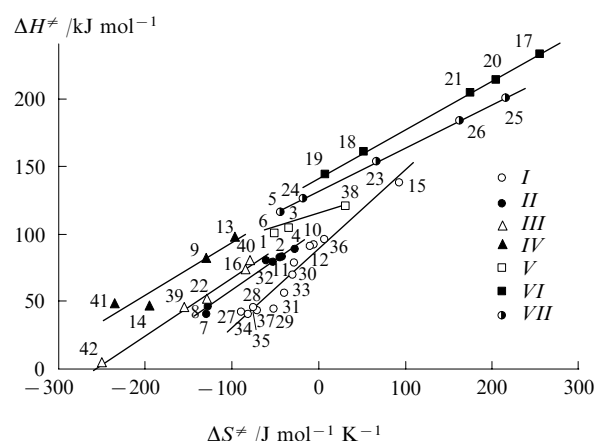


Figure 1. Compensation plots for the S_NAr reactions of substituted arenes ArLG with charged nucleophiles (the numbering of the points corresponds to the entries in Table 3).

(I) $r = 0.975$, $n = 13$, $s = 6.9$; (II) $r = 0.990$, $n = 7$, $s = 2.89$; (III) $r = 0.996$, $n = 5$, $s = 3.16$; (IV) $r = 0.959$, $n = 4$, $s = 8.8$; (V) $r = 0.999$, $n = 3$, $s = 0.46$; (VI) $r = 0.999$, $n = 5$, $s = 0.52$; (VII) $r = 0.999$, $n = 4$, $s = 0.88$.

Table 3. Rate constants and activation parameters for S_NAr reactions at the sp²-hybridised carbon atom in compounds ArLG with charged nucleophiles.

Substrate	Entry	Nucleophile	Temperature /°C	Solvent	k_2 /litre mol ⁻¹ s ⁻¹	$\Delta H^\ddagger$	$-\Delta S^\ddagger$	$\Delta G^\ddagger$	Ref.
Ar	LG								
4-NO ₂ C ₆ H ₄	I	1	PhSNa	0	MeOH	3.40×10^{-6}	81.1	60.3	46, 47
	F	2	PhSNa	0	MeOH	7.79×10^{-6}	82.8	43.9	47
	I	3	MeONa	0	MeOH	2.45×10^{-9}	104.5	34.3	46, 47
	F	4	MeONa	0	MeOH	6.26×10^{-6}	88.6	27.6	46, 47
	I	5	NaN ₃	0	MeOH	3.67×10^{-12}	116.2	43.9	46, 47
	F	6	NaN ₃	0	MeOH	1.55×10^{-9}	100.7	52.3	47
	F	7	9-PhFlK ^a	35	DMSO	8.48×10^{-2}	41.8	129.6	52
	F	8	9-PhFlK ^a	35.5	DMSO	1.55×10^{-2}	46.6	128.3	52
	Br	9	4-NO ₂ C ₆ H ₄ ONa	120	1,3-DMI ^b	1.76×10^{-5}	81.9	129.2	50
	NO ₂	10	MeONa	25	MeOH	1.7×10^{-4}	91.1	10.5	53
	F	11	RbF	25	DMSO	0.928×10^{-4}	83.6	41.8	54
	NO ₂	12	CsF	80	DMSO	1.0×10^{-4}	92.0	8.4	55
	2-NO ₂ C ₆ H ₄ O	13	4-NO ₂ C ₆ H ₄ ONa	120	1,3-DMI ^b	6.22×10^{-6}	97.8	97.4	50
	2-NO ₂ C ₆ H ₄ O	14	3-NO ₂ C ₆ H ₄ ONa	120	1,3-DMI ^b	2.8×10^{-4}	47.2	194.8	50
4-NCC ₆ H ₄	NO ₂	15	CsF	80	DMSO	1.58×10^{-7}	137.9	-92.0	55
	NO ₂	16	3,4-Me ₂ C ₆ H ₃ OH · K ₂ CO ₃	130	DMAA	0.1	73.2	84.7	56
3-NO ₂ C ₆ H ₄	NO ₂	17	3,4-Me ₂ C ₆ H ₃ OH · K ₂ CO ₃	150	DMAA	3.16×10^{-3}	232.4	-254.7	56
	NO ₂	18	3-NO ₂ C ₆ H ₄ OH · K ₂ CO ₃	125	DMF	4.0×10^{-6}	160.0	-52.0	57
	F	19	3-NO ₂ C ₆ H ₄ OH · K ₂ CO ₃	125	DMF	2.0×10^{-6}	144.0	-7.0	57
	NO ₂	20	PhOH · K ₂ CO ₃	125	DMF	2.0×10^{-5}	215.0	-204.0	57
	F	21	PhOH · K ₂ CO ₃	125	DMF	1.0×10^{-5}	205.0	-175.0	57
	NO ₂	22	3,4-Me ₂ C ₆ H ₃ OH · K ₂ CO ₃	90	DMF	6.6×10^{-2}	51.2	128.4	56
3-NO ₂ -5-CF ₃ C ₆ H ₃	NO ₂	23	3-NO ₂ C ₆ H ₄ OH · K ₂ CO ₃	70	DMF	7.0×10^{-8}	154.0	-66.0	57
	F	24	3-NO ₂ C ₆ H ₄ OH · K ₂ CO ₃	70	DMF	5.0×10^{-8}	126.0	18.0	57
	NO ₂	25	PhOH · K ₂ CO ₃	70	DMF	3.0×10^{-7}	201.0	-215.0	57
	F	26	PhOH · K ₂ CO ₃	70	DMF	3.0×10^{-7}	183.0	-162.0	57
2,4-(NO ₂) ₂ C ₆ H ₃	I	27	PhSNa	0	MeOH	5.17	44.7	74.8	47
	Cl	28	PhSNa	0	MeOH	3.90	40.8	82.2	48
	F	29	PhSNa	0	MeOH	1.29×10^2	44.7	52.3	47
	I	30	MeONa	0	MeOH	3.08×10^{-4}	79.2	28.4	47
	F	31	MeONa	0	MeOH	1.74	56.4	40.1	47
	I	32	NaN ₃	0	MeOH	1.74×10^{-5}	79.2	53.5	47
	F	33	NaN ₃	0	MeOH	2.04×10^{-2}	69.6	30.5	47
	Cl	34	Et ₄ NN ₃	-20	DMF	0.153	45.6	75.7	21
	4-NO ₂ C ₆ H ₄ O	35	Et ₄ NN ₃	-20	DMF	0.217	42.2	89.1	21
	I	36	Et ₄ NCl	60	DMF	1.05×10^{-2}	96.3	-6.1	21
	NO ₂	37	MeONa	25	MeOH	16.3	43.9	72.7	53
	Cl	38	NaN ₃	0	MeOH	1.90×10^{-9}	121.0	-30.8	48
(η ⁶ -C ₆ H ₅)Fe(C ₅ H ₅) ⁺ (see ^c)	Cl	39	4-MeOC ₆ H ₄ ONa	40	MeOH	1.40×10^{-3}	45.1	154.2	51
5-NO ₂ C ₆ H ₃ N	2-Cl	40	4-NO ₂ C ₆ H ₄ ONa	40	MeOH	0.24×10^{-4}	79.8	78.6	51
C ₅ F ₄ N	4-F	41	4-NO ₂ C ₆ H ₄ OK	30	MeCN	0.72	48.5	235.2	58
	4-C ₆ F ₅ O	42	KF	30	MeCN	5.14	3.8	250.0	58

^a 9-Phenylfluorenylpotassium; ^b 1,3-dimethylimidazolidin-2-one; ^c in this case, η⁶-coordinated PhCl serves as the substrate.

entropy of solvation. Line *II* in Fig. 1 includes rather slow reactions with $k_2 = 1 \times 10^{-6} - 1 \times 10^{-2}$ litre mol⁻¹ s⁻¹ (entries 1, 2, 4, 7, 8, 11 and 32 in Table 3) with the most typical activation parameters.⁴⁶ Line *III* contains points for both fast (entry 42 in Table 3) and rather slow reactions (entries 16, 22, 39 and 40 in Table 3). The characteristic feature of the latter plot is a very strong decrease in the entropy in entries 22, 39 and 42. This can be attributed to an increase in the desolvation energy of the localised nucleophile (*cf.* entries 39 and 40 in Table 3)⁵¹ or an increase in the desolvation energy of the nucleophile due to the formation of the early transition state with a more electrophilic substrate (*cf.* entries 16 and 22 in Table 3)⁵³ as well as to a switch from the S_NAr mechanism to the concerted mechanism (entry 42 in Table 3).⁵⁸ Line *IV* (Fig. 1) includes data for reactions (entries 9, 13, 14 and 41 in Table 3) with low $\Delta S^\ddagger$. Low $\Delta S^\ddagger$ for reactions 14 and 41 were discussed above. A decrease in $\Delta S^\ddagger$ for slow reactions 9 and 13 can be attributed to the formation of the early transition state.^{48, 53} The reactions of halogen-substituted arenes with sodium methoxide and azide are described by straight line *V* (entries 3, 5, 6 and 38 in Table 3). It should be noted that these reactions are very slow and characterised by high $\Delta H^\ddagger$ and $\Delta S^\ddagger$ due apparently to stabilisation of the ground state of the nucleophile and, as a consequence, the formation of the late transition state.^{48, 53}

Lines *VI* (entries 17–21 in Table 3) and *VII* (entries 23–26) in Fig. 1 characterise slow reactions with very high $\Delta H^\ddagger$ and $\Delta S^\ddagger$, both relationships being isokinetic.⁵⁷ The activation free energies (120–140 kJ mol⁻¹) for all reactions corresponding to lines *VI* and *VII* are close to the range of $\Delta G^\ddagger$ determining the kinetics of S_NAr reactions of weakly activated arenes with O-charged nucleophiles.⁴⁶ The enthalpy and entropy of activation for the reactions of *meta*-substituted arenes with complexes of phenols with K₂CO₃ (Scheme 1) vary in unusually broad ranges. High sensitivity of the parameters $\Delta H^\ddagger$ and $\Delta S^\ddagger$ to the structure of the reagents is due to the possible changes in the geometry of complex **1**.^{66, 67} Apparently, it is this property of complex **1** that determines similarity of these reactions to heterogeneous and enzymatic catalysis characterised by unusually broad ranges of $\Delta H^\ddagger$ and $\Delta S^\ddagger$.^{68–70} Then the transformation of complex **1** can occur either synchronously *via* the transition state TS-8 or stepwise *via* complex **2** and the transition state TS-9. Both pathways afford σ complex **3**. The formation of the latter is the rate-determining step and is characterised by usual activation free energies $\Delta G^\ddagger$.⁴⁶

The chemical nature of the observed compensation relations is confirmed by the fact that the observed compensation temperatures are noticeably different from the experimental temperature

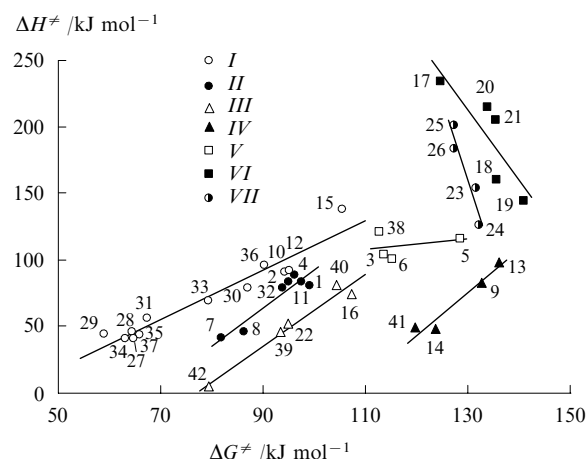


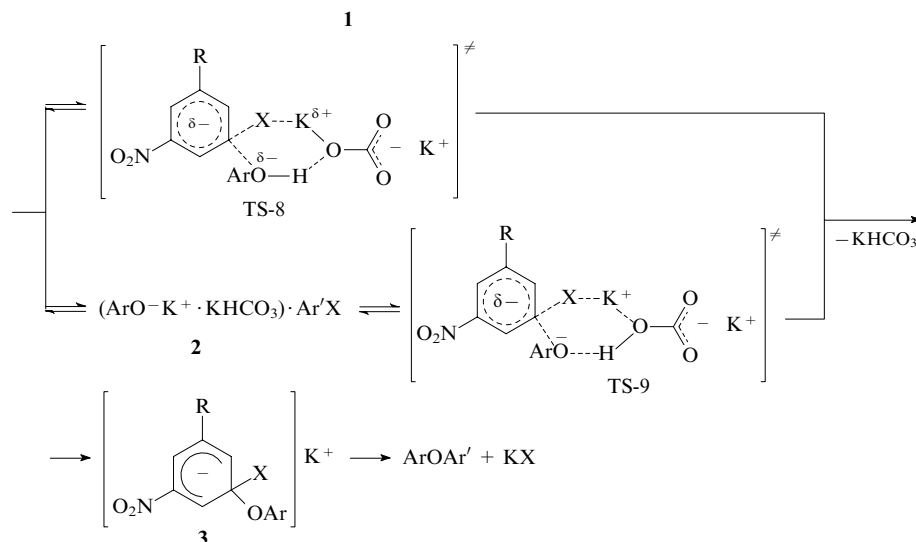
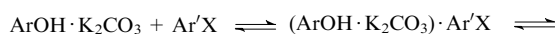
Figure 2. Plots of the enthalpies vs the activation free energies for the S_NAr reactions of substituted arenes ArLG with charged nucleophiles (the numbering of the points corresponds to the entries in Table 3).

(*I*) $r = 0.966$, $n = 13$, $s = 8.0$; (*II*) $r = 0.949$, $n = 7$, $s = 6.6$; (*III*) $r = 0.983$, $n = 5$, $s = 6.4$; (*IV*) $r = 0.971$, $n = 4$, $s = 7.4$; (*V*) $r = 0.950$, $n = 3$, $s = 3.6$; (*VI*) $r = 0.835$, $n = 5$, $s = 24.0$; (*VII*) $r = 0.951$, $n = 4$, $s = 12.5$.

range. In addition, the relationships between the enthalpies of activation and the activation free energies for these reactions were found (Fig. 2).^{71–73} The opposite slopes of the lines in Fig. 2 are associated with considerable positive values of $\Delta H^\ddagger$ and $\Delta S^\ddagger$ for the reactions described by lines *VI* and *VII*. As a result, $\Delta H^\ddagger$ can be larger than $\Delta G^\ddagger$ (entries 17–21, 23, 25 and 26 in Table 3).

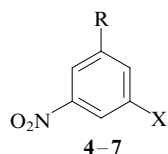
Due to the kinetic enthalpy–entropy compensation effect represented by lines *I*, *II*, *VI* and *VII* in Fig. 1 for different S_NAr reactions, it became possible to compare the substitution effect of the nitro group and the fluorine atom on the energetics of these reactions.⁷⁴ For example, a comparison of the activation parameters ($\Delta H^\ddagger$ and $\Delta S^\ddagger$) for the substitution of the nitro group and the fluorine atom in 1,4-dinitro- and 4-fluoronitrobenzene in the reactions with ¹⁸F-labelled fluoride ions in DMSO (entries 11 and 12 in Table 3) demonstrated that the selectivity of replacement of these groups ($k_{\text{NO}_2}/k_{\text{F}}$ ratio) is controlled by the entropy of activation.^{53, 54} Evidently, the replacement of the nitro group (entry 11) is characterised by the earlier transition state on the

Scheme 1



reaction coordinate compared to the replacement of the fluorine atom (entry 12).⁷⁴

Recently, it has been demonstrated^{57, 66, 75} that the selectivity of replacement of the nitro group and the fluorine atom in the reactions of *meta*-substituted nitrobenzenes with phenols and arenethiols in the presence of K₂CO₃ in DMF at 40–125 °C is entropy-controlled because in all cases $T\Delta\Delta S^\ddagger > \Delta\Delta H^\ddagger$, where $\Delta\Delta S^\ddagger = \Delta S^\ddagger_{\text{NO}_2} - \Delta S^\ddagger_{\text{F}}$ and $\Delta\Delta H^\ddagger = \Delta H^\ddagger_{\text{NO}_2} - \Delta H^\ddagger_{\text{F}}$. Changes in the entropy $\Delta\Delta S^\ddagger$ have positive values (*cf.* entries 18 and 19, 20 and 21, 23 and 24, 25 and 26 in Table 3, lines VI and VII in Fig. 1), and, consequently, the reactions of fluoroarenes **4** and **5** with the ArOH·K₂CO₃ complexes are more organised than analogous reactions of nitroarenes **6** and **7**.



X = F: R = H (**4**), CF₃ (**5**); X = NO₂: R = H (**6**), CF₃ (**7**).

Hence, the S_NAr substitution of the nitro group in compounds **6** and **7** is characterised by the earlier transition state on the reaction coordinate compared to the substitution of the fluorine atom in compounds **4** and **5**.^{57, 66, 75} It should be noted that the replacement of the nucleophile ArOH·K₂CO₃ by 2 ArOH·K₂CO₃ has no effect on the character of the control of the reactivity of compounds **5** and **7**. In this case, the selectivity of substitution is also entropy-controlled.⁷⁶

It was demonstrated^{77, 78} that changes in the nature of the medium can lead to a switch from the entropy control of regioselectivity in S_NAr reactions to the enthalpy control. For example, the *ortho* to *para* isomer ratio in S_NAr reactions resulting in the replacement of halogens in alcohols as the solvents is entropy-controlled.^{79, 80} A comparison of the substitution of the fluorine and chlorine atoms in halonitrobenzenes shows that the fluorine atoms in monohalonitrobenzenes are replaced primarily due to smaller steric requirements of the *ortho*-fluorine atom (Table 4). However, the reverse situation is observed for dihalonitrobenzenes because the entropy control of the reactions in MeOH favours the *ortho*-substitution due to steric hindrance for solvation in the transition state (see Table 4).⁸⁰ However, the entropy control of the reactions of fluoronitrobenzenes with alkoxides changes to the enthalpy control at low temperature in liquid NH₃, resulting in sharp enhancement of *ortho*-substitution (see Table 4).

Table 4. Rate constant ratios of the replacement of halogens in the *ortho* and *para* positions of halonitrobenzenes with sodium methoxide in methanol (25 °C) or liquid ammonia (–70 °C) and the differences between the activation parameters for these reactions.

Compound	Solvent	k_o/k_p	$\Delta\Delta H^\ddagger$ (see ^a)	$\Delta\Delta S^\ddagger$ (see ^a)	$\Delta\Delta G^\ddagger$ (see ^a)	Ref.
2- and 4-ClC ₆ H ₄ NO ₂	MeOH	0.27 ^b	5.77	13.4	0.91	80
2,4-Cl ₂ C ₆ H ₃ NO ₂	MeOH	1.98 ^b	—	—	—	80
2- and 4-FC ₆ H ₄ NO ₂	MeOH	0.69	–4.56	–9.6	–1.7	79–81
	NH ₃ (liq.)	2.85	–8.38	–24.7	–5.0	77
	NH ₃ (liq.)	1.60 ^c	—	—	—	78
2,4-F ₂ C ₆ H ₃ NO ₂	MeOH	1.22	—	—	—	80
		1.35	—	—	—	81
	NH ₃ (liq.)	2.6	–5.23	–9.94	–2.0	78
		(3.3 ^d)	—	—	—	78
		1.85 ^c	—	—	—	78

^a Here and in Table 5, $\Delta\Delta H^\ddagger = \Delta H^\ddagger_o - \Delta H^\ddagger_p$, $\Delta\Delta S^\ddagger = \Delta S^\ddagger_o - \Delta S^\ddagger_p$ and $\Delta\Delta G^\ddagger = \Delta G^\ddagger_o - \Delta G^\ddagger_p$; ^b at 90 °C; ^c at –33 °C; ^d in the reaction with MeOK.

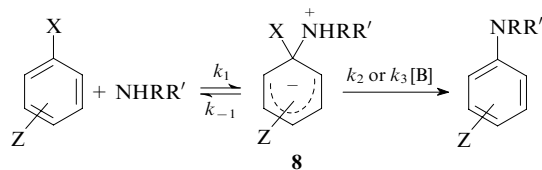
Table 5. Rate constant ratios of the replacement of the fluorine atom in the *ortho* and *para* positions of 2,4-difluoronitrobenzene with lithium phenolates 4-RC₆H₄OLi in liquid NH₃ (–55 °C) and the differences between the activation parameters for these reactions.^{82, 83}

R in 4-RC ₆ H ₄ OLi	k_o/k_p	$\Delta\Delta H^\ddagger$	$\Delta\Delta S^\ddagger$	$\Delta\Delta G^\ddagger$
Bu ^t	0.96	2.7	12.0	0.09
Me	1.30	–1.7	–5.3	–0.54
H	1.45	–0.9	–1.1	–0.66
	(2.36) ^a	(–4.4) ^a	(–11.9) ^a	(–1.81) ^a
F	1.58	–0.9	–0.5	–0.79
MeO	1.20	–2.1	–8.3	–0.29

^a Data for the reaction with PhONa at –55 °C (see ⁷⁸).

The regioselectivity of replacement of the halogen atom can be influenced also by the structure of the nucleophile. Table 5 gives data on the regioselectivity of replacement of the fluorine atom in 2,4-difluoronitrobenzene under the action of lithium phenolates 4-RC₆H₄OLi in liquid ammonia. From these data it follows that the replacement of the *ortho*-fluorine atom is more favourable from the point of view of the enthalpy than the replacement of the *para*-fluorine atom. For the substituents R in nucleophiles, this tendency decreases in the series 4-MeO > 4-Me > H ≈ F. However, the enthalpy favours the replacement of the *para*-fluorine atom in the case of R = Bu^t.⁸³ This fact is associated with a change in the structure of the transition state. The replacement of the *ortho*-fluorine atom under the action of lithium phenolates containing electron-donating substituents where the higher positive charge is localised on the *ortho*-carbon atom with respect to the nitro group gives the early transition state. A decrease in the nucleophilicity of 4-Bu^tC₆H₄OLi due to the greater polarisability of the Bu^t group shifts the transition state toward the intermediate σ complex, *i.e.*, favours the formation of the late transition state and the replacement of the *para*-fluorine atom.⁸³

Of neutral nucleophiles, only amines were studied in detail in aromatic nucleophilic substitution reactions.^{45, 74} Unlike the reactions of charged nucleophiles, S_NAr reactions of primary and secondary amines can be catalysed by bases. The second amine molecule can serve as such a base.



The apparent second-order rate constant k_A at a stationary concentration of σ complex **8** can be calculated from the commonly accepted mechanism of S_NAr reactions with amines:^{45, 74}

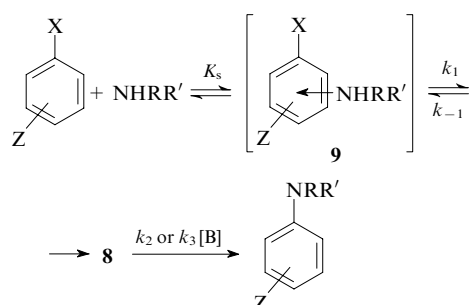
$$k_A = \frac{k_1(k_2 + k_3[B])}{k_{-1} + k_2 + k_3[B]}.$$

Table 6 lists the rate constants (k_A) and the activation parameters for S_NAr reactions of various arenes ArLG with primary and secondary amines in protic, aprotic polar and non-polar solvents. It should be noted that for most of the reactions listed in Table 6 (entries 1, 2, 4–15 and 18–23), $k_A = k_1$ because $k_2 + k_3[B] \gg k_{-1}$, and the formation of σ complex **8** is the rate-determining step of the reaction. However, the reactions in non-polar n-hexane (entries 3, 16 and 17, Table 6) are characterised by a more complex dependence of k_A on [B], which includes the equilibrium constant K_s of the formation of $n-\pi$ -electron-donating complex **9** prior to the formation of σ complex **8**, decomposition of the latter being the rate-determining step.⁸⁵

Table 6. Rate constants and activation parameters for the S_NAr reactions at the sp²-hybridised carbon atom in compounds ArLG with amines.

Substrate ArLG		Entry	Nucleophile	Temper- ature /°C	Solvent	k_A /litre mol ⁻¹ s ⁻¹	$\Delta H^\ddagger$	$-\Delta S^\ddagger$	$\Delta G^\ddagger$	Ref.
Ar	LG									
4-NO ₂ C ₆ H ₄	NO ₂	1	piperidine	25	MeCN	2.3×10^{-6}	48.1	192.3	105.4	84
2,4-(NO ₂) ₂ C ₆ H ₃	Cl	2	piperidine	0	MeOH	1.95×10^{-3}	46.2	126.2	80.7	48
	Cl	3	Bu ⁿ NH ₂	26	n-C ₆ H ₁₄	2.35×10^{-2}	21.0	218.0	86.2	85
	Cl	4	piperidine	40	MeCO ₂ Et – CHCl ₃ ^a	0.29×10^{-2}	25.5	174.4	80.1	86
	Cl	5	piperidine	40	PhMe – MeOH ^a	3.45×10^{-2}	47.4	113.3	82.9	87
	Cl	6	piperidine	40	1,1,1-Cl ₃ CMe – MeOH ^a	3.93×10^{-2}	34.3	175.6	89.3	87
	Cl	7	PhNH ₂	50	EtOH	2.69×10^{-4}	44.1	177.2	101.3	88
	F	8	PhNH ₂	50	EtOH	1.68×10^{-2}	24.1	204.0	90.0	88
	NO ₂	9	PhNH ₂	50	EtOH	2.11×10^{-1}	29.9	165.7	83.4	88
	Cl	10	morpholine	0	MeOH	1.7×10^{-3}	48.9	126.2	83.4	48
	Cl	11	(NH ₂) ₂ C=NH	0	MeOH	3.5×10^{-3}	51.7	108.6	81.3	48
	Cl	12	(NH ₂) ₂ C=S	0	MeOH	7.1×10^{-8}	76.1	108.6	105.7	48
2,6-(NO ₂) ₂ C ₆ H ₃	Cl	13	PhNH ₂	50	EtOH	1.98×10^{-4}	56.7	140.4	102.0	89
	F	14	PhNH ₂	50	EtOH	8.77×10^{-3}	36.6	171.0	91.8	89
	NO ₂	15	PhNH ₂	50	EtOH	3.26×10^{-1}	34.5	145.5	81.5	89
3-NO ₂ -5-CF ₃ C ₆ H ₃	Cl	16	Bu ⁿ NH ₂	27	n-C ₆ H ₁₄	9.4×10^{-6}	18.0	267.0	97.8	85
	Cl	17	piperidine	26	n-C ₆ H ₁₄	3.6×10^{-4}	27.0	206.0	88.6	85
2,4,6-(NO ₂) ₃ C ₆ H ₂	Cl	18	PhNH ₂	50	EtOH	3.34	29.9	142.8	76.0	89
	F	19	PhNH ₂	50	EtOH	334	15.7	148.5	63.7	89
	NO ₂	20	PhNH ₂	50	EtOH	4.21×10^3	15.7	127.5	56.9	89
(η^6 -C ₆ H ₅)Fe(C ₅ H ₅) ⁺ (see ^b)	Cl	21	piperidine	0	MeOH	3.37×10^{-7}	73.5	98.0	100.3	48
	Cl	22	morpholine	0	MeOH	3.08×10^{-9}	82.0	105.0	110.7	48
	Cl	23	(NH ₂) ₂ C=NH	0	MeOH	1.09×10^{-3}	29.4	193.0	82.1	48

^a Molar ratio is 1 : 1; ^b in this case, η^6 -coordinated PhCl serves as the substrate.

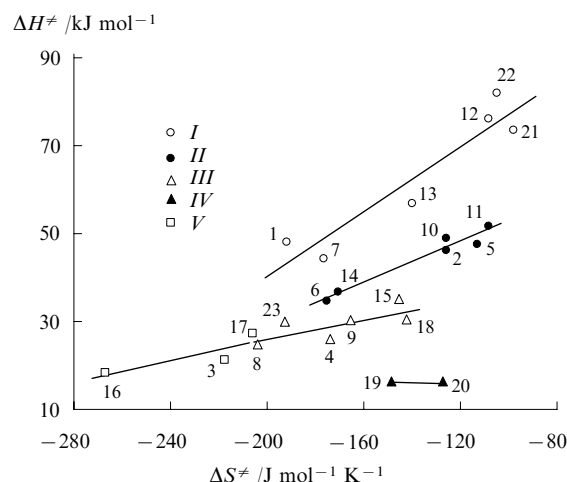


As can be seen from Table 6, $\Delta S^\ddagger$ varies from -265 to -98 J mol⁻¹ K⁻¹ and $\Delta H^\ddagger$ varies from 15.7 to 82.0 kJ mol⁻¹. It should be noted that low $\Delta H^\ddagger$ correlate with very low $\Delta S^\ddagger$, which corresponds to the entropy control of the reactivity, i.e., $T\Delta S^\ddagger > \Delta H^\ddagger$ (entries 1, 3, 4, 6–9, 14–20 and 23, Table 6). However, in other cases, where both the entropy and enthalpy noticeably increase (entries 2, 5, 10–13, 21 and 22, Table 6), the reactivity is controlled by the enthalpy regardless of the structure of the amine and substrate.

The entropy control can be switched to the enthalpy control by changing the solvent. For example, the reactions in a binary solvent system including MeOH is entropy-controlled if 1,1,1-trichloroethane is used as the second component, whereas these reactions are enthalpy-controlled in the presence of toluene instead of 1,1,1-trichloroethane due to a change in the contribution of the hydrogen bond between piperidine and MeOH (entries 5 and 6, Table 6).⁸⁷

Analysis of the activation parameters for the S_NAr reactions with amines revealed a number of the enthalpy–entropy compensation relations (Fig. 3). Straight line *I* in Fig. 3 includes data for very slow reactions (entries 1, 7, 12, 13 and 22, Table 6) with the rate constants $k_A = 3.08 \times 10^{-9}$ – 2×10^{-4} litre mol⁻¹ s⁻¹ and

high $\Delta H^\ddagger$ and $\Delta S^\ddagger$. Line *II* (entries 2, 5, 6, 10, 11 and 14) relates to the data for rather slow S_NAr reactions with amines. Faster reactions are described by line *III* (entries 4, 8, 9, 15, 18 and 23); very fast reactions, by line *IV* (entries 19 and 20). The reactions described by the compensation plots *III* and *IV* are characterised by very low $\Delta H^\ddagger$ and $\Delta S^\ddagger$. Line *V* (entries 3, 16 and 17, Table 6) almost coincides with line *III*, but low $\Delta H^\ddagger$ and $\Delta S^\ddagger$ for these reactions are associated with a change in the mechanism of S_NAr

**Figure 3.** Compensation plots for the S_NAr reactions of substituted arenes ArLG with amines (the numbering of the points corresponds to the entries in Table 6).

(*I*) $r = 0.940$, $n = 6$, $s = 6.0$; (*II*) $r = 0.975$, $n = 6$, $s = 1.74$; (*III*) $r = 0.73$, $n = 6$, $s = 2.8$; (*IV*) and (*V*) $r = 0.864$, $n = 3$, $s = 3.3$.

reactions in nonpolar *n*-hexane due to formation of complex **9** (see above).⁸⁵

Analysis of the relationships between the enthalpies of activation and the activation free energies for the same S_NAr reactions with amines (Fig. 4) confirms the chemical nature of the observed enthalpy–entropy compensations presented in Fig. 3,^{71–73} and reveals the following characteristic feature: slower reactions are described by line *I* with the opposite slope compared to lines *II–IV* for faster reactions (see Fig. 4). The latter fact reflects the highest sensitivity of changes in $\Delta H^\ddagger$ depending on $\Delta S^\ddagger$ for the same reactions (line *I* in Fig. 3 has the largest slope).

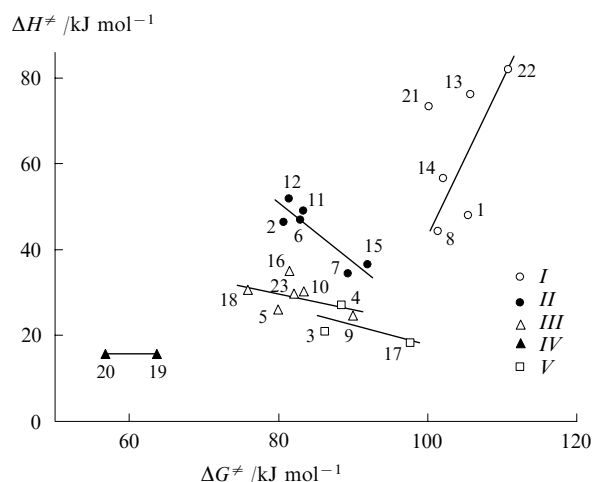


Figure 4. Plots of the enthalpies vs the activation free energies for the S_NAr reactions of substituted arenes $ArLG$ with amines (the numbering of the points corresponds to the entries in Table 6).

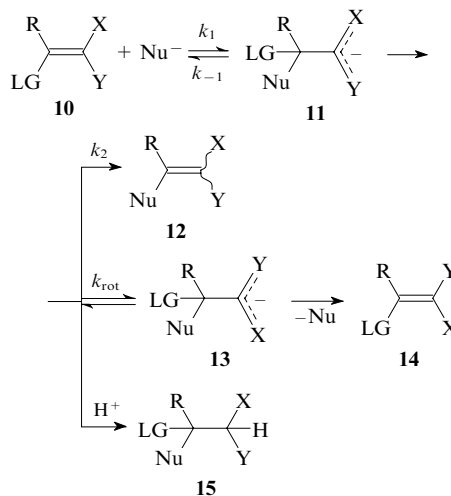
A comparison of the activation parameters for the substitution of the nitro group and the fluorine atom in a series of nitro- and fluoroarenes under the action of aniline (entries 8 and 9, 14 and 15, 19 and 20, Table 6) shows that the selectivity of replacement of these groups ($k_A^{NO_2}/k_A^F$ ratio) is controlled by the entropy of activation. Evidently, the replacement of the nitro group (entries 9, 15 and 20) is characterised by the earlier transition state on the reaction coordinate compared to the replacement of the fluorine atom (entries 8, 14 and 19).

To summarise the results of consideration of the activation parameters for S_NAr reactions, let us note the following characteristic features: $\Delta H^\ddagger$, $\Delta S^\ddagger$ and $\Delta G^\ddagger$ vary in very broad ranges and there is no common enthalpy–entropy compensations for the reactions with both charged and neutral nucleophiles even in terms of the same reaction mechanism involving the formation of a σ complex as the rate-determining step. It should be emphasised that complexation between the substrate and the nucleophile can contribute significantly to changes in the activation parameters.

IV. S_NV and Ad_N reactions

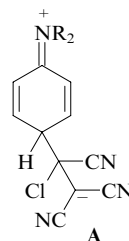
Nucleophilic vinylic substitution (S_NV) can proceed by different mechanisms.^{90–94} If the S_NV reaction proceeds according to the addition–elimination mechanism, it has much in common with the nucleophilic addition to electron-deficient alkenes **10** (Ad_N reaction) because both S_NV and Ad_N reactions involve the same addition step of the nucleophile to the double bond to form carbanion **11** (products **12** and **15**, respectively). As a rule, the nucleophilic attack is the rate-determining step (rate constant k_1), but this is not necessarily the case.^{91,95,96} For example, the apparent second-order rate constant for *E–Z* isomerisation of compound **10** under the action of various amines giving rise to product **14** is not the constant k_1 but reflects a more complex process where the internal rotation with the constant k_{rot} giving

rise to carbanion **13** can be the rate-determining step. This conclusion is supported by very low values of $\Delta H^\ddagger$ (8.8–18.4 kJ mol^{−1}) and $\Delta S^\ddagger$ (from −242.4 to −179.7 J mol^{−1} K^{−1}) for these reactions.⁹¹

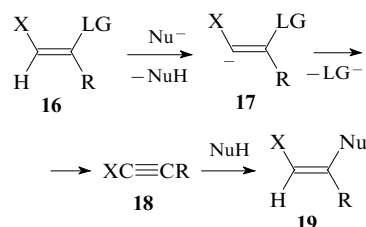


X and Y are electron-withdrawing groups.

Very low values of $\Delta H^\ddagger$ are also typical of S_NV reactions with amines in which the nucleophilic attack with the rate constant k_1 is not the rate-determining step.^{90,96} For example, very low $\Delta H^\ddagger$ (3.3–8.4 kJ mol^{−1}) and $\Delta S^\ddagger$ (from −234.1 to −217.4 J mol^{−1} K^{−1}) for the S_NV reactions of tricyanovinyl chloride with *N,N*-dialkylanilines in chloroform are indicative of the complex character of the apparent rate constant, which is evidently close to the rate constant for elimination of the chloride ion from intermediate zwitterion **A**.^{90,91}



The activation parameters are also useful in proving the elimination–addition ($E–Ad_N$) mechanism of S_NV reactions.⁹² It appeared that positive values of $\Delta S^\ddagger$ provide reliable evidence that S_NV reactions proceed by this mechanism. Under the action of strong bases, a proton can be abstracted from compound **16** to give carbanion **17**, from which the LG group is eliminated to form acetylenic derivative **18**, and the latter is involved in the addition reaction producing alkene **19**.



X is an electron-withdrawing group.

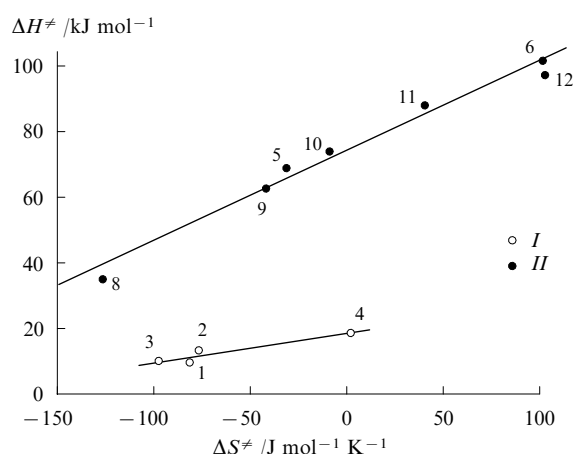
For example, *Z* isomer **16** (the *trans* orientation of the H atom and the leaving group LG) reacts with both hard nucleophiles RO^- and soft nucleophiles RS^- to form acetylenic derivative **18** and substitution product **19**.^{92,97} The fact that the reactions of *Z* isomers **16** with alkoxides RO^- proceed according to the $E–Ad_N$ mechanism is evidenced by positive values of $\Delta S^\ddagger$ (entries 4 and 6, Table 7).^{97,98}

Table 7. Apparent rate constants and activation parameters for S_NV reactions of a series of substrates with charged nucleophiles.^a

Substrate	Entry	Nucleophile	Temperature / °C	Solvent	<i>k</i> / litre mol ⁻¹ s ⁻¹	Δ <i>H</i> [‡]	−Δ <i>S</i> [‡]	Δ <i>G</i> [‡]	Ref.
(E)-ClCH=CHC(O)C ₆ H ₄ OMe-4 (20)	1	PhSNa	−10	MeOH	4.97	9.4	−81.5	30.8	97
	2	MeONa	0	MeOH	1.84 × 10 ^{−2}	13.1	−76.9	34.1	97
(Z)-ClCH=CHC(O)C ₆ H ₄ OMe-4 (21)	3	PhSNa	−10	MeOH	0.304	9.8	−97.8	35.5	97
	4	MeONa	0	MeOH	1.27 × 10 ^{−2}	18.5	2.1	17.9	97
(E)-ClCH=CHCN (22)	5	EtONa	0	EtOH	2.90 × 10 ^{−2}	68.5	−31.4	77.1	98
(Z)-ClCH=CHCN (23)	6	EtONa	0	EtOH	15.5 × 10 ^{−2}	101.2	101.2	73.6	98
(E)-BrCH=CHCN (24)	7	EtONa	0	EtOH	3.25 × 10 ^{−2}	74.4	−8.8	76.8	98
Cl ₂ C=CHSO ₂ Ph (25)	8	4-MeOC ₆ H ₄ SNa	30	MeOH	1.58	34.9	−127	73.4	99
	9	PhSNa	30	MeOH	0.767	62.4	−41.9	75.1	99
	10	4-NO ₂ C ₆ H ₄ SNa	30	MeOH	0.522	73.3	−9.2	76.1	99
	11	MeONa	30	MeOH	0.655	87.9	40.2	75.7	100
	12	EtONa	20	EtOH	7.5	97.1	102.5	67.1	100

^a LG = Cl, except for entry 7, where LG = Br.

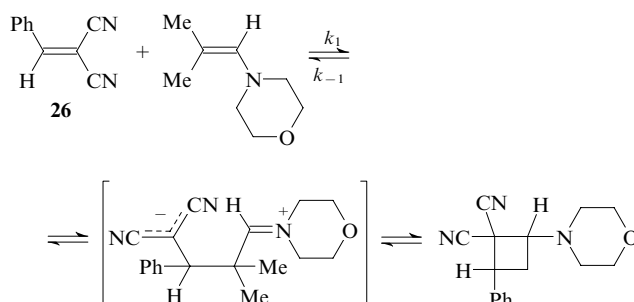
The S_NV reactions with charged nucleophiles resulting in the replacement of halogen in compounds **20**–**25** proceed at similar rates (see Table 7) and their activation parameters obey the enthalpy–entropy compensations (Fig. 5). Straight line *I* includes the reactions of compounds **20** and **21** with O- and S-anions characterised by very low Δ*H*[‡], whereas line *II* includes data for the reactions of compounds **22**–**25** with O- and S-anions characterised by high Δ*H*[‡]. It should be noted that changes in Δ*H*[‡] are little sensitive to changes in Δ*S*[‡] for the reactions of compounds **20** and **21** (line *I*) due apparently to the entropy control of these reactions. The linear relationship between Δ*H*[‡] and Δ*G*[‡] is observed only for these reactions, the sensitivity of Δ*H*[‡] to changes in Δ*G*[‡] is also very weak. By contrast, Δ*G*[‡] for the reactions of compounds **22**–**25** varies in a narrow range (74.4 ± 2.4 kJ mol^{−1}, see Table 7), resulting in the absence of the dependence of Δ*H*[‡] on Δ*G*[‡] and the enthalpy control of these reactions.

**Figure 5.** Compensation plots for the S_NV reactions resulting in the replacement of halogen in compounds **20**–**25** with charged nucleophiles (the numbering of the points corresponds to the entries in Table 7). (*I*) *r* = 0.947, *n* = 4, *s* = 1.6; (*II*) *r* = 0.988, *n* = 8, *s* = 3.48.

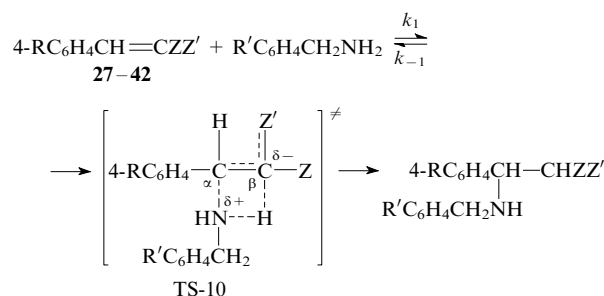
In the case of charged nucleophiles, the nucleophilic addition to activated alkenes **10** via intermediate carbanion **11** giving rise to Ad_N reaction product **15** occurs very rapidly in both water or 50% aqueous DMSO⁹³ and anhydrous DMSO.¹⁰¹ The rate constant *k*₁ (20 °C) varies in the range of 10⁴–10⁷ litre mol^{−1} s^{−1} depending on the nature of substrate **10** and the nucleophile, but the data on the activation parameters for these reactions are lacking.^{93, 101} The

Ad_N reactions of activated alkenes with neutral nucleophiles proceed much more slowly.^{93, 101} For some of these reactions, the activation parameters were determined.^{101–110}

The rate constant *k*₁ (20 °C) of the reaction of benzylidene-malononitrile (**26**) with morpholinobutene as a π-nucleophile in CH₂Cl₂ is 1.24 × 10^{−2} litre mol^{−1} s^{−1}, and the activation parameters Δ*H*[‡] = 19.8 kJ mol^{−1} and Δ*S*[‡] = −214 kJ mol^{−1} K^{−1}.¹⁰¹ The [2 + 2]-cycloaddition reactions proceeding (the entropy control) stepwise via a zwitterionic intermediate are characterised by very low Δ*S*[‡] (as in this reaction).^{101, 111}

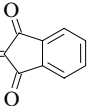
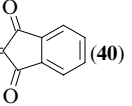


The rate constants and the activation parameters for the Ad_N reactions of activated alkenes with amines in acetonitrile are given in Table 8. Depending on the electrophilicity of alkene and the nucleophilicity of the amine, the rate constants vary by five orders of magnitude, Δ*H*[‡] varies from 2 to 65 kJ mol^{−1}, and Δ*S*[‡] varies from −267 to −40 J mol^{−1} K^{−1}. These substantial changes in the activation parameters are associated with the difference in the mechanism of these reactions. It was demonstrated^{105–110} that activated alkenes **27**–**42** react with benzylamines in acetonitrile according to the concerted mechanism in one step via the cyclic four-membered transition state TS-10.



Hence, these reactions are characterised by low Δ*H*[‡] and Δ*S*[‡] and the entropy control of the reactivity (entries 1–8, 11–14,

Table 8. Rate constants and activation parameters for the Ad_N reactions of activated alkenes with amines in MeCN.

Substrate	Entry	Nucleophile	Temperature / °C	<i>k</i> / litre mol ⁻¹ s ⁻¹	Δ <i>H</i> [‡]	–Δ <i>S</i> [‡]	Δ <i>G</i> [‡]	Ref.
4-MeOC ₆ H ₄ CH=C(NO ₂)Ph (27)	1	4-MeOC ₆ H ₄ CH ₂ NH ₂	25	1.90 × 10 ⁻²	15.5	221.5	81.5	106
	2	4-ClC ₆ H ₄ CH ₂ NH ₂	25	0.89 × 10 ⁻²	20.1	213.2	83.6	106
4-BrC ₆ H ₄ CH=C(NO ₂)Ph (28)	3	4-MeOC ₆ H ₄ CH ₂ NH ₂	25	11.3 × 10 ⁻²	15.9	209.0	78.2	106
	4	4-ClC ₆ H ₄ CH ₂ NH ₂	25	3.69 × 10 ⁻²	19.2	204.8	80.2	106
4-MeOC ₆ H ₄ CH=C(CN)C ₆ H ₄ NO ₂ -4 (29)	5	4-MeOC ₆ H ₄ CH ₂ NH ₂	30	1.17 × 10 ⁻³	29.3	200.6	89.1	106
	6	4-ClC ₆ H ₄ CH ₂ NH ₂	30	0.399 × 10 ⁻³	28.8	213.2	92.3	106
4-BrC ₆ H ₄ CH=C(CN)C ₆ H ₄ NO ₂ -4 (30)	7	4-MeOC ₆ H ₄ CH ₂ NH ₂	30	4.74 × 10 ⁻³	28.4	192.3	85.7	106
	8	4-ClC ₆ H ₄ CH ₂ NH ₂	30	1.07 × 10 ⁻³	31.3	196.5	89.8	106
PhCH=C(CN)C ₆ H ₄ NO ₂ -4 (31)	9	PhCH ₂ NH ₂	30	1.26 × 10 ⁻³	—	—	—	106
	10	PhCH ₂ NH ₂	30	5.54 ^a	33.3	120.3	69.8	102
(<i>E</i>)-4-MeC ₆ H ₄ CH=CHNO ₂ (32)	11	4-MeOC ₆ H ₄ CH ₂ NH ₂	25	2.55 × 10 ⁻²	2.1	267.5	81.9	105
	12	4-ClC ₆ H ₄ CH ₂ NH ₂	25	0.649 × 10 ⁻²	2.1	254.9	78.2	105
(<i>E</i>)-4-NO ₂ C ₆ H ₄ CH=CHNO ₂ (33)	13	4-MeOC ₆ H ₄ CH ₂ NH ₂	25	1.28	3.8	229.9	72.3	105
	14	4-ClC ₆ H ₄ CH ₂ NH ₂	25	0.206	4.2	242.4	76.5	105
(<i>E</i>)-PhCH=CHNO ₂ (34)	15	PhNH ₂	25	41.1 × 10 ⁻⁵	48.2	148.0	92.3	103
	16	3-MeOC ₆ H ₄ NH ₂	25	64.6 × 10 ⁻⁵	43.0	162.0	91.3	103
	17	3-NO ₂ C ₆ H ₄ NH ₂	25	2.70 × 10 ⁻⁵	57.0	141.0	99.0	103
	18	4-MeOC ₆ H ₄ NH ₂	25	337.0 × 10 ⁻⁵	38.8	163.0	87.4	103
	19	4-NO ₂ C ₆ H ₄ NH ₂	25	3.06 × 10 ⁻⁵	56.6	142.0	98.9	103
4-MeC ₆ H ₄ CH=C(CN) ₂ (35)	20	4-MeOC ₆ H ₄ CH ₂ NH ₂	25	4.44	23.4	133.8	63.3	107
	21	4-ClC ₆ H ₄ CH ₂ NH ₂	25	0.831	25.5	137.9	66.6	107
4-NO ₂ C ₆ H ₄ CH=C(CN) ₂ (36)	22	4-MeOC ₆ H ₄ CH ₂ NH ₂	25	1.65	24.2	146.3	67.8	107
	23	4-ClC ₆ H ₄ CH ₂ NH ₂	25	0.204	24.2	158.8	71.5	107
PhCH=C(CN) ₂ (26)	24	PhCH ₂ NH ₂	25	7.14 × 10 ⁻³ (see ^b)	36.1	163.0	84.6	104
	25	PhCH ₂ NH ₂	25	1.45 ^c	47.1	82.0	71.3	104
	26	4-MeOC ₆ H ₄ CH ₂ NH ₂	20	4.06 ^c	41.7	92.0	68.9	104
	27	4-NO ₂ C ₆ H ₄ CH ₂ NH ₂	20	0.18 ^c	51.0	80.0	74.5	104
	28	3-NO ₂ C ₆ H ₄ CH ₂ NH ₂	20	0.14 ^c	65.1	40.0	76.8	104
	29	3-NH ₂ C ₆ H ₄ CH ₂ NH ₂	20	3.20 ^c	40.6	97.0	69.5	104
4-MeOC ₆ H ₄ CH=C(CO ₂ Et) ₂ (37)	30	4-MeOC ₆ H ₄ CH ₂ NH ₂	20	2.08 × 10 ⁻²	25.5	209.0	86.7	108
	31	4-ClC ₆ H ₄ CH ₂ NH ₂	20	0.559 × 10 ⁻²	27.2	209.0	88.4	108
4-BrC ₆ H ₄ CH=C(CO ₂ Et) ₂ (38)	32	4-MeOC ₆ H ₄ CH ₂ NH ₂	20	9.37 × 10 ⁻²	26.8	192.3	83.1	108
	33	4-ClC ₆ H ₄ CH ₂ NH ₂	20	1.86 × 10 ⁻²	27.2	200.6	86.0	108
4-MeOC ₆ H ₄ CH=C() (39)	34	4-MeOC ₆ H ₄ CH ₂ NH ₂	25	2.08	25.5	154.7	71.6	109
4-BrC ₆ H ₄ CH=C() (40)	35	4-MeOC ₆ H ₄ CH ₂ NH ₂	25	3.76	26.3	158.8	73.6	109
4-MeOC ₆ H ₄ CH=C(Ac)CO ₂ Et (41)	36	4-MeOC ₆ H ₄ CH ₂ NH ₂	25	0.767 × 10 ⁻²	20.5	217.4	85.3	110
4-ClC ₆ H ₄ CH=C(CO ₂ Et) ₂ (42)	37	4-MeOC ₆ H ₄ CH ₂ NH ₂	25	2.38 × 10 ⁻²	22.2	200.6	82.0	110

^a The second-order rate constant (*k*₁) of the addition of benzylamine to substrate **31**.¹⁰² ^b The second-order rate constant (*k*) of the addition of the nucleophile to substrate **26** according to a non-catalytic mechanism: $k = k_1 k_2 / k_{-1}$.¹⁰⁴ ^c The second-order rate constant (*k*₁) of the addition of the nucleophile to substrate **26** to form a zwitter-ionic intermediate.¹⁰⁴

20–23 and 30–37, Table 8). The formation of the transition state TS-10 occurs due to a lag in the resonance delocalisation of the negative charge of the C_β atom to the activating groups Z and Z' and a higher degree of N–H bond cleavage, than would be expected in the case of synchronous resonance delocalisation.^{105–110} The compensation plots of Δ*H*[‡] vs Δ*S*[‡] for the Ad_N reactions of alkenes **26**–**42** with amines are shown in Fig. 6. Straight line *I* in this figure represents the reactions of β-nitrostyrenes **32** and **33** with benzylamines. These reactions are characterised by the late transition state TS-10 on the reaction coordinate and the lowest values of Δ*H*[‡] and Δ*S*[‡].¹⁰⁵ The reactions of β-nitrostilbenes **27** and **28**, β-cyano-4'-nitrostilbenes **29** and **30**, benzylidenemalonates **37** and **38** and ethyl α-acetyl-β-phenylacrylates **41** and **42** with benzylamines are characterised by enthalpy–entropy compensation plot *II* (see Fig. 6). The transition state TS-10 for these reactions is earlier because the degree of

the lag in the resonance delocalisation of the negative charge of the C_β atom to the activating groups Z and Z' decreases.^{106, 108, 110}

It should be noted that the activation parameters for the reactions of benzylideneindane-1,3-diones **39** and **40** and -malononitriles **35** and **36** with benzylamines form straight line *III* (Fig. 6) with the almost constant Δ*H*[‡] due to the difference in the structure of TS-10. The reactions of compounds **39** and **40** afford the more loose transition state TS-10.^{107, 109} For compounds **35** and **36** possessing substantially higher electrophilicity,¹¹² the C_α reaction centre becomes more positive in TS-10 compared to the starting compounds due to strong polarisation of the C_α–C_β bond by two CN groups.¹⁰⁷

The activation parameters for the reactions of β-nitrostyrene (**34**) with anilines (entries 15–19, Table 8) and the reactions of compound **26** with benzylamines (entries 25–29, Table 8) in MeCN are described by compensation plots *IV* and *V*, respec-

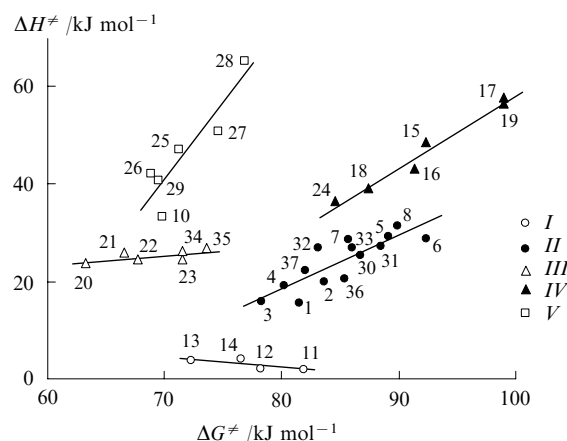
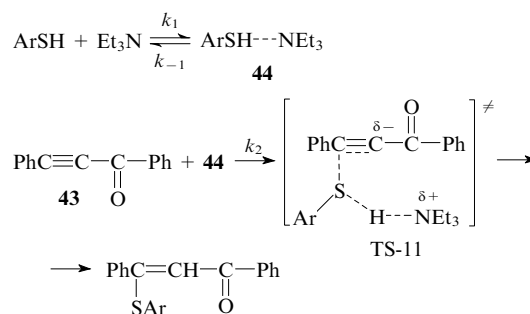


Figure 7. Plots of the enthalpies vs the activation free energies for the Ad_N reactions of activated alkenes with amines in MeCN (the numbering of the points corresponds to the entries in Table 8).

–300 to –120 J mol^{–1} K^{–1} (Table 9). Interestingly, there are Ad_N reactions of activated alkynes with nucleophiles for which the enthalpy of activation is equal to zero (entries 1–5 and 10, Table 9).^{113, 114, 116}

In the attack of arenethiols ArSH on the triple bond of 1,3-diphenylprop-1-yn-3-one (**43**) in the presence of the non-nucleophilic base Et₃N in toluene, the nucleophile is involved in the reaction as complex **44**.¹¹³



Hence, the effective rate constant of the process is $k_{\text{eff}} = (k_1/k_{-1})k_2$, and the enthalpy of formation of complex **44** is close to the activation energy of the rate-determining step of the reaction with the rate constant k_2 via the transition state TS-11. Very low negative values of $\Delta S^\ddagger$ and the isoenthalpy character of the reaction are consistent with the structure of TS-11, in which Et₃N is involved in the S–H bond cleavage (entries 1–4, Table 9).¹¹³ Complex **44** can also be formed in the analogous reaction in a more polar medium (in methanol), but at a low concentration of Et₃N. An increase in the concentration of Et₃N in methanol leads to the formation of the ion pairs {ArS–Et₃HN⁺} and a sharp increase in the activation parameters $\Delta H^\ddagger$ and $\Delta S^\ddagger$ for their reactions with compound **43** (entries 5 and 6, Table 9).¹¹⁴ Consequently, the formation of H-complex **44** before the formation of the transition state TS-11 is responsible for the entropy control of the reaction of compound **43** with arenethiols in the presence of Et₃N.^{113, 114}

The rates of the Ad_N reactions of alkyne **43** with amines at low concentrations of the latter (0.03–0.2 mol litre⁻¹) are independent of the concentration of amines if the reactions proceed in ethanols or aprotic polar solvents (entries 7–23, Table 9).^{115–119} This is possible if $k_2 + k_3[\text{amine}] \gg k_1$. In the latter case, the rate of the overall process is controlled by the rate of the nucleophilic attack of amine (k_1). Based on the activation parameters $\Delta H^\ddagger$ and $\Delta S^\ddagger$ for these reactions, it can be concluded that the reaction mechanism changes from stepwise (*via* zwitterion **45**) to concerted

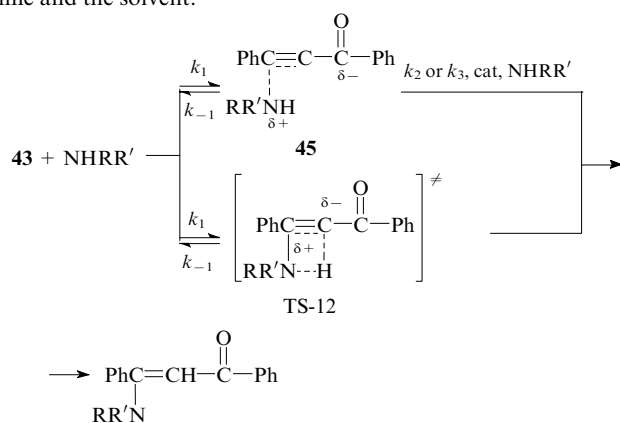
The Ad_N reactions of activated alkynes with various nucleophiles proceeded rather rapidly, and the activation parameters vary in the ranges of $\Delta H^\ddagger$ from 0 to 54.3 kJ mol⁻¹ and of $\Delta S^\ddagger$ from

Table 9. Rate constants and activation parameters for the Ad_N reactions of 1,3-diphenylprop-1-yn-3-one (**43**) with arenethiols in the presence of Et₃N and with amines.

Nucleophile	Entry	Temperature / °C	Solvent	<i>k</i> / litre mol ⁻¹ s ⁻¹	Δ <i>H</i> [‡]	–Δ <i>S</i> [‡]	Δ <i>G</i> [‡]	Ref.
4-MeOC ₆ H ₄ SH – Et ₃ N	1 ^a	0	PhMe	3.6 × 10 ⁻³ (see ^b)	0	288.4	78.7	113
PhSH – Et ₃ N	2 ^a	0	PhMe	4.4 × 10 ⁻³ (see ^b)	0	280.1	76.4	113
4-NO ₂ C ₆ H ₄ SH – Et ₃ N	3 ^a	0	PhMe	20.0 × 10 ⁻³ (see ^b)	0	217.4	59.3	113
4-MeC ₆ H ₄ SH – Et ₃ N	4 ^a	0	PhMe	4.0 × 10 ⁻³ (see ^b)	0	284.2	77.6	113
	5 ^c	0	MeOH	0.37 (see ^b)	0	250.0	68.3	114
	6 ^d	0	MeOH	7.4 (see ^b)	39.0	83.0	61.7	114
Piperidine	7	40	95% EtOH	5.1 × 10 ⁻²	44.7	126.6	83.6	115
Morpholine	8	40	95% EtOH	1.5 × 10 ⁻²	39.7	152.6	86.5	115
	9	40	MeCN	3.06 × 10 ⁻³	16.3	241.0	91.7	116
	10	40	DMF	4.2 × 10 ⁻³	—	300.0	93.9	116
Et ₂ NH	11	40	95% EtOH	1.25 × 10 ⁻²	39.3	154.7	86.9	115
Bu ⁱ NH	12	40	95% EtOH	2.76 × 10 ⁻³	30.9	194.8	91.1	115
PhNH ₂	13	50	EtOH	1.55 × 10 ⁻⁴	42.2	187.3	102.7	117
	14	50	95% EtOH	1.85 × 10 ⁻⁴	39.7	193.5	99.5	118
4-MeOC ₆ H ₄ NH ₂	15	50	95% EtOH	1.86 × 10 ⁻³	38.9	175.6	92.0	118
4-BrC ₆ H ₄ NH ₂	16	50	95% EtOH	0.92 × 10 ⁻⁴	39.3	200.6	101.2	118
4-ClC ₆ H ₄ NH ₂	17	50	95% EtOH	0.94 × 10 ⁻⁴	39.3	200.6	101.2	118
Bu ⁿ NH ₂	18	40	95% EtOH	5.8 × 10 ⁻³	47.6	137.9	90.1	119
	19	40	MeCN	5.27 × 10 ⁻³	42.9	152.0	90.5	116
	20	40	DMF	2.88 × 10 ⁻²	28.9	183.0	86.2	116
Bu ⁱ NH ₂	21	40	95% EtOH	3.26 × 10 ⁻³	51.4	127.9	91.4	119
PhCH ₂ NH ₂	22	40	95% EtOH	4.18 × 10 ⁻³	48.1	136.7	90.9	119
HOCH ₂ CH ₂ NH ₂	23	40	95% EtOH	2.85 × 10 ⁻³	54.3	120.0	91.8	119

^a An excess of Et₃N with respect to arenethiol; [Et₃N] = 0.1 mol litre⁻¹; ^b the apparent second-order rate constant; ^c at [Et₃N] = 1.5 × 10⁻⁵ mol litre⁻¹; ^d at [Et₃N] = 1.5 × 10⁻² mol litre⁻¹.

(via the cyclic transition state TS-12) depending on the nature of amine and the solvent.

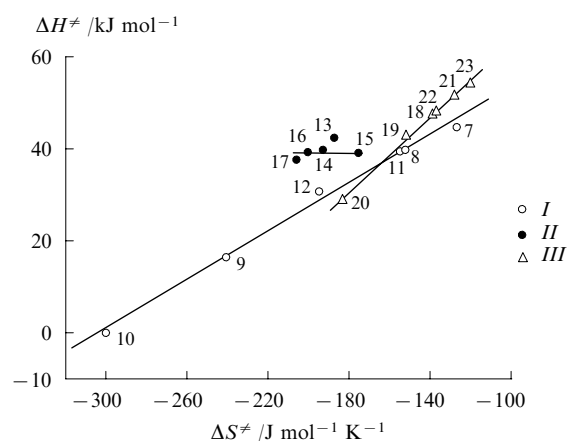


Aprotic polar solvents are more favourable for the concerted mechanism due to weak solvation of zwitterion **45**.

Figure 8 presents the enthalpy–entropy compensations for the Ad_N reactions of compound **43** with amines. Plot *I* characterises the reactions of alkyne **43** with secondary aliphatic amines, which have very low Δ*H*[‡] and Δ*S*[‡] and are entropy-controlled (entries 7–12 in Table 9). Correspondingly, the transition state TS-12 is late.

The activation parameters for the reactions of compound **43** with anilines are described by straight line *II* with almost constant Δ*H*[‡] (see Fig. 8). In spite of high Δ*H*[‡], these reactions are also characterised by low Δ*S*[‡] and, on the whole, the entropy control (entries 13–17, Table 9). Evidently, these reactions have the earlier transition state TS-12.

The reactions of alkyne **43** with primary aliphatic amines (line *III*, Fig. 8) are characterised by high Δ*H*[‡] and Δ*S*[‡] and the enthalpy control (entries 18–23 in Table 9). In this case, the reactions proceed stepwise via zwitterion **45**.¹¹⁶

**Figure 8.** Compensation plots for the Ad_N reactions of activated alkyne **43** with amines in various media (the numbering of the points corresponds to the entries in Table 9).

(*I*) $r = 0.997$, $n = 6$, $s = 1.54$; (*II*) $r = 0.947$, $n = 4$, $s = 2.53$ (point 13 is omitted); (*III*) $r = 0.998$, $n = 6$, $s = 0.62$.

A comparison of the relationships between the enthalpies and the activation free energies for the Ad_N reactions of compound **43** with amines (Fig. 9) shows that lines *I* and *III* have opposite slopes, which confirms the above conclusion about the difference in the character of the control of the reaction depending on the structure of primary or secondary amines. Line *II* in Fig. 9 demonstrates that Δ*H*[‡] is independent of changes in Δ*G*[‡] for the reactions of alkyne **43** with anilines (*cf.* line *II* in Fig. 8).

Both the S_NV and Ad_N reactions are characterised by Δ*H*[‡], Δ*S*[‡] and Δ*G*[‡] varying in very broad ranges and the absence of the common enthalpy–entropy compensation effect. It should also be noted that positive Δ*S*[‡] allow the reliable identification of the

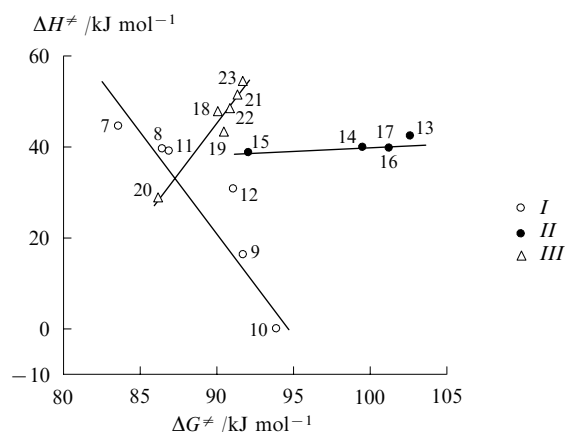


Figure 9. Plots of the enthalpies vs the activation free energies for the Ad_N reactions of activated alkyne **43** with amines in various media (the numbering of the points corresponds to the entries in Table 9). (I) $r = 0.975$, $n = 5$, $s = 4.9$; (II) $r = 0.697$, $n = 5$, $s = 0.29$; (III) $r = 0.967$, $n = 6$, $s = 2.5$.

E-Ad_N mechanism in $\text{S}_\text{N}\text{V}$ reactions and that complexation of a nucleophile with a base and the use of aprotic polar solvents can substantially change the activation parameters for Ad_N reactions.

V. Reactions at the carbonyl carbon

The energetics of bimolecular nucleophilic reactions at the carbonyl carbon atom was extensively analysed.^{6, 71, 72, 120, 121} In the last 10–15 years, these reactions were also extensively studied, the main attention being given to elucidation of their detailed mechanism based on both the kinetic data at different temperatures and for different substrates, nucleophiles and solvents and the data on the kinetic isotope exchange.^{5, 41, 122–128}

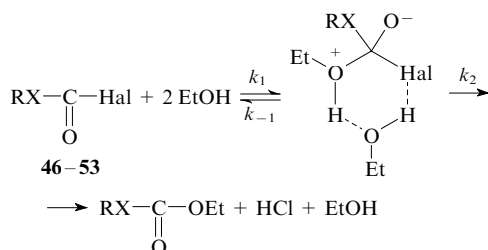
Table 10 gives the rate constants and the activation parameters for bimolecular reactions of carboxylic acid halides with neutral nucleophiles (alcohols and amines) in various media. The rate constants of these reactions vary by 4–5 orders of magnitude; $\Delta H^\ddagger$, from 14.9 to 82.3 kJ mol^{−1}; $\Delta S^\ddagger$, from −238 to −53.8 J mol^{−1} K^{−1}. The fact that the activation parameters vary in broad ranges is attributed to the difference in the mechanisms of these reactions. Ethanolysis of haloformates **46–53** was demonstrated^{129, 130} to proceed as addition–elimina-

Table 10. Apparent rate constants and activation parameters for bimolecular reactions of carboxylic and thiocarboxylic acid halides with alcohols and amines in various media.

Substrate	Entry	Nucleophile	Temperature /°C	Solvent	k /litre mol ^{−1} s ^{−1}	$\Delta H^\ddagger$	$-\Delta S^\ddagger$	$\Delta G^\ddagger$	Ref.
MeOC(O)Cl (46)	1	EtOH	30.3	EtOH	0.69×10^{-4} (see ^a)	58.0	155.0	105.0	129
	2	EtOH	30.0	EtOH	0.38×10^{-5}	59.0	154.0	105.7	130
	3	cyclo-C ₆ H ₁₁ OH	30.0	cyclo-C ₆ H ₁₁ OH	0.10×10^{-6}	69.0	134.0	109.6	130
EtOC(O)Cl (47)	4	EtOH	30.2	EtOH	0.56×10^{-4} (see ^a)	65.0	135.0	105.9	129
	5	PhNH ₂	25	Dioxane	0.206	20.5	189.0	77.8	131
	6	PhNHMe	25	Dioxane	0.196	24.5	174.0	77.2	131
	7	PhNHPr ⁿ	25	Dioxane	0.0379	21.4	201.0	82.3	131
	8	PhNHPr ⁱ	25	Dioxane	0.2699×10^{-3}	61.1	108.0	93.8	131
	9	PhNHC ₆ H ₁₁ -cyclo	25	Dioxane	0.2944×10^{-3}	67.9	84.0	93.3	131
Pr ⁿ OC(O)Cl (48)	10	EtOH	35.7	EtOH	1.05×10^{-4} (see ^a)	54.0	169.0	105.2	129
Pr ⁱ OC(O)Cl (49)	11	EtOH	35.3	EtOH	0.26×10^{-4} (see ^a)	82.0	87.0	108.4	129
PhCH ₂ OC(O)Cl (50)	12	EtOH	29.6	EtOH	1.2×10^{-4} (see ^a)	60.0	143.0	103.3	129
PhOC(O)Cl (51)	13	EtOH	30.7	EtOH	44.0×10^{-4} (see ^a)	47.0	156.0	94.3	129
	14	4-ClC ₆ H ₄ NH ₂	15	MeCN	1.16	23.8	142.1	66.8	132
	15	3-ClC ₆ H ₄ NH ₂	15	MeCN	0.550	23.8	163.0	73.2	132
	16	3-NO ₂ C ₆ H ₄ NH ₂	15	MeCN	0.0931	32.6	146.3	76.9	132
	17	PhNH ₂	15	MeCN	4.25	21.7	154.7	68.6	132
PhOC(O)F (52)	18	EtOH	35.0	EtOH	61.0×10^{-4} (see ^a)	47.0	157.0	94.6	129
EtSC(O)Cl (53)	19	EtOH	39.8	EtOH	0.88×10^{-4} (see ^a)	53.0	173.0	105.4	129
4-MeOC ₆ H ₄ OC(O)Cl (54)	20	4-MeC ₅ H ₄ N	25	MeCN	11.5	29.7	125.4	67.7	133
	21	4-NCC ₅ H ₄ N	25	MeCN	0.0201	28.0	183.9	83.7	133
	22	C ₅ H ₅ N	25	MeCN	5.50	28.8	133.8	69.3	133
	23	C ₅ H ₅ N	25	MeCN	58.9	30.1	108.7	63.0	133
4-NO ₂ C ₆ H ₄ OC(O)Cl (55)	24	4-MeOC ₆ H ₄ NH ₂	15	MeCN	1.12	16.3	188.1	73.3	134
4-MeOC ₆ H ₄ OC(S)Cl (56)	25	4-ClC ₆ H ₄ NH ₂	15	MeCN	0.0669	15.9	209.0	79.2	134
4-ClC ₆ H ₄ OC(S)Cl (57)	26	4-MeOC ₆ H ₄ NH ₂	15	MeCN	8.68	17.1	196.5	76.6	134
	27	4-ClC ₆ H ₄ NH ₂	15	MeCN	0.361	16.7	196.5	76.2	134
	28	MeOH ^b	30	C ₆ H ₆	29.23×10^{-3}	49.2	111.0	83.2	135
Me ₂ C=CHC(O)Cl (58)	29	MeOH ^b	30	CCl ₄	63.59×10^{-3}	30.8	166.0	81.2	136
	30	MeOH ^b	30	Me ₂ CO	1.09×10^{-3}	29.8	203.0	91.4	136
	31	EtOH ^b	30	C ₆ H ₆	10.57×10^{-3}	35.7	165.0	85.7	135
	32	Bu ⁿ OH ^b	30	C ₆ H ₆	9.98×10^{-3}	30.1	184.0	85.9	135
	33	PhCH ₂ OH ^b	30	C ₆ H ₆	6.75×10^{-3}	14.9	238.0	86.9	135
	34	Bu ⁱ OH ^b	30	C ₆ H ₆	1.21×10^{-3}	65.4	85.0	91.2	135
	35	MeOH ^b	30	C ₆ H ₆	0.60×10^{-3}	29.7	208.6	92.9	137
CH ₂ =C(Me)C(O)Cl (59)	36	MeOH ^c	30	C ₆ H ₆	1.03×10^{-3}	47.6	143.3	91.0	137
	37	MeOH ^d	30	C ₆ H ₆	4.37×10^{-3}	71.6	53.8	87.9	137

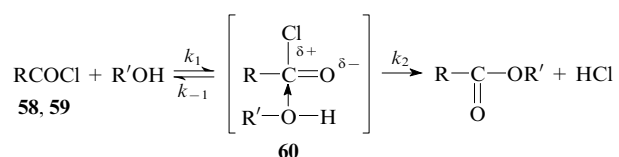
^a The apparent first-order rate constant /s^{−1}; ^b the molar ratio substrate : nucleophile is 1 : 1; ^c the molar ratio substrate : MeOH is 4 : 1; ^d the molar ratio substrate : MeOH is 7 : 1.

tion *via* a cyclic intermediate due to the involvement of the associated form of ethanol.



R = Alk, Ar; Hal = F, Cl; X = O, S.

Alcoholysis of acid chlorides **58** and **59** proceeds apparently through the initial formation of charge-transfer complex **60**, which is transformed into an activated complex and then into the reaction products.¹³⁵⁻¹³⁷



The rate constants of alcoholysis of compounds **58** and **59** depend on the nature of the solvent (entries 28–30 in Table 10),¹³⁶ the structure of alcohol (entries 28 and 31–34 in Table 10)¹³⁵ and the acid chloride to alcohol ratio (entries 35–37 in Table 10).¹³⁷

Figure 10 shows the compensation plots for alcoholysis of compounds **46–53**, **58** and **59**. Line *I* describes ethanolysis reactions characterised by high $\Delta H^\ddagger$ and $\Delta S^\ddagger$ and the enthalpy control in spite of the proposed structure of the cyclic six-membered transition state.¹²⁹

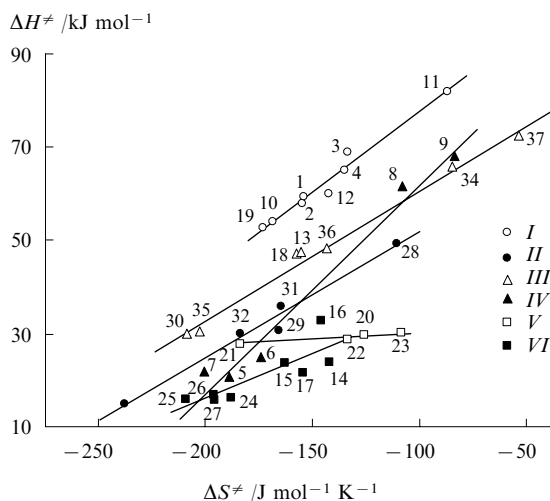


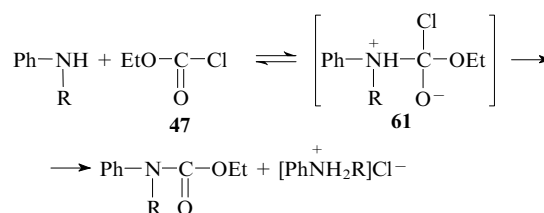
Figure 10. Compensation plots for the reactions of carboxylic and thio-carboxylic acid halides with alcohols and amines (the numbering of the points corresponds to the entries in Table 10).

(I) $r = 0.985$, $n = 8$, $s = 1.75$; (II) $r = 0.989$, $n = 5$, $s = 2.1$; (III) $r = 0.994$, $n = 7$, $s = 1.94$; (IV) $r = 0.988$, $n = 5$, $s = 4.1$; (V) $r = 0.943$, $n = 4$, $s = 0.4$; (VI) $r = 0.844$, $n = 8$.

The alcoholysis reactions of phenyl haloformates **51** and **52** together with the reactions of acid chlorides **58** and **59** form compensation line *III* (see Fig. 10) because of conjugation of the double bond with the C=O group in these compounds. Hence, these reactions proceed *via* complex **60** with both the enthalpy and entropy control.

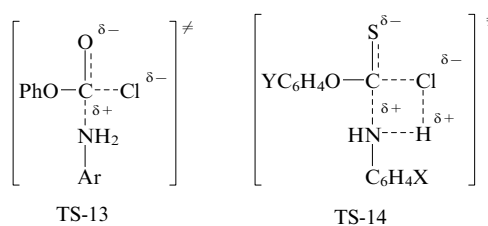
The reactions of acid chloride **58** with primary alcohols in low polar solvents are described by compensation plot *II* (see Fig. 10) with the lowest $\Delta H^\ddagger$ and $\Delta S^\ddagger$, the reactivity being entropy-controlled. Apparently, the formation of complex **60** plays an essential role under these conditions.^{135, 137}

A comparison of the activation parameters for the reactions of ethyl (**47**) and aryl chloroformates **51**, **54** and **55** and their sulfur-containing analogues **56** and **57** with pyridines and anilines (see Table 10) shows that changes in the parameters depend on the nature of the nucleophile.¹³¹⁻¹³⁴ For example, $\Delta H^\ddagger$ and $\Delta S^\ddagger$ are low (entries 5–7, 14–17 and 20–27 in Table 10) and aminolysis reactions of these compounds are entropy-controlled. However, aminolysis of these compounds is characterised by different compensation plots (lines *IV–VI* in Fig. 10). For example, line *IV* relates to the activation parameters for the reactions of chloroformate **47** with *N*-alkylanilines (entries 5–9 in Table 10) and is indicative of a high degree of order of the transition state giving rise to intermediate **61** the decomposition of which affords reaction products.¹³¹

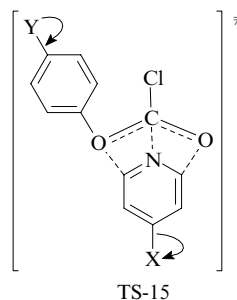


An increase in steric hindrance to the attack on *N*-isopropyl- and *N*-cyclohexylanilines (entries 8 and 9 in Table 10) leads to an increase in $\Delta H^\ddagger$ and $\Delta S^\ddagger$ and, consequently, to a looser transition state, the reactions being enthalpy-controlled.¹³¹

Compensation plot *VI* (see Fig. 10) combines the activation parameters for the reactions of anilines with phenyl chloroformate **51** and its sulfur-containing analogues **56** and **57**. These results do not contradict to the concerted mechanism of these reactions in MeCN *via* the transition state TS-13 for compound **51**^{132, 133} and TS-14 for compounds **56** and **57**.¹³⁴ However, these reactions in aqueous solution proceed stepwise to form intermediate **61**.¹³⁴



Aminolysis of aryl chloroformates **54** and **55** with pyridines in MeCN also proceeds stepwise and involves the formation of intermediate **61** as the rate-determining step *via* the transition state TS-15, which is generated as a result of conjugation of the O–C–O fragment in aryl chloroformate with the π system of the pyridine ring.¹³³



Compensation plot *V* (Fig. 10) is close to the isenthalpy relation and reflects the interaction between the substituent Y in

the aryl fragment and the pyridine fragment through the π -bond system in TS-15.¹³³

A comparison of the relationships between the enthalpies and the activation free energies for the above-described reactions (Fig. 11) confirms the chemical nature of the compensation plots presented in Fig. 10.^{71–73} Lines I, IV and II, III, V, VI in Fig. 11 have opposite slopes due to the difference in the character of the control of the reactivity depending on the structure of the nucleophile.

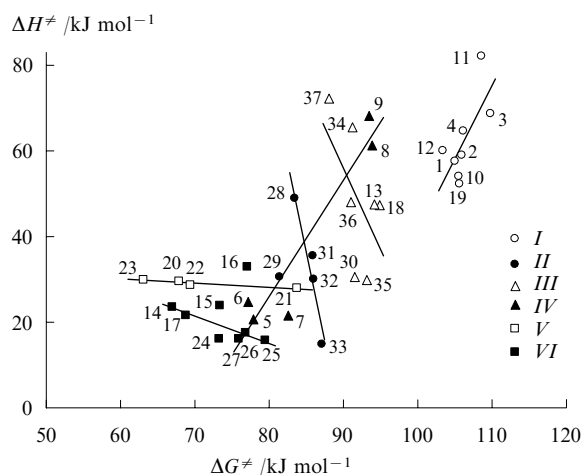
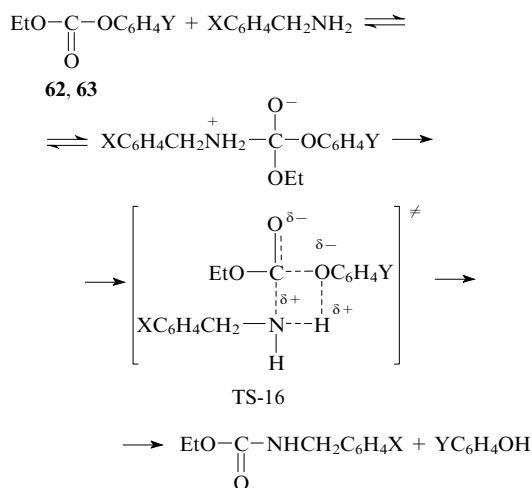


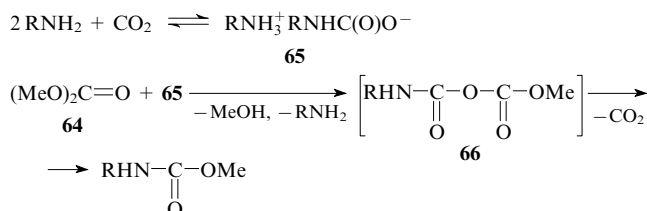
Figure 11. Plots of the enthalpies vs the activation free energies for the reactions of compounds **46**–**59** with alcohols and amines (the numbering of the points corresponds to the entries in Table 10).

Aryl chloroformates **51**, **54** and **55** are good models for calculations of the electrophilicity and prediction of the reaction mechanism with neutral and charged nucleophiles.¹³⁸ The electrophilicities of alkyl aryl and diaryl carbonates were also calculated.¹³⁸ Hence, it is of interest to compare the rate constants and the activation parameters for the reactions of carbonates with nucleophiles and the mechanisms of these reactions. Aminolysis of aryl ethyl carbonates **62** and **63** with benzylamines in MeCN is characterised by high $\Delta H^\ddagger$ and $\Delta S^\ddagger$ (entries 1 and 2 in Table 11) and proceeds stepwise *via* a zwitterionic intermediate, the transformation of which into the reaction products *via* TS-16 is the rate-determining step of the reaction.¹³⁹ Low rate constants of the reactions of carbonates **62** and **63** characterise their moderate electrophilicities.¹³⁸



Y = 3-NO₂ (**62**), 4-CN (**63**); X = 4-MeO, 3-Cl.

Aminolysis of dimethyl carbonate **64** in the presence of CO₂ involves two steps; it is a slower reaction and is characterised by the activation parameters varying in a very broad range depending on the structure of alkylamine (entries 3–7 in Table 11).¹⁴⁰ The nucleophilic attack of the ion pair of carbamate anion **65** on the carbonyl carbon atom in compound **64** giving intermediate **66** is the rate-determining step.



A steric interaction between the substituents R in ion pair **65** and the methyl groups in compound **64** results in changes in $\Delta H^\ddagger$ and $\Delta S^\ddagger$,¹⁴⁰ which are described by the compensation relation (line I, Fig. 12)

$$\Delta H^\ddagger = 118.1 + 0.34 \Delta S^\ddagger \quad (r = 0.996, s = 3.28, n = 5).$$

However, the same reactions on the $\Delta H^\ddagger$ – $\Delta G^\ddagger$ coordinates form two lines with opposite slopes, which reflects the enthalpy (entries 3, 6 and 7 in Table 11) and entropy (entries 4 and 5 in Table 11) control of the reactivity.

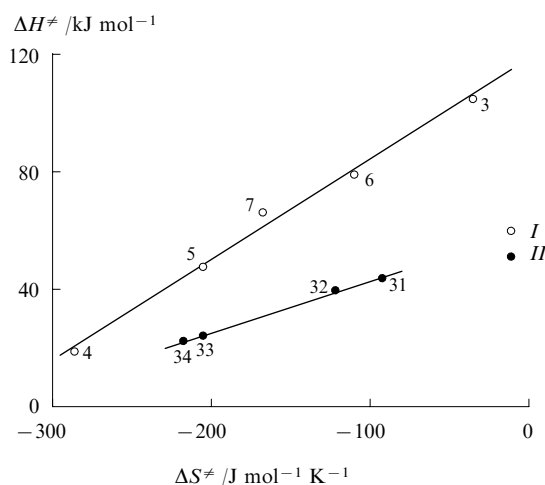


Figure 12. Compensation plots for the reactions of carbonyl compounds **64** and **81**, **82** with amines (the numbering of the points corresponds to the entries in Table 11).

Aminolysis reactions of esters **67**–**74** and thioesters **75**–**79** with benzylamines (entries 8–21, 24 and 25 in Table 11), piperidine, piperazine (entries 28–30 in Table 11) and anilines (entries 22, 23, 26 and 27 in Table 11) involve two steps, where elimination of the leaving group from tetrahedral intermediate **87** is the rate-determining step.^{141–147} The only exception is the reaction of thioester **80** with piperidine in water (entry 30 in Table 11) where the formation of an intermediate is the rate-determining step.¹⁴⁷ Decomposition of zwitterionic intermediate **87** occurs *via* the cyclic transition state TS-17.^{141–147}

The reactions of compounds **67**–**70** with benzylamines (entries 8–15 in Table 11) and the reactions of compounds **77** and **78** with benzylamines and anilines (entries 24–27 in Table 11) are characterised by high activation parameters $\Delta H^\ddagger$ and $\Delta S^\ddagger$ due to which these reactions are enthalpy-controlled. On the contrary, the reactions of compounds **71**–**76** with benzylamines and

Substrate	Entry	Nucleophile	Temperature / °C	Solvent	k / litre mol ⁻¹ s ⁻¹	$\Delta H^\ddagger$	$-\Delta S^\ddagger$	$\Delta G^\ddagger$	Ref.
EtOCO ₂ C ₆ H ₄ NO ₂ -3 (62)	1	4-MeOC ₆ H ₄ CH ₂ NH ₂	25	MeCN	1.10×10^{-3}	62.7	71.1	83.8	139
EtOCO ₂ C ₆ H ₄ CN-4 (63)	2	3-ClC ₆ H ₄ CH ₂ NH ₂	25	MeCN	0.477×10^{-3}	60.2	87.8	86.4	139
(MeO) ₂ C=O (64) ^a	3	Pr ⁿ NH ₂	71.2	—	11.19×10^{-6}	104.9	35.6	109.1	140
	4	PhCH ₂ NH ₂	72.2	—	11.28×10^{-6}	18.8	285.8	117.2	140
	5	CH ₂ =CHCH ₂ NH ₂	72.2	—	7.64×10^{-6}	47.6	205.6	118.6	140
	6	Bu ⁿ NH ₂	71.2	—	13.05×10^{-6}	79.0	109.7	116.7	140
	7	Bu ^s NH ₂	70.2	—	1.086×10^{-6}	66.0	167.4	123.5	140
	8	4-MeC ₆ H ₄ CH ₂ NH ₂	25	DMSO	0.102	52.7	87.8	78.9	141
	9	4-ClC ₆ H ₄ CH ₂ NH ₂	25	DMSO	0.039	52.3	96.1	80.9	141
MeCO ₂ C ₆ H ₄ CN-4 (68)	10	4-MeC ₆ H ₄ CH ₂ NH ₂	25	DMSO	1.65	45.6	96.1	74.3	141
	11	4-ClC ₆ H ₄ CH ₂ NH ₂	25	DMSO	1.03	43.5	100.3	73.4	141
Bu ^t CO ₂ C ₆ H ₄ Cl-4 (69)	12	4-MeC ₆ H ₄ CH ₂ NH ₂	35	DMSO	0.068×10^{-3}	56.4	121.2	92.5	141
	13	4-ClC ₆ H ₄ CH ₂ NH ₂	35	DMSO	0.0266×10^{-3}	61.0	133.8	100.9	141
Bu ^t CO ₂ C ₆ H ₄ CN-4 (70)	14	4-MeC ₆ H ₄ CH ₂ NH ₂	35	DMSO	25.3×10^{-3}	46.8	125.4	84.2	141
	15	4-ClC ₆ H ₄ CH ₂ NH ₂	35	DMSO	17.3×10^{-3}	48.9	129.6	87.5	141
cyclo-C ₃ H ₅ CO ₂ C ₆ H ₄ CN-3 (71)	16	4-MeC ₆ H ₄ CH ₂ NH ₂	35	MeCN	0.675×10^{-3}	22.5	234.1	94.6	142
cyclo-C ₃ H ₅ CO ₂ C ₆ H ₄ NO ₂ -4 (72)	17	4-MeC ₆ H ₄ CH ₂ NH ₂	35	MeCN	39.4×10^{-3}	27.2	183.9	83.8	142
cyclo-C ₄ H ₇ CO ₂ C ₆ H ₄ CN-3 (73)	18	4-MeC ₆ H ₄ CH ₂ NH ₂	35	MeCN	1.49×10^{-3}	22.6	225.7	92.1	143
cyclo-C ₄ H ₇ CO ₂ C ₆ H ₄ NO ₂ -4 (74)	19	4-MeC ₆ H ₄ CH ₂ NH ₂	35	MeCN	86.6×10^{-3}	22.2	192.3	81.4	143
PhCH ₂ C(S)SC ₆ H ₄ Br-4 (75)	20	4-MeOC ₆ H ₄ CH ₂ NH ₂	-25	MeCN	241.0	10.9	154.7	50.8	144
PhCH ₂ C(S)SC ₆ H ₄ Me-4 (76)	21	4-CF ₃ C ₆ H ₄ CH ₂ NH ₂	-25	MeCN	0.083	10.9	221.5	68.1	144
	22	4-MeOC ₆ H ₄ NH ₂	35	MeCN	5.34×10^{-4}	18.4	246.6	94.4	145
	23	3-ClC ₆ H ₄ NH ₂	35	MeCN	0.061×10^{-4}	19.6	280.1	105.9	145
	24	PhCH ₂ NH ₂	-25	MeCN	98.2	37.2	96.1	62.0	146
EtC(S)SC ₆ H ₄ Me-4 (78)	25	PhCH ₂ NH ₂	-25	MeCN	7.25	35.5	83.6	57.1	146
	26	4-MeOC ₆ H ₄ NH ₂	35	MeCN	5.05×10^{-3}	53.1	117.0	89.1	145
	27	3-ClC ₆ H ₄ NH ₂	35	MeCN	0.0242×10^{-3}	66.9	117.0	102.9	145
MeC(O)SPh (79)	28	piperidine	45	H ₂ O	56.9	31.8	111.6	67.3	147
	29	piperazine	45	H<					

$$\begin{array}{c}
 \text{R}-\text{C}-\text{XAr} + 2 \text{R}'\text{R}''\text{NH} \rightleftharpoons \text{R}-\overset{\text{Y}^-}{\underset{\text{HNR}'\text{R}''}{\text{C}}}-\text{XAr} \longrightarrow \\
 \parallel \\
 \text{Y} \\
 \text{67-74, 79, 80} \qquad \qquad \qquad \text{87}
 \end{array}$$

$$\longrightarrow \left[\begin{array}{c} \text{Y}^{\delta-} \\ \vdots \\ \text{R}-\text{C} \cdots \text{X}^{\delta-}\text{C}_6\text{H}_4\text{Z} \\ \vdots \\ \text{R}'-\text{N}^{\delta+} \cdots \text{H}^{\delta+} \\ \vdots \\ \text{R}'' \end{array} \right] \neq \longrightarrow$$

$$\text{TS-17}$$

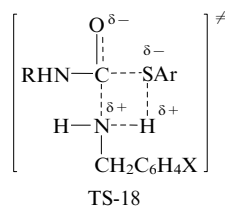
$$\longrightarrow \text{R}-\overset{\text{Y}}{\underset{\text{Y}}{\text{C}}}-\text{NR}'\text{R}'' + \text{ArX}^- + \text{R}'\text{R}''\text{NH}_2^+$$

anilines (entries 16–23 in Table 11) and of compound **79** with piperidine (entry 28 in Table 11) are characterised by lower activation parameters $\Delta H^\ddagger$ and $\Delta S^\ddagger$ and the entropy control. The activation parameters for aminolysis of compounds **67–79** fall within two ranges (with low and high $\Delta H^\ddagger$ and $\Delta S^\ddagger$), however no enthalpy–entropy compensation effect is observed. The more organised transition states of the TS-17 type for aminolysis of compounds **71–76** are attributed to hydrogen bonding with the $\text{ZC}_6\text{H}_4\text{X}^-$ leaving group.^{142, 143}

A decrease in the contribution of the latter to the structure of TS-17 due to an increase in the steric effect of the substituent R in the substrate (for example, R = Et)¹⁴⁵ or the solvent effect^{141, 147} results in a looser structure of the transition state TS-17 and an increase in the activation parameters.

A much stronger donor effect of the PhNH and EtNH groups in thiocarbamates **81** and **82** leads to a switch from the stepwise mechanism to the concerted mechanism in the reactions of these compounds with benzylamines (entries 31–34 in Table 11).^{148, 149} The transition state TS-18 for these reactions involves a four-

membered ring, which is more rigid in the presence of a strong electron-donating substituent ($R = \text{Et}$).¹⁴⁹



The activation parameters for these aminolysis reactions are characterised by the compensation relations between $\Delta H^\ddagger$ and $\Delta S^\ddagger$ (line II in Fig. 12) and between $\Delta H^\ddagger$ and $\Delta G^\ddagger$:

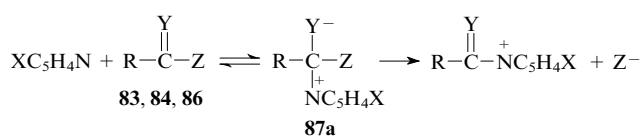
$$\Delta H^\ddagger = 60.0 + 0.17 \Delta S^\ddagger \quad (r = 0.999, s = 0.38, n = 4),$$

$$\Delta H^\ddagger = 138.1 - 1.31 \Delta G^\ddagger \quad (r = 0.997, s = 0.94, n = 4),$$

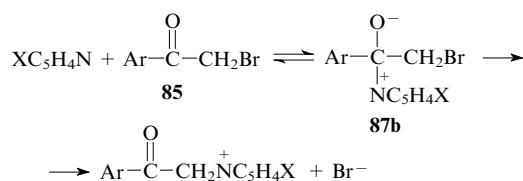
which confirms the chemical nature of the compensation effect.^{71–73}

It should be noted that the activation parameters for aminolysis of thiocarbonates **81** and **82** proceeding by the concerted mechanism and aminolysis of esters and thioesters proceeding by the stepwise mechanism vary in the same range. Recently, it has been demonstrated that the activation parameters $\Delta H^\ddagger$ and $\Delta S^\ddagger$ for the aminolysis of carbonates **62** and **63**¹³⁹ are rather close to those of related thiocarbonates¹³⁸ although the reactions of carbonates proceed by the stepwise mechanism, whereas the reactions of thiocarbonates occur by the concerted mechanism.^{139, 148, 154} Evidently, to estimate unambiguously the reaction mechanism, it is necessary to use the activation parameters along with the correlation analysis and data on the kinetic isotope effect.^{5, 41, 122–128}

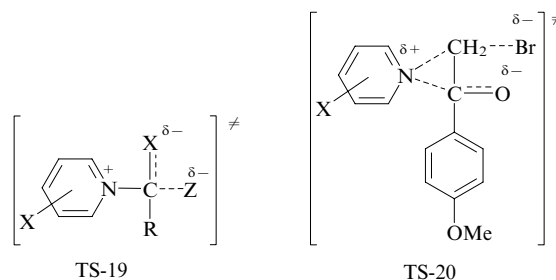
The reactions of ester **86** and thioesters **83** and **84** with pyridines proceed stepwise *via* tetrahedral intermediate **87a**.^{150, 151, 153}



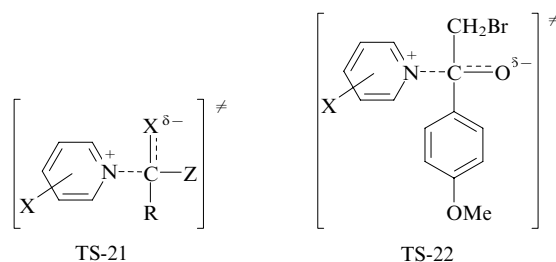
The reaction of phenacyl bromide **85** also proceed *via* an analogous intermediate.¹⁵²



The formation of intermediates **87a,b** was demonstrated to be the rate-determining step of the reactions with more basic pyridines, whereas decomposition of these intermediates is the rate-determining step of the reactions with weakly basic pyridines in low polar MeCN (entries 35–40 in Table 11).^{150–152} However, the influence of the basicity of pyridines on the reaction mechanism in aqueous-alcoholic media is less significant due to an increase in the contribution of solvation of the transition state TS-19. As a result, decomposition of the corresponding intermediate was the rate-determining step for all the pyridines examined.¹⁵³ Aminolysis reactions with pyridine, in which decomposition of intermediates is the rate-determining step, are characterised by much lower entropies of activation (entries 36, 38, 40 and 41 in Table 11). The latter fact is associated with the more organised and more solvated transition states TS-19 and TS-20 for the transformations of intermediates **87a** and **87b**, respectively.^{150–152}

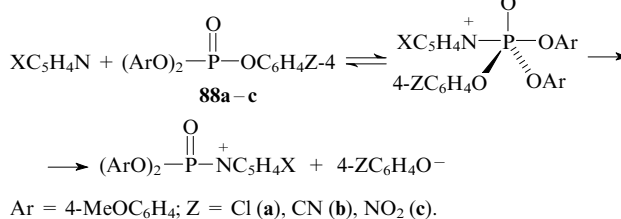


The less organised and less solvated transition states TS-21 and TS-22 are typical of the reactions of pyridine with compounds **83–86** involving the formation of the corresponding intermediates as the rate-determining step.

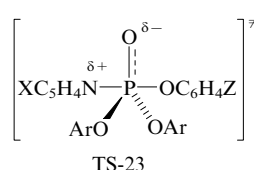


An increase in $\Delta S^\ddagger$ is either not accompanied by changes in $\Delta H^\ddagger$ (entries 35–38 in Table 11) or is accompanied by a decrease (entries 39 and 40 in Table 11) or even an increase in these parameters (entries 41 and 42 in Table 11). Therefore, no compensation effects were observed for the reactions of compounds **83–86** with pyridine, although almost all reactions are entropy-controlled (entries 35–41 in Table 11). The reaction of ester **86** with weakly basic pyridine in aqueous EtOH, which is enthalpy-controlled is the exception (entry 42 in Table 11).¹⁵³

Aminolysis of carbonyl compounds with pyridine is similar in the energetics and the reaction mechanism to analogous reactions of triaryl phosphates. For example, study of the kinetics of the reactions of aryl bis(4-methoxyphenyl) phosphates **88a–c** with pyridines in MeCN showed that the activation parameters vary in broad ranges depending on the basicity of pyridine and the nature of the substituent Z in the leaving group ($\Delta H^\ddagger$ from 5.4 to 39.3 kJ mol^{−1} and $\Delta S^\ddagger$ from −259.2 to −137.9 J mol^{−1} K^{−1}). The use of less basic pyridine ($X = 3\text{-Cl}$) and a better nucleofuge containing an electron-withdrawing substituent Z ($Z = \text{CN}$ or NO_2) leads to a sharp decrease in the activation parameters.¹⁵⁵



This is associated with the fact that the reaction proceeds by the concerted mechanism *via* the transition state TS-23 with the apical arrangement of the nucleophile and the leaving group.



The more basic pyridine ($X = 4\text{-Me}$) and the poorer leaving group in the substrate ($Z = \text{Cl}$) lead to an increase in $\Delta H^\ddagger$ and $\Delta S^\ddagger$,

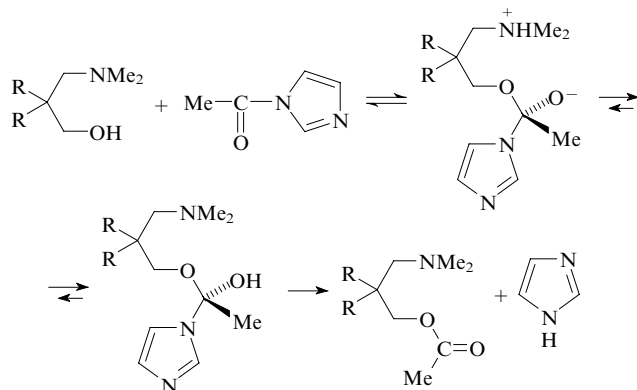
which is associated with the fact that this reaction proceeds by the stepwise mechanism involving the formation of an intermediate as the rate-determining step.¹⁵⁵ The activation parameters are described by the common compensation relations

$$\Delta H^\ddagger = 77.83 + 0.279 \Delta S^\ddagger \quad (r = 1.0, s = 0.014, n = 3),$$

$$\Delta H^\ddagger = 524.11 - 5.74 \Delta G^\ddagger \quad (r = 0.999, s = 0.167, n = 3)$$

for the reactions proceeding by different mechanisms.¹⁵⁵

Alcoholysis of *N*-acetylimidazole with 2,2-dialkyl-3-(*N,N*-dimethylamino)propan-1-ols in MeCN at 25–65 °C occurs stepwise and involves, as the rate-determining step, the formation of a tetrahedral intermediate, which is then transformed into the reaction products.⁶²

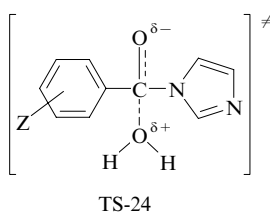


These reactions are characterised by very low entropies of activation ($\Delta S^\ddagger$ from -210 to -171 J mol⁻¹ K⁻¹), moderate enthalpies of activation ($\Delta H^\ddagger = 27.4$ – 40.9 kJ mol⁻¹) and the entropy control.⁶² There is the enthalpy–entropy compensation

$$\Delta H^\ddagger = 91.2 + 0.30 \Delta S^\ddagger \quad (r = 0.935, s = 1.43, n = 8).$$

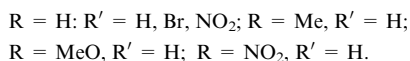
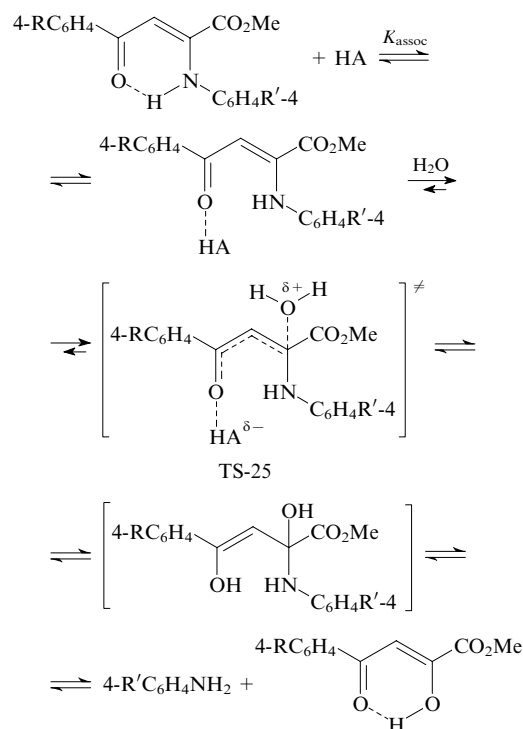
However, the isokinetic relationships between the activation parameters depend on the structures of the substituents *R* in the starting amino alcohol.⁶²

Non-catalysed hydrolysis of substituted *N*-benzoylimidazoles in 10% aqueous MeCN proceeds *via* the transition state TS-24 with pronounced charge separation. The substituent *Z* has a considerable effect on solvation and $\Delta S^\ddagger$.



For example, $\Delta S^\ddagger$ varies from -186.4 J mol⁻¹ K⁻¹ for *Z* = 4-Me to -136.7 J mol⁻¹ K⁻¹ for *Z* = 4-NO₂; $\Delta H^\ddagger$, from 43.5 to 50.6 kJ mol⁻¹ for *Z* = Me and NO₂, respectively. The entropy control of the reaction changes to the enthalpy control with increasing electron-withdrawing properties of the substituent *Z*.¹⁵⁶ Evidently, the energy parameters for alcoholysis of acylimidazoles are very close to those for hydrolysis of these compounds.

Hydrolysis of enamines in 50% aqueous dioxane in the presence of an acetate buffer occurs stepwise and involves the addition *via* the transition state TS-25 as the rate-determining step to form an intermediate and then the reaction products.¹⁵⁷

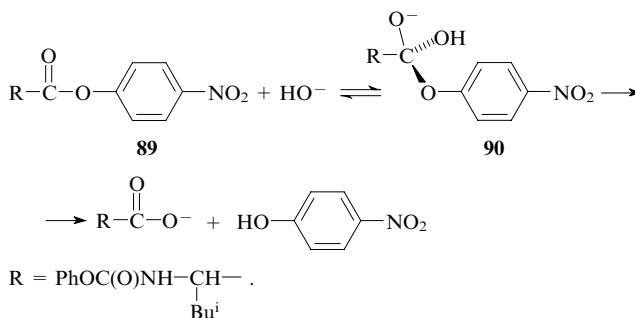


The activation parameters are close to those for hydrolysis of *N*-benzoylimidazoles in the case of the entropy control of the reaction.¹⁵⁷ The hydrolysis reactions of the above-mentioned enamines are characterised by the following relation

$$\Delta H^\ddagger = 107.4 + 0.31 \Delta S^\ddagger \quad (r = 0.990, s = 1.5, n = 8),$$

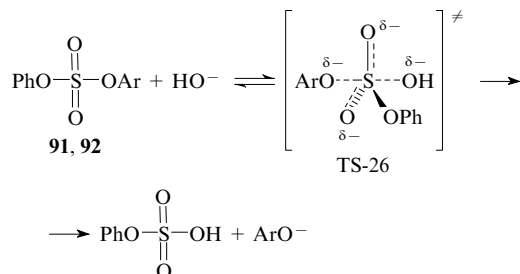
which indicates that the equilibrium constant of association of the substrate with the buffer component HA makes a contribution to the apparent rate constant.¹⁵⁷

Alkaline hydrolysis of esters occurs stepwise and involves the formation of a tetrahedral intermediate as the rate-determining step.¹²⁵ For example, hydrolysis of ester **89** in 10% aqueous MeCN proceeds *via* intermediate **90** and is characterised by very low activation parameters: $\Delta H^\ddagger = 13.5$ kJ mol⁻¹ and $\Delta S^\ddagger = -277.1$ J mol⁻¹ K⁻¹.



Hydrolysis is sharply accelerated in the presence of polymeric bases as catalysts. In this case, the activation parameters are substantially higher: $\Delta H^\ddagger = 55.6$ – 65.6 kJ mol⁻¹, $\Delta S^\ddagger$ from -62.7 to -12.6 J mol⁻¹ K⁻¹. The reaction is controlled by the enthalpy.¹⁵⁸ The isokinetic relationship with $\beta = 313$ K found for the catalytic process is due to the contribution of the equilibrium constant between substrate **89** and the catalyst to the apparent rate constant.¹⁵⁸

In 10% aqueous dioxane, alkaline hydrolysis of diaryl sulfates **91** and **92**, *viz.*, sulfur-containing analogues of diaryl carbonates, proceeds apparently by the concerted mechanism *via* the transition state TS-26 and is characterised by high activation parameters ($\Delta H^\ddagger = 88.0$ and 84.8 kJ mol^{-1} and $\Delta S^\ddagger = -37.0$ and $-50.2 \text{ J mol}^{-1} \text{ K}^{-1}$ for compounds **91** and **92**, respectively) and the enthalpy control of the reactivity.¹⁵⁹

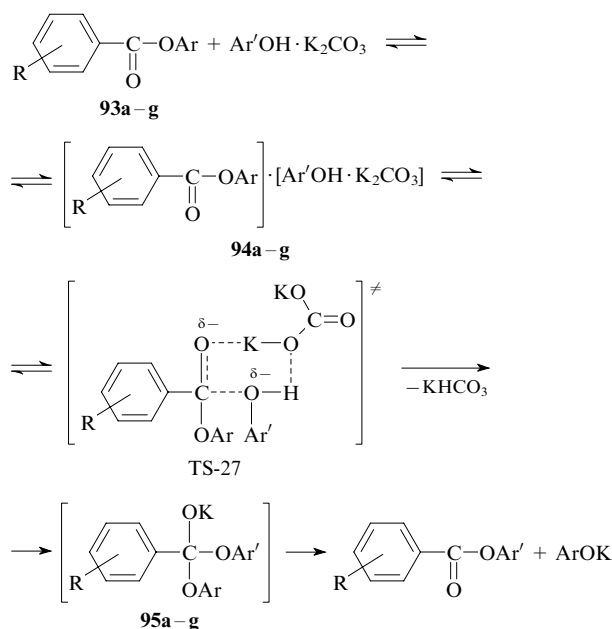


Ar = 4-Cl-3-NO₂C₆H₃ (**91**), 4-NO₂C₆H₄ (**92**).

It should be noted that the reactions of diaryl carbonates with phenolate anions in aqueous solution also proceed by the concerted mechanism.¹⁶⁰

Transesterification can occur by different mechanisms.¹²⁵ For example, the reaction of 4-nitrophenyl acetate with 4-chlorophenolate in aqueous media proceeds through the one-step concerted mechanism¹²³ with the activation parameters $\Delta H^\ddagger = 51.4 \text{ kJ mol}^{-1}$, $\Delta S^\ddagger = -75.7 \text{ J mol}^{-1} \text{ K}^{-1}$ and $\Delta G^\ddagger = 74.0 \text{ kJ mol}^{-1}$. These parameters are only slightly smaller for the reaction in 90% aqueous DMSO or for the reaction with butane-2,3-dione monooximate as the nucleophile, the enthalpy control being retained.¹⁶¹

The activation parameters for transesterification of 4-nitrophenyl benzoates **93a–g** with the nucleophile 4-ClC₆H₄O[−]·K⁺ differ substantially from those for the reaction with the 4-ClC₆H₄OH·K₂CO₃ complex.^{67, 162}



R = 4-MeO (**a**), 4-Me (**b**), H (**c**), 4-Br (**d**), 4-CF₃ (**e**), 3-NO₂ (**f**), 4-NO₂ (**g**); Ar = 4-NO₂C₆H₄, Ar' = 4-ClC₆H₄.

An increase in the electron-withdrawing properties of the substituent R in benzoates **93a–g** leads to a substantial decrease in the relative values of the parameters $\Delta\Delta H^\ddagger$ and $\Delta\Delta S^\ddagger$ for transesterification reactions due apparently to the characteristic features of complexes **94a–g**. The transformation of the latter through the cyclic transition state TS-27 into intermediates **95a–g**

is the rate-determining step of the process.¹⁶² The reactions of benzoates **93a–g** are characterised by the compensation relations

$$\Delta\Delta H^\ddagger = 2.23 + 0.39 \Delta\Delta S^\ddagger \quad (r = 0.999, s = 1.67, n = 7),$$

$$\Delta\Delta H^\ddagger = -9.49 + 4.64 \Delta\Delta G^\ddagger \quad (r = 0.984, s = 6.35, n = 7)$$

the reactivity being enthalpy-controlled.¹⁶² It should be noted that the isokinetic relationship for transesterification reactions is observed only for benzoates **93c–g** (see Ref. 162) due to destabilisation of the ground state of these compounds.^{125, 163–165}

Bimolecular nucleophilic reactions at the carbonyl carbon atom, like the reactions considered in the previous sections, are characterised by very broad ranges of the activation parameters within one class of substrates. It should be noted that complexation between carbonyl compounds and nucleophiles plays a considerable role in the changes in the activation parameters.

VI. Reactions of carbocations with nucleophiles

The energetics of the reactions of stable carbocations with nucleophiles is of particular interest because, first, the formation of the bond between these species is the rate-determining step and, second, most of these reactions are described by either Ritchie's equation^{166, 167}

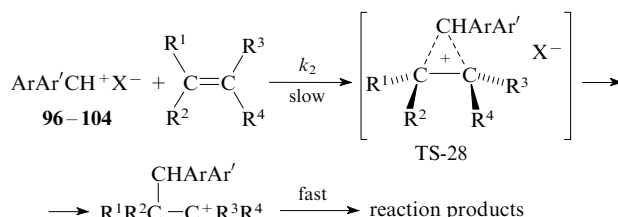
$$\log \frac{k}{k_0} = N_+,$$

where k and k_0 are the rate constants of the reaction of the substrate with this nucleophile and water, respectively, and N_+ is the nucleophilicity, or by the equation proposed by Mayr and co-workers,^{167–169}

$$\log k(20^\circ \text{C}) = s(N + E),$$

where s is the specific parameter of the nucleophile ($s = 1$ for 2-methylpent-1-ene), N is the nucleophilicity for the nucleophile and E is the electrophilicity for the electrophile.

The rate constants and the activation parameters for the reactions of benzhydryl and benzopyrylium cations with neutral π -nucleophiles (alkenes and dienes) vary within broad ranges. The rate constants vary by 7–8 orders of magnitude; $\Delta H^\ddagger$, from 0 to 53 kJ mol^{−1}; $\Delta S^\ddagger$, from −180 to −80 J mol^{−1} K^{−1}.^{168–175} These broad ranges are attributed to the fact that the structure of the transition state TS-28 and its position on the reaction coordinate substantially depend on the nature of the reagents.^{170, 171, 175}



Hence, there is no common enthalpy–entropy compensations for the above-mentioned reactions of cations with π -nucleophiles. However, the compensation relations are observed for the reactions of benzhydryl cations with the same nucleophile, for example, for the reactions of cations **96–100** with alkene PrⁿMeC=CH₂ (entries 1, 4, 6, 8 and 10, Table 12) or Me₂C=CHMe (entries 2, 5, 7, 9 and 11 in Table 12), the reactions of cations **101–104** with alkene CH₂=C(OPh)OSiMe₃ (entries 12, 15, 18 and 20 in Table 12) or with 1-(trimethylsilyloxy)cyclopentene (entries 14, 17 and 19 in Table 12) and the reactions of cations **96**, **101** and **102** with alkenes Me₂C=CMe₂ and Me₂C=C(OMe)OSiMe₃ (entries 3, 13 and 16 in Table 12).

In the reactions of the cations with π -nucleophiles characterised by the activation parameters $\Delta H^\ddagger < 30 \text{ kJ mol}^{-1}$ and $\Delta S^\ddagger < -100 \text{ J mol}^{-1} \text{ K}^{-1}$, the reactivity is entropy-controlled. If these parameters are larger than the above-mentioned values,

Table 12. Rate constants and activation parameters for bimolecular reactions of benzhydryl carbocations with alkenes in CH_2Cl_2 .^a

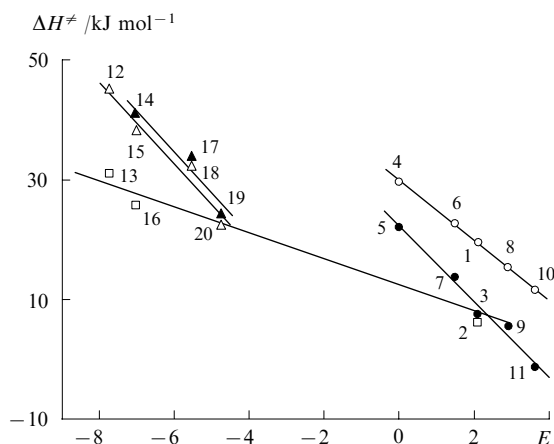
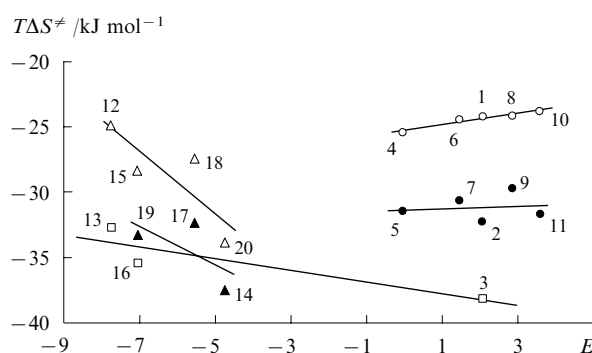
Substrate	Entry	Nucleophile	k_2 /litre mol ⁻¹ s ⁻¹	$\Delta H^\ddagger$	$-\Delta S^\ddagger$	$\Delta G^\ddagger$	Ref.
4-MeOC ₆ H ₄ (Ph)CH ⁺ (96)	1	Pr ⁿ MeC=CH ₂	2.58×10^1	19.5	119.0	43.7	168
	2	Me ₂ C=CHMe	2.47×10^2	7.5	159.0	39.8	168
	3	Me ₂ C=CMe ₂	5.62	8.0	188.0	46.2	168
(4-MeOC ₆ H ₄) ₂ CH ⁺ (97)	4	Pr ⁿ MeC=CH ₂	2.92×10^{-2}	29.7	125.0	55.1	170
	5	Me ₂ C=CHMe	8.38×10^{-2}	21.9	155.0	53.4	170
4-MeOC ₆ H ₄ (4-MeC ₆ H ₄)CH ⁺ (98)	6	Pr ⁿ MeC=CH ₂	3.38	22.7	120.0	47.1	170
	7	Me ₂ C=CHMe	1.83×10^1	13.6	151.0	44.3	170
4-PhOC ₆ H ₄ (Ph)CH ⁺ (99)	8	Pr ⁿ MeC=CH ₂	2.86×10^2	15.3	119.0	39.4	170
	9	Me ₂ C=CHMe	3.92×10^3	5.3	147.0	35.1	170
(4-MeC ₆ H ₄) ₂ CH ⁺ (100)	10	Pr ⁿ MeC=CH ₂	3.40×10^3	11.6	117.0	35.4	170
	11	Me ₂ C=CHMe	6.79×10^4	-1.4	117.0	156.0	170
(4-pyr-C ₆ H ₄) ₂ CH ⁺ (101) ^b	12	CH ₂ =C(OPh)OSiMe ₃	2.35	44.9	85.0	69.8	171
	13	Me ₂ C=C(OMe)OSiMe ₃	2.32×10^1	31.1	112.0	63.9	171
(4-Me ₂ NC ₆ H ₄) ₂ CH ⁺ (102)	14	1-Me ₃ SiO-C ₅ H ₇ -cyclo	3.61×10^{-1}	40.8	114.0	74.2	171
	15	CH ₂ =C(OPh)OSiMe ₃	9.45	37.9	97.0	66.3	171
	16	Me ₂ C=C(OMe)OSiMe ₃	7.96×10^1	25.7	121.0	61.1	171
(4-mor-C ₆ H ₄) ₂ CH ⁺ (103) ^c	17	1-Me ₃ SiO-C ₅ H ₇ -cyclo	1.05×10^1	33.6	111.0	66.1	171
	18	CH ₂ =C(OPh)OSiMe ₃	1.38×10^2	32.3	94.0	59.8	171
(4-Ph ₂ NC ₆ H ₄) ₂ CH ⁺ (104)	19	1-Me ₃ SiO-C ₅ H ₇ -cyclo	5.80×10^1	24.3	128.0	61.8	171
	20	CH ₂ =C(Ph)OSiMe ₃	5.41×10^2	22.5	116.0	56.5	171

^a Reactions were carried out at -70 °C (entries 1–11) and 20 °C (entries 12–20); ^b pyr is pyrrolidino; ^c mor is morpholino.

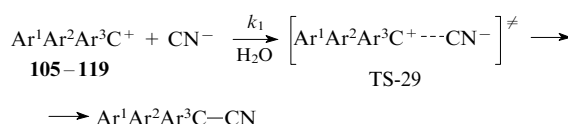
the enthalpy makes a larger contribution to the activation free energy of these reactions.

The fast reactions of highly electrophilic benzhydryl cations **96**, **99** and **100** with alkenes Me₂C=CHMe and Me₂C=CMe₂ are characterised by very low $\Delta H^\ddagger$ and $\Delta S^\ddagger$ (entries 2, 3, 9, 11 in Table 12).^{168, 170, 175} Changes in the electrophilicity of the benzhydryl cations were demonstrated¹⁷⁵ to have a stronger effect on $\Delta H^\ddagger$ than on $\Delta S^\ddagger$ (Figures 13 and 14). Hence, negative $\Delta H^\ddagger$ for the reactions of highly electrophilic carbocations can be attributed to the shift of the transition state TS-28 to the earlier position on the reaction coordinate, which is accompanied by an increase in the entropy of activation (entries 3 and 11 in Figures 13 and 14).¹⁷⁵

The reactivity of carbocations of the triarylmethane series **105–119** in the reactions with cyanide ions in aqueous media described by Ritchie's equation is substantially lower than that of the benzhydryl cations, and $\Delta H^\ddagger$ and $\Delta S^\ddagger$ vary in the ranges from 31 to 52 kJ mol⁻¹ and from -187 to -40 J mol⁻¹ K⁻¹, respectively (Table 13).¹⁷⁶ There is no common compensation relations

**Figure 13.** Plots of the enthalpy of activation vs the electrophilicity for the reactions of benzhydryl cations with neutral π -nucleophiles (the numbering of the points corresponds to the entries in Table 12).**Figure 14.** Plots of the entropy ($T\Delta S^\ddagger$) vs the electrophilicity for the reactions of benzhydryl cations with neutral π -nucleophiles (the numbering of the points corresponds to the entries in Table 12).

for the latter reactions (as in the case of the reactions of benzhydryl cations). Only certain series of these cations are characterised by the compensation (isokinetic) relations between $\Delta H^\ddagger$ and $\Delta S^\ddagger$ (Fig. 15).¹⁷⁶

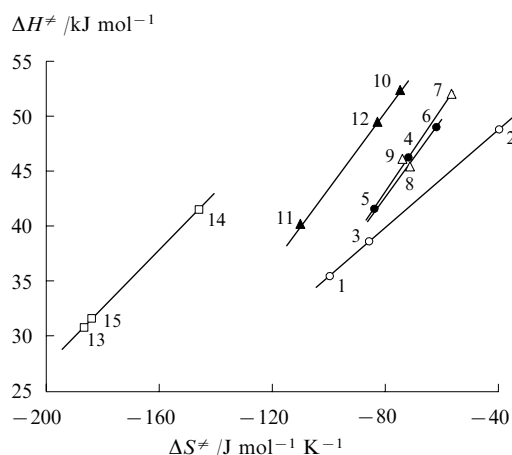
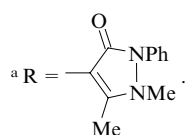


The structure of the transition state TS-29 for the reactions of cations **105–116** controlled by the enthalpy of activation is described by a solvent-separated ion pair, whereas the structure of TS-29 for the reactions of cations **117–119** controlled by the entropy of activation can be represented as a contact ion pair.¹⁷⁶

The reaction of the most reactive cation **106** with the CN^- ions is characterised by the highest value of $\Delta S^\ddagger$, whereas the analogous reaction of the least reactive cation **117** is characterised by very low $\Delta S^\ddagger$ (see Table 13). The earlier and less-organised transition state TS-29 and the later and well-organised transition state TS-29 for the reactions of cations **106** and **117**, respectively,

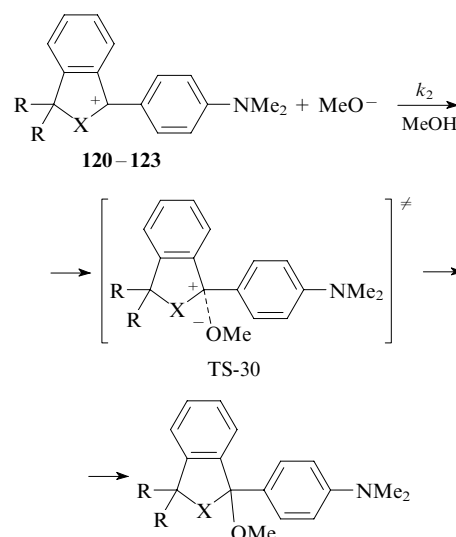
Table 13. Rate constants and activation parameters for bimolecular reactions of cations of the triarylmethane series with the CN^- anion in water at 30 °C.¹⁷⁶

Cation	Entry	k_1 /litre mol ⁻¹ s ⁻¹	$\Delta H^\ddagger$	$-\Delta S^\ddagger$	$\Delta G^\ddagger$
(4-MeC ₆ H ₄)R ₂ C ⁺ (105) ^a	1	28.5	35.5	100.0	65.8
(3-NO ₂ C ₆ H ₄)R ₂ C ⁺ (106) ^a	2	180	48.9	40.0	61.0
PhR ₂ C ⁺ (107) ^a	3	42.9	38.7	86.0	64.8
Ph(4-Me ₂ NC ₆ H ₄)(4-MeC ₆ H ₄)C ⁺ (108)	4	11.5	46.1	72.0	67.9
Ph(4-Me ₂ NC ₆ H ₄)(3-NO ₂ C ₆ H ₄)C ⁺ (109)	5	16.5	41.6	84.0	67.1
Ph ₂ (4-Me ₂ NC ₆ H ₄)C ⁺ (110) ^b	6	12.7	49.0	62.0	67.8
(4-MeOC ₆ H ₄)(4-Me ₂ NC ₆ H ₄)(4-MeC ₆ H ₄)C ⁺ (111)	7	7.00	51.9	57.0	69.2
(4-MeOC ₆ H ₄)(4-Me ₂ NC ₆ H ₄)(3-NO ₂ C ₆ H ₄)C ⁺ (112)	8	26.5	45.6	72.0	67.4
(4-MeOC ₆ H ₄)(4-Me ₂ NC ₆ H ₄)(Ph)C ⁺ (113)	9	9.25	46.0	74.0	68.4
(4-Me ₂ NC ₆ H ₄) ₂ (4-MeC ₆ H ₄)C ⁺ (114)	10	0.743	52.3	75.0	75.0
(4-Me ₂ NC ₆ H ₄) ₂ (3-NO ₂ C ₆ H ₄)C ⁺ (115)	11	1.45	40.1	110.0	73.4
(4-Me ₂ NC ₆ H ₄) ₂ PhC ⁺ (116)	12	0.836	40.4	83.0	74.5
(4-O ⁻ -3-MeOC ₆ H ₃) ₂ (4-MeC ₆ H ₄)C ⁺ (117)	13	4.73×10^{-3}	30.9	187.0	87.6
(4-O ⁻ -3-MeOC ₆ H ₃) ₂ (3-NO ₂ C ₆ H ₄)C ⁺ (118)	14	9.48×10^{-3}	41.6	146.0	85.8
(4-O ⁻ -3-MeOC ₆ H ₃) ₂ PhC ⁺ (119)	15	7.94×10^{-3}	31.7	184.0	87.4

**Figure 15.** Compensation plots for the reactions of cations **105**–**119** with the cyanide ion (the numbering of the points corresponds to the entries in Table 13).

are not contradictory to the reaction mechanisms through solvent-separated and contact ion pairs.

Heterocarbocations **120**–**123** are very reactive in the reactions with the MeO^- anion in MeOH. Both series of the cations (with $\text{X} = \text{O}$ and $\text{X} = \text{S}$) are characterised by isokinetic relationships and the enthalpy control of the reaction.¹⁷⁷ An increase in the charge on the carbocationic centre leads not only to an increase in the rate constant but also to a decrease in the activation parameters $\Delta H^\ddagger$ and $\Delta S^\ddagger$, which is more pronounced in the case of less stabilised oxygen-containing cations **120** and **121**.¹⁷⁷ Presumably, the transition state TS-30 as the solvent-separated ion pair (as in the reactions of cations **105**–**116** with the CN^- anion) provides the best explanation for the character of changes in the activation parameters for the above-mentioned reactions.



Compound	R	X	$k_2(25^\circ\text{C})$ /litre mol ⁻¹ s ⁻¹	$\Delta H^\ddagger$	$-\Delta S^\ddagger$
120	Me	O	8.71×10^4	30	49
121	3-BrC ₆ H ₄	O	26.3×10^4	19	76
122	Me	S	0.107×10^4	46	32
123	Ph	S	0.16×10^4	42	40

Therefore, the reactions of cationic substrates with neutral and charged nucleophiles are characterised by broad ranges of the rate constants and the activation parameters. Depending on the electrophilicity of the cation and the nature of the nucleophile, the reactions proceed by different mechanisms, which is reflected in the relationship between the activation parameters.

Table 14. Inversion temperatures and differences between the activation parameters for bimolecular addition reactions of BuⁿLi and EtMgBr with (2*S*)-lactaldehyde derivatives.

Substrate	Nucleophile	Solvent	$T_{\text{inv}} / ^\circ\text{C}$	$T > T_{\text{inv}}$		$T < T_{\text{inv}}$		Ref.
				$\Delta\Delta H_1^\ddagger$ (see ^a)	$\Delta\Delta S_1^\ddagger$ (see ^a)	$\Delta\Delta H_2^\ddagger$ (see ^a)	$\Delta\Delta S_2^\ddagger$ (see ^a)	
126	Bu ⁿ Li	THF	−26.8	−0.42	−6.65	18.0	68.5	179
	Bu ⁿ Li	n-hexane	7.9	−2.42	−18.0	−9.2	−43.5	179
127	EtMgBr	THF	13.9	−5.85	−10.45	−0.25	9.2	183
	EtMgBr	Et ₂ O	−18.1	−0.42	1.67	−4.85	15.5	183
	EtMgBr	PhOMe	−14.1	3.76	10.45	−2.51	−13.0	183

^a $\Delta\Delta H^\ddagger = \Delta H_{\text{anti}}^\ddagger - \Delta H_{\text{syn}}^\ddagger$, $\Delta\Delta S^\ddagger = \Delta S_{\text{anti}}^\ddagger - \Delta S_{\text{syn}}^\ddagger$.

VII. Miscellaneous reactions

This section deals with the energetics of bimolecular nucleophilic reactions and their stereoselectivities, touches on certain aspects of micellar catalysis and considers the reactions of halide anions with aryl radicals and the reactions of organometallic compounds with neutral and charged nucleophiles.

For kinetically controlled reactions giving rise to two stereoisomers, the selectivity *S* is expressed by the equation

$$S = \frac{k}{k'},$$

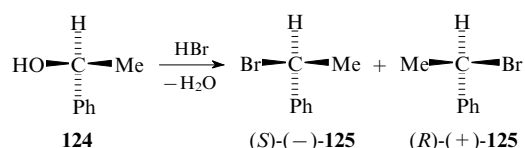
where *k* and *k'* are the overall reaction rate constants for the formation of two stereoisomers.¹⁷⁸ The linear dependence of the stereoselectivity on the reverse temperature is described by the modified Eyring equation:¹⁷⁸

$$\ln \frac{k}{k'} = -\frac{\Delta\Delta H^\ddagger}{RT} + \frac{\Delta\Delta S^\ddagger}{R}.$$

Therefore, the stereoselectivity is expressed in terms of the differences between the enthalpies ($\Delta\Delta H^\ddagger$) and entropies ($\Delta\Delta S^\ddagger$) of activation for two reaction pathways.^{178, 179} The entropy and enthalpy can play opposite roles in the formation of a particular stereoisomer, resulting in the selectivity inversion with changes in the reaction temperature and the appearance of the inversion temperature T_{inv} and two systems of the activation parameters: $\Delta\Delta H_2^\ddagger$ and $\Delta\Delta S_2^\ddagger$ at $T < T_{\text{inv}}$ and $\Delta\Delta H_1^\ddagger$ and $\Delta\Delta S_1^\ddagger$ at $T > T_{\text{inv}}$. In other words, T_{inv} is the temperature at which the domination of the enthalpy or entropy changes (the transition point in an Eyring plot).^{162, 163} The isoinversion temperature $T_i^\ddagger$ at which the maximum stereoselectivity is expected, is also an important characteristics of the stereochemical results of the reaction. For example, the asymmetric synthesis of esters by the addition of achiral alcohols to non-symmetric disubstituted ketenes catalysed by chiral tertiary amines is characterised by $T_i^\ddagger = 210$ K, whereas for the non-catalysed addition of racemic secondary alcohols to non-symmetrically disubstituted ketenes, $T_i^\ddagger = 259$ K (Ref. 178).

The result of the asymmetric synthesis of amides by the addition of chiral primary amines to non-symmetric disubstituted ketenes also substantially depends on the temperature.¹⁷⁸

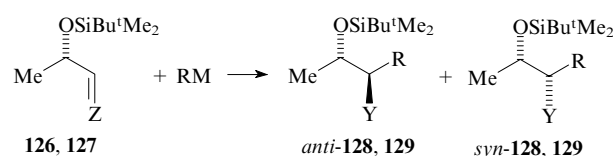
The nucleophilic substitution in secondary alcohol **124** with gaseous HBr affords enantiomers of (*S*)- and (*R*)-1-(bromoethyl)-benzene (**125**) with the ratio depending on the temperature ($T_{\text{inv}} = 248$ K).



$\dagger T_i = \partial(\Delta\Delta H^\ddagger) / \partial(\Delta\Delta S^\ddagger)$, where $\Delta\Delta H^\ddagger = \Delta\Delta H_2^\ddagger - \Delta\Delta H_1^\ddagger$, $\Delta\Delta S^\ddagger = \Delta\Delta S_2^\ddagger - \Delta\Delta S_1^\ddagger$.

At $T > T_{\text{inv}}$, the activation parameters $\Delta\Delta H_1^\ddagger$ and $\Delta\Delta S_1^\ddagger$ are low (-38 kJ mol^{−1} and -161.4 J mol^{−1} K^{−1}, respectively) and the reaction affords predominantly enantiomer (*R*)-**125** with inversion of the initial configuration (*S*_N2 mechanism). However, at $T < T_{\text{inv}}$, $\Delta\Delta H_2^\ddagger$ and $\Delta\Delta S_2^\ddagger$ are high (11.1 kJ mol^{−1} and -36.6 J mol^{−1} K^{−1}, respectively), resulting in the formation of an intermediate adduct of alcohol with HBr, and the reaction proceeds by the *S*_Ni mechanism to give predominantly enantiomer (*S*)-**125** in which the initial configuration is retained.¹⁷⁸

The stereoselectivity of the reaction is controlled not only by the temperature but also by the nature of the solvent. The latter is well exemplified by the reactions of carbonyl compounds and their derivatives with various nucleophiles in various media.^{179–183} For example, the diastereoselectivity (the ratio of *anti* to *syn* isomers **128** and **129**) of the reactions of (2*S*)-lactaldehyde derivatives **126** and **127** with BuⁿLi and EtMgBr in various ethers and n-hexane was found to depend strongly on solvation of the starting substrate^{179, 183} and, to a lesser degree, on the nature of the nucleophile.¹⁸⁰



Z = NSiMe₃ (**126**), O (**127**); RM = BuⁿLi (for **126**), EtMgBr (for **127**); Y = NH₂, R = Buⁿ (**128**); Y = OH, R = Et (**129**).

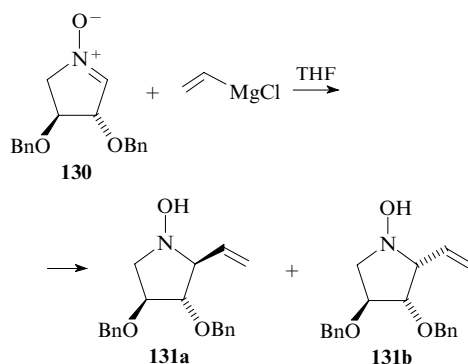
Table 14 gives the inversion temperatures and the differences between the activation parameters for two straight regions in the Eyring plot at $T > T_{\text{inv}}$ and $T < T_{\text{inv}}$. As can be seen from Table 14, T_{inv} strongly depends on the nature of the solvent and, therefore, this is the temperature at which one solvation cluster is transformed into another cluster, resulting in changes in the difference between the activation parameters and the ratio of *anti* to *syn* diastereomers **128** and **129**.¹⁸³

Negative values of $\Delta\Delta H^\ddagger$ signify that $\Delta H_{\text{syn}}^\ddagger > \Delta H_{\text{anti}}^\ddagger$, i.e., the enthalpy of activation corresponds to the predominant formation of the *anti* isomer. Positive values of $\Delta\Delta H^\ddagger$ are favourable for the predominant formation of the *syn* isomer.

Since the addition reactions are accompanied by a decrease in the entropy, the transition state leading to the *anti* isomer is more ordered at negative $\Delta\Delta S^\ddagger$ than TS through which the *syn* isomer is formed, and the entropy is favourable for the formation of the *syn* isomer. Positive values $\Delta\Delta S^\ddagger$ are favourable for the formation of the *anti* isomer. The diastereoselectivity, particularly, for the reactions with low $\Delta\Delta H_1^\ddagger$ or $\Delta\Delta H_2^\ddagger$, is entropy-controlled.¹⁸³

The diastereoselectivity of the reaction of chiral nitron **130** with vinylmagnesium chloride in THF is also entropy-controlled. The ratio of diastereomers **131a**:**131b** = 93:7 was demonstrated¹⁸⁴ to remain unchanged in the temperature range from 20 to -80 °C and the diastereoselectivity is entropy-controlled ($\Delta\Delta H^\ddagger = 0$ kJ mol^{−1}, $\Delta\Delta S^\ddagger = 21.7$ J mol^{−1} K^{−1}), which is

indicative of the absence of steric interactions between the substituents in compound **130** and the Grignard reagent.



However, acceleration of the reaction in the presence of Et_2AlCl as the catalyst leads to the following two regions in the Eyring plot: in the range from 40 to 0 °C, the entropy control of the reactivity and the above-mentioned ratio of diastereomers are retained, whereas the stereoselectivity is almost completely lost in the range from 0 to –94 °C (**131a**:**131b** = 55:45 at –94 °C). In the latter case, substantial changes in the parameters $\Delta\Delta H^\ddagger$ and $\Delta\Delta S^\ddagger$ are observed, which apparently reflects changes in the reaction mechanism at low temperature with the result that the stereoselectivity of the process changes.¹⁸⁴

The most pronounced changes in stereoselectivity due to changes in the activation parameters for different reaction pathways are the most pronounced in biochemical processes.^{185–187} The enantioselectivity E' was found¹⁸⁵ to be changed depending on the temperature in hydrolysis of enantiomeric derivatives of α -amino acids catalysed by the enzyme α -chymotrypsin. For example, E' for the hydrolysis reactions of L- (**132a**) and D-tyrosine methyl esters (**132b**), as well as of *N*-Boc-L- (**132c**) and *N*-Boc-D-tyrosines (**132d**), which is determined by the equation

$$E' = \ln \frac{k_L}{k_D},$$

where k_L and k_D are the apparent second-order reaction rate constants for the L- and D-enantiomers, respectively, can be expressed in terms of the differences between the activation parameters $\Delta\Delta H$ and $\Delta\Delta S$ with the use of the modified Eyring equation.

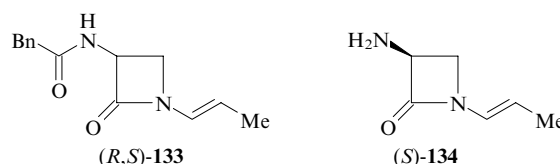
Compound	$\Delta\Delta H$ /kJ mol ^{–1}	$\Delta\Delta S$ /J mol ^{–1} K ^{–1}	T_{inv} /°C
132a,b	–22	–31	436
132c,d	25	174	–129

Here, $\Delta\Delta H = \Delta\Delta H^\ddagger - \Delta\Delta H_b$ and $\Delta\Delta S = \Delta\Delta S^\ddagger - \Delta\Delta S_b$, and the subscript b indicates binding in a substrate–enzyme–nucleophile complex.

From the Eyring plot it follows that $\Delta\Delta H$ is dominant at $T < T_{\text{inv}}$ and the stereochemical purity of the hydrolysis product

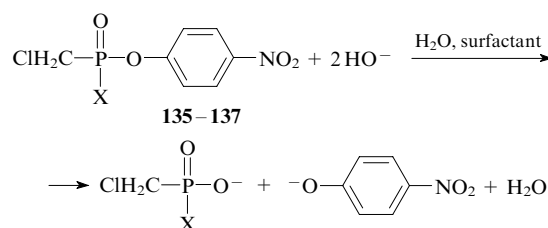
(α -amino acid) decreases with increasing temperature, whereas $\Delta\Delta S$ prevails at $T > T_{\text{inv}}$ and the stereochemical purity increases with increasing temperature.¹⁸⁵

The kinetic resolution of racemic β -lactam **133** by enzymatic hydrolysis in aqueous acetone in the presence of penicillin G acylase leads to an enantiomeric excess of the (*S*) isomer of compound **134** and the non-consumed (*R*) isomer of **133**, the maximum enantioselectivity $E' = 130$ being achieved at 328 K, which is higher than $T_{\text{inv}} = 301$ K. This reaction also exemplifies the fact that the formation of clusters of the substrate and the solvent influences both the relative contributions of the activation parameters and the enantioselectivity.¹⁸⁶



The enantioselectivity of enzyme-catalysed transesterification of vinyl acetate with a pair of *R*- and *S*-enantiomeric secondary alcohols in Pr_2O in the presence of subtilysine was estimated.¹⁸⁷ The enantioselectivity $E' = \ln(k_R/k_S)$ was demonstrated to decrease with increasing temperature. In this case, the enthalpy–entropy compensation effect and the enthalpy control of the reactivity are observed.¹⁸⁷

The catalytic effect of supramolecular systems in nucleophilic substitution reactions, in particular, the influence of solubilisation of reagents in micelles of surfactants, was studied.^{188,189} Such nucleophilic reactions as $\text{S}_{\text{N}}2$,¹⁹⁰ $\text{S}_{\text{N}}\text{Ar}$ ¹⁹¹ and alkaline hydrolysis of phosphonates,¹⁹² proceed more rapidly in micellar solution compared to the same reactions in the absence of surfactants. A comparison of the activation parameters for alkaline hydrolysis of esters **135** and **136** shows that these parameters for the reactions in a micellar pseudophase are lower than those in the absence of surfactants (Table 15).



X = EtO (**135**), *n*-C₆H₁₃O (**136**), ClCH₂ (**137**).

In a more concentrated micellar solution, the loss of entropy is apparently associated with a decrease in the degree of mixing and mobility of the reagents.¹⁹³ The activation parameters $\Delta H^\ddagger$ and $\Delta S^\ddagger$ are described by the compensation relation

$$\Delta H^\ddagger = 64.61 + 0.242 \Delta S^\ddagger \quad (r = 0.995, s = 0.84, n = 4)$$

Table 15. Rate constants of the formation of the transition state as the rate-determining step and activation parameters for hydrolysis of phosphonates **135** and **136** and solvolysis of ester **137** in ethylene glycol in the absence and presence of surfactants at 25 °C.

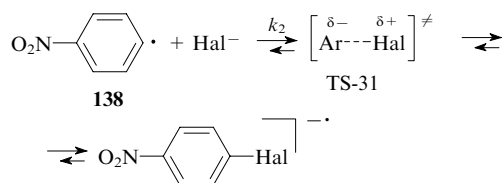
Substrate	Solvent	Surfactant	k_2 /litre mol ^{–1} s ^{–1}	$\Delta H^\ddagger$	$-\Delta S^\ddagger$	$\Delta G^\ddagger$	Ref.
135	H ₂ O	DDPB ^a	4.0	39.3	100.6	69.3	193
	H ₂ O	—	4.0	46.2	78.6	69.6	193
136	H ₂ O	DDPB ^a	0.90	30.0	144.4	73.0	193
	H ₂ O	—	3.0	40.8	98.9	70.2	193
137	HOCH ₂ CH ₂ OH	SDDS ^b	0.23×10^{-3} (see ^c)	95.8	20.1	102.3	194
	HOCH ₂ CH ₂ OH	—	0.17×10^{-3} (see ^c)	76.8	66.6	98.3	194

^a DDPB is dodecylpyridinium bromide; ^b SDDS is sodium dodecylsulfate; ^c at 50 °C.

for the reactions of ester **135** with the enthalpy control of the reactivity and the reactions of ester **136** with the entropy control. In the latter case, it is the entropy term that is responsible for a decrease in the reactivity in a micellar pseudophase.¹⁹³

However, solvolysis of ester **137** in ethylene glycol in the presence of surfactants is characterised by higher activation parameters compared to those for the reaction in the absence of surfactants, the reactivity being enthalpy-controlled in both reactions (see Table 15). Apparently, an increase in the entropy term for the reaction in the presence of surfactants is attributed to an increase in the contribution of the S_N1 mechanism compared to the S_N2 mechanism, and the reaction rate increases.¹⁹⁴

The energetics of very fast bimolecular reactions of halide anions with 4-nitrophenyl radical (**138**) in DMF is of interest because such reactions are the key step in processes proceeding by the S_{RN}1 mechanism.¹⁹⁵



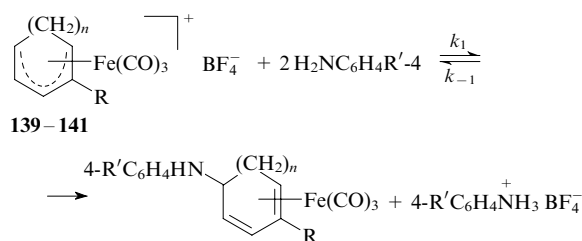
A substantial increase in $\Delta S^\ddagger$ for Br[−] and Cl[−] compared to that for I[−] is apparently due to desolvation of these ions on going from the initial state to the transition state TS-31, and the reactivity is controlled by the enthalpy of activation (Table 16).¹⁹⁵ These reactions are characterised by the compensation relation

$$\Delta H^\ddagger = -25.8 + 1.8 \Delta G^\ddagger \quad (r = 0.954, s = 4.8, n = 3).$$

Table 16. Rate constants and activation parameters for the reactions of radical **138** with halide anions in DMF.¹⁹⁵

Hal [−]	$k_2(295\text{ K})$ /litre mol ^{−1} s ^{−1}	$\Delta H^\ddagger$	$-\Delta S^\ddagger$	$\Delta G^\ddagger$
I [−]	2.0×10^9	7.6	39.3	19.3
Br [−]	1.3×10^8	25.1	2.5	25.8
Cl [−]	1.4×10^7	28.9	7.9	31.2

The kinetics of the addition of various nucleophiles to coordinated π -hydrocarbons to form new organometallic derivatives of 1,3-dienes was studied in detail, and the energy parameters for these processes were estimated.^{168–171, 196, 197} These reactions are characterised by low activation parameters $\Delta H^\ddagger$ and $\Delta S^\ddagger$.^{196, 197} For example, the dissociative addition reactions of anilines to complexes **139–141** have high negative $\Delta S^\ddagger$



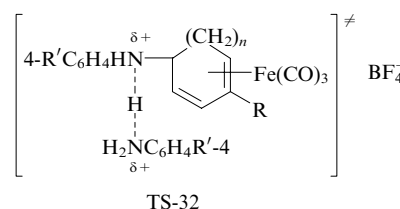
$n = 1$: R = H (**139**), 2-MeO (**140**); $n = 2$, R = H (**141**); R' = H, Cl.

Table 17. Rate constants and activation parameters for the addition reactions of anilines to complexes **139–141** in MeCN at 20 °C.¹⁹⁶

Substrate	Entry	Nucleophile	k_1 /litre mol ^{−1} s ^{−1} (see ^a)	$\Delta H^\ddagger$	$-\Delta S^\ddagger$
139	1	PhNH ₂	2560 ^b	6.2	150
	2	4-ClC ₆ H ₄ NH ₂	993 ^c	23.7	103
140	3	PhNH ₂	641	17.1	132
	4	4-ClC ₆ H ₄ NH ₂	158 ^c	39.0	64
141	5	PhNH ₂	397	30.1	92
	6	4-ClC ₆ H ₄ NH ₂	122	28.7	106

^a Calculated from the equation $k_{\text{obs}} = k_1[\text{amine}] + k_{-1}$; ^b at 15.1 °C; ^c at 10.4 °C.

due to formation of the highly organised transition state TS-32 on the coordinate of these reactions (Table 17).¹⁹⁶

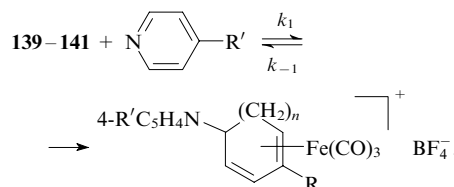


In the absence of steric hindrance in a nucleophile, the following compensation relation is observed:

$$\Delta H^\ddagger = 62.2 + 0.350 \Delta S^\ddagger \quad (r = 0.980, s = 2.40, n = 6)$$

the association process being controlled by either enthalpy (entries 4 and 5 in Table 17) or entropy (entries 1–3, 6 in Table 17).¹⁹⁶

The addition of pyridine derivatives to the coordinated dienyl ligand in complexes **139–141** occurs according to the equation



The rate constants k_1 and the activation parameters for the process strongly depend on the basicity of pyridine and steric hindrance in the substrate in the formation of the transition state (Table 18).¹⁹⁷ The reaction with more basic pyridine leads to localisation of an early transition state in which the associative bond formation plays an important role. This is confirmed by negative activation volumes $\Delta V_1^\ddagger$, the reactivity being entropy-controlled (entries 2 and 5–8 in Table 18). The late transition state for slow reactions with $\Delta V_1^\ddagger$ equal to zero is characteristic of weakly basic pyridines and substrate **141** with the enthalpy control of the reactivity (entries 1, 6 and 7 in Table 18).¹⁹⁷ The most basic 4-ethylpyridine always leads to negative $\Delta V_1^\ddagger$; the least basic 4-cyanopyridine, to the zero value. Since 4-formylpyridine is intermediate in basicity between the above-mentioned pyridines, the nature of the substrate plays an important role. For the fast reactions (entries 2 and 4), $\Delta V_1^\ddagger$ are negative; for the slow reaction (entry 7), the activation volume is equal to zero.

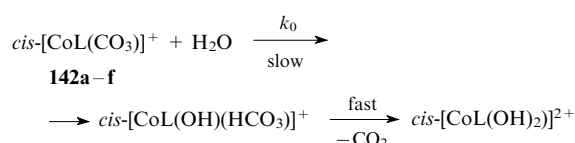
Very broad ranges of the activation parameters are observed for decarboxylation of the cobalt(III) carbonate complexes *cis*-

Table 18. Rate constants and activation parameters for the addition reactions of pyridines to complexes **139–141** in MeCN at 25 °C.¹⁹⁷

Substrate	Entry	Nucleophile	k_1 /litre mol ⁻¹ s ⁻¹ (see ^a)	$\Delta H^\ddagger$	$\Delta S^\ddagger$	$\Delta V^\ddagger$ /cm ³ mol ⁻¹
139	1	4-NCC ₅ H ₄ N	1.2×10^3	42	46	0
	2	4-CHOC ₅ H ₄ N	1.8×10^3	25	100	-2.9
	3	4-EtC ₅ H ₄ N	1.9×10^4	16.9	106	(see ^b)
140	4	4-CHOC ₅ H ₄ N	4.4×10^2	21	123	-9.8
	5	4-EtC ₅ H ₄ N	3.1×10^3	15.5	126	-7.8
141	6	4-NCC ₅ H ₄ N	30	38	89	0
	7	4-CHOC ₅ H ₄ N	80	30	107	0
	8	4-EtC ₅ H ₄ N	8.4×10^2	26	102	-6.4

^a Calculated from the equation $k_{\text{obs}} = k_1[\text{pyridine}] + k_{-1}$; ^b cannot be determined due to a high reaction rate.

[CoL(CO₃)]⁺ (**142a–f**) with water, which occurs according to the scheme



L = (NH₃)₄ (**a**), (en)₂ (**b**), (py)₄ (**c**), *cis*-(en)₂(H₂O)₂ (**d**), *trans*-5,12-dimethyl-1,4,8,11-tetraazacyclotetradeca-4,11-diene (**e**), 1,4,8,12-tetraazacyclopentadecane (**f**).

Depending on the structure of the ligand L, $\Delta H^\ddagger$ and $\Delta S^\ddagger$ can be either low or very high (Table 19). The first step involving the carbonate ring opening is rate-determining, which is apparently responsible for high positive $\Delta S^\ddagger$ for the reactions of substrates **142c,d,f**. The reactivity of all complexes **142a–f** is enthalpy-controlled. The activation parameters $\Delta H^\ddagger$ and $\Delta S^\ddagger$ are described by the compensation relation¹⁹⁸

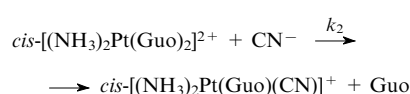
$$\Delta H^\ddagger = 96.6 + 0.28 \Delta S^\ddagger \quad (r = 0.985, s = 9.2, n = 6).$$

Table 19. Rate constants and activation parameters for decarboxylation of Co(III) carbonate complexes with water at 25 °C.¹⁹⁸

Substrate	$10^4 k_0$ /s ⁻¹ (see ^a)	$\Delta H^\ddagger$	$\Delta S^\ddagger$	$\Delta G^\ddagger$
142a	1.3	50	-155	96.2
142b	1.2	75	-63	93.7
142c	1.3×10^{-2}	139	109	106.5
142d	710	169	300	79.6
142e	0.75	115	65	95.6
142f	1.2	162	211	99.1

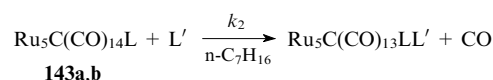
^a Pseudo-first-order reaction.

The reactivity of guanosine (Guo) in the substitution reaction of the platinum(II) complex *cis*-(NH₃)₂Pt(Guo)₂Cl₂ with the cyanide ion in water is also enthalpy-controlled.¹⁹⁹ This reaction is rather slow ($k_2 = 2.5 \times 10^{-4}$ litre mol⁻¹ s⁻¹ at 30 °C) and has high enthalpy of activation ($\Delta H^\ddagger = 76.2$ kJ mol⁻¹) and moderate negative entropy of activation ($\Delta S^\ddagger = -75.2$ J mol⁻¹ K⁻¹), which is attributed to the associative mechanism.¹⁹⁹



Analogous activation parameters are also typical of other substitution reactions of platinum(II) complexes.¹⁹⁹

Associative substitution reactions of the ruthenium carbonyl clusters Ru₅C(CO)₁₄L (**143a,b**) involving phosphorus-containing n-nucleophiles L' are either enthalpy- or entropy-controlled depending on the structures of the substrate and the nucleophile (Table 20).²⁰⁰



L = P(OPh)₃ (**a**), P(cyclo-C₆H₁₁)₃ (**b**).

Unexpectedly, faster reactions of compound **143a** with certain P-nucleophiles have positive entropies of activation (entries 1–3 in Table 20). The latter fact can be attributed to weaker binding of the reagents in the transition state accompanied by cleavage of the cluster.²⁰⁰ Nevertheless, the activation parameters for the reactions of cluster **143a** with P-nucleophiles (entries 1–7 in Table 20) are described by the compensation relation

$$\Delta H^\ddagger = 70.06 + 0.254 \Delta S^\ddagger \quad (r = 0.996, s = 2.41, n = 7).$$

The reactions of cluster **143b** containing the bulky ligand L with P-nucleophiles are characterised by very low $\Delta S^\ddagger$, resulting in the compensation straight line with a smaller slope

$$\Delta H^\ddagger = 70.43 + 0.186 \Delta S^\ddagger \quad (r = 0.995, s = 1.13, n = 3),$$

which apparently indicates that the entropy makes a larger contribution to the reactivity of cluster **143b** than to that of cluster **143a**.²⁰⁰

Evidently, the kinetics of nucleophilic substitution reactions in complex compounds has a number of specific features. This problem was discussed in the corresponding sections of the reviews.^{201–206}

Table 20. Rate constants and activation parameters for the substitution reactions of clusters **143a,b** involving phosphorus-containing nucleophiles in n-heptane at 25 °C.²⁰⁰

Substrate	Entry	Nucleophile L'	k_2 (see ^a)	$\Delta H^\ddagger$	$\Delta S^\ddagger$	$\Delta G^\ddagger$
143a	1	P(OCH ₂) ₃ CEt	3.942	80.9	38.4	69.5
	2	P(OMe) ₃	11.22	81.5	48.9	66.9
	3	P(OEt) ₃	4.262	74.6	17.5	69.4
	4	PPh(OMe) ₂	1.838	54.1	-58.7	71.6
	5	P(OPh) ₃	0.1739	50.1	-91.0	77.2
	6	PPh ₂ OEt	1.127	30.1	-142.7	72.6
	7	PPh ₃	0.0428	17.8	-211.5	80.8
143b	8	P(OPh) ₃	0.956 ^b	32.9	-199.5	92.4
	9	PPhMe ₂	20.40	48.7	-113.4	82.5
	10	PPh ₂ Me	2.797	44.4	-144.5	87.5

^a In litre mol⁻¹ s⁻¹; ^b at 45 °C.

VIII. The role of the enthalpy – entropy compensation effect

The role of the enthalpy–entropy compensation effect and the isokinetic relationship in the elucidation of reaction mechanisms and estimation of their thermodynamic parameters based on correlation series has been extensively discussed in the literature.^{6, 63–65, 68–73, 207–214} It should be emphasised that for the true (not erroneous) compensation effect to be manifested, the series of the activation parameters $\Delta H^\ddagger$ and $\Delta S^\ddagger$ must cover ranges substantially larger than the experimental errors.^{71, 213} Undoubtedly, the compensation effect for reactions in the condensed phase has a cooperative character and correlates with the motion of the reagent and solvent molecules during an elementary event.^{65, 68, 70, 208–210, 213, 214} Based on the data surveyed in the present review, conclusions about the role of the compensation effect in bimolecular nucleophilic reactions can be drawn.

For example, the compensation temperature for the S_NAr reactions of substituted arenes with amines was demonstrated to be substantially higher for slow reactions (see Fig. 3). An analogous effect is observed in the reactions of EtI with Et₃N and Et₃P (see Table 2)³⁹ and the reactions of clusters **143a,b** with P-nucleophiles (Table 20).²⁰⁰ Evidently, an increase in the compensation temperature for related reactions may be indicative of a decrease in the reaction rate.

For bimolecular nucleophilic reactions at the carbonyl carbon atom,^{62, 157, 162} with carbocations^{168, 170, 171, 176, 177} and with organometallic complexes,^{198, 200} the compensation effects are observed with changes in the nature of the substituent in the substrate^{157, 162, 168, 170, 171, 176, 177, 198} or the nucleophile,^{62, 200} the reaction mechanism remaining unchanged. The slopes of the compensation plots of $\Delta H^\ddagger$ vs $\Delta S^\ddagger$ vary in rather broad ranges (from 200 to 700 K).

The reliable determination of the isokinetic relationship for a reaction series suggests a unified mechanism of the processes.^{6, 63–65, 69} However, the compensation relations can include the activation parameters for related BNR proceeding by different mechanisms. For example, the compensation relations for the S_NV reactions resulting in the replacement of chlorine in compounds **20–25** include the activation parameters for reactions proceeding as both addition–elimination and elimination–addition (see Fig. 5).^{97–100} The compensation relations for the reactions of triaryl phosphates **88a–c** with pyridines also include the activation parameters that characterise different substitution mechanisms (stepwise and concerted).¹⁵⁵ The compensation relations for the Ad_N reactions of alkyne **43** with amines include the activation parameters corresponding to the reactions proceeding by the same mechanism (see Fig. 8).^{115, 116} The compensation relations for alcoholysis of compounds **51, 52, 58** and **59**^{129, 135–137} and aminolysis of compounds **47, 51** and **54–57** (see Fig. 10)^{131–134} also characterise the same mechanism.

The compensation plots of $\Delta H^\ddagger$ vs $\Delta G^\ddagger$ for the Ad_N reactions of alkyne **43** with amines have opposite slopes depending on the structure of the nucleophile. A positive slope is indicative of the enthalpy control of the reaction, whereas a negative slope confirms the entropy control (see Fig. 9).^{115, 116, 119} Analogous compensation plots of $\Delta H^\ddagger$ vs $\Delta G^\ddagger$ are observed for the reactions of carbonyl compounds **46–59** with alcohols and amines (see Fig. 11)^{129–137} and of dimethyl carbonate **64** with alkylamines.¹⁴⁰

However, this is not true for the S_NAr reactions (see Figs 3 and 4) because the compensation relations include the activation parameters with a higher contribution of either the enthalpy or entropy term.^{46–48, 52–58, 84–89} The inclusion of substantially different $\Delta H^\ddagger$ and $\Delta S^\ddagger$ in the same compensation relation is also observed for hydrolysis of esters **135** and **136**,¹⁹³ the addition of anilines to carbocationic complexes **139–141**¹⁹⁶ and substitution reactions of clusters **143a,b** with P-nucleophiles.²⁰⁰

It should be noted that no compensation effects are observed for certain BNR. For example, the absence of compensation relations for aminolysis of carbonyl compounds **67–79** (see

Table 11),^{141–147} the reactions of carbonyl compounds **83–86** with pyridine (see Table 11)^{150–153} and the reactions of carbocations **96–104** with neutral π -nucleophiles is apparently associated with the difference in the structure of transition states for each type of reactions.

IX. Relationship between the mechanisms of bimolecular nucleophilic reactions and activation parameters

For bimolecular reactions, $\Delta S^\ddagger$ varies from -41 to $-210 \text{ J mol}^{-1} \text{ K}^{-1}$, and $\Delta S^\ddagger$ for reactions with moderate-density transition states vary in narrower ranges, from -125 to $-167 \text{ J mol}^{-1} \text{ K}^{-1}$.²¹¹ The latter values are similar to the range of $\Delta S^\ddagger$ from -62 to $-125 \text{ J mol}^{-1} \text{ K}^{-1}$ for BNR. This criterion is not rigorous because not all factors that influence $\Delta S^\ddagger$ (for example, changes in solvation of the transition states compared to the initial state) were taken into account.²¹⁵

Table 21 gives the limiting values of the activation parameters $\Delta H^\ddagger$ and $\Delta S^\ddagger$ for all types of reactions, which were discussed in Sections II–VII of the present review. As can be seen from this table, $\Delta H^\ddagger$ varies from 0 to 232 kJ mol^{-1} ; $\Delta S^\ddagger$, from $+300$ to $-300 \text{ J mol}^{-1} \text{ K}^{-1}$. These limiting values of $\Delta S^\ddagger$ noticeably extend the range of this parameter compared to that published earlier.²¹⁵ Although $\Delta S^\ddagger$ are calculated by extrapolation to an uncertain temperature,²¹⁶ a comparison of the numerical values of $\Delta S^\ddagger$ for various bimolecular reactions may be useful for elucidation of their mechanisms.²¹⁷

Table 21. Limiting activation parameters $\Delta H^\ddagger$ and $\Delta S^\ddagger$ for various BNR.

Reaction type	Type of nucleophile	$\Delta H^\ddagger$		$-\Delta S^\ddagger$	
		min	max	min	max
S_N2	charged	8.0	100.8	2.3	277
	neutral	19.2	78.6	87.8	220
S_NAr	charged	3.8	232	-255	250
	neutral	15.7	82.0	98.0	265
S_NV	charged	9.4	101	-102	127
	neutral	3.3	18.4	179	242
Ad_N	charged	0	39.0	83.0	288
	neutral	2.0	65.0	40.0	300
Reactions at carbonyl C	charged	13.5	88.0	12.6	277
	neutral	6.7	105	35.6	285
Reactions of carbocations	charged	19.0	52.0	32.0	187
	neutral	0	53.0	46.0	180
Substitution in metal complexes	neutral	17.8	169	-300	211

Of special interest are the limiting values of the activation parameters $\Delta H^\ddagger$ and $\Delta S^\ddagger$ for BNR (see Table 21). For example, very low $\Delta H^\ddagger$ ($0–8 \text{ kJ mol}^{-1}$) are typical of certain S_N2 , S_NAr and Ad_N reactions proceeding by the concerted mechanism.^{10, 58, 105} The structural features of the transition state can also lead to low $\Delta H^\ddagger$ in S_NV reactions,^{90, 91} Ad_N reactions^{113, 114, 116} and the reactions of carbonyl compounds and carbocations with neutral nucleophiles.^{152, 175} Evidently, low values of $\Delta H^\ddagger$ in these reactions are compensated by very low $\Delta S^\ddagger$.

It is worthy of note that certain S_NAr and S_NV reactions with charged nucleophiles^{56, 57, 92, 97, 98, 100} and the reactions of organometallic compounds with neutral nucleophiles^{198, 200} are characterised by positive $\Delta S^\ddagger$, which is rather unusual for BNR.¹⁵⁶ The positive values of $\Delta S^\ddagger$ can be attributed to either the influence of the intermediate complex of a substrate with a nucleophile that is formed in S_NAr reactions⁵⁷ or the intermediate formation of an acetylene derivative in S_NV reactions^{92, 97, 98} or, alternatively, to

the structural features of substrates resulting in an increase in the entropy for the transition state.^{198,200} Positive $\Delta S^\ddagger$ were also observed for catalysed hydrolysis of substituted *N*-benzoylimidazoles in 10% aqueous MeCN due to desolvation of the hydroxide ion.¹⁵⁶

In some cases, the activation parameters appeared to be useful for elucidation of the reaction mechanisms. For example, positive $\Delta S^\ddagger$ for S_NV reactions confirm the $E-Ad_N$ mechanism.^{92,97,98,100} In two-step substitution reactions of carbonyl compounds, the values of $\Delta S^\ddagger$ allow one to identify the rate-determining step.^{150–152} An increase in the activation parameters for the reactions of triaryl phosphates with pyridines made it possible to identify the two-step and concerted mechanisms.¹⁵⁵ An increase in these parameters for the reactions of triarylmethyl cations with cyanide ion allowed the researchers to refine the details of the ion-pair mechanism.¹⁷⁶ The activation parameters play an important role in the analysis of the stereochemical result of the reaction.^{178–187} It should also be noted that an increase in $\Delta S^\ddagger$ in solvolysis of phosphonate **137** is associated with the change in the reaction mechanism from S_N2 to S_N1 .¹⁹⁴ There are also examples of related BNR, which proceed by different mechanisms but are characterised by similar activation parameters.^{139,148,154} In these cases, it is necessary to use other methods for elucidation of the reaction mechanism.^{41,122–128,217,218}

Solvation can have a noticeable effect on $\Delta S^\ddagger$. The latter fact is particularly pronounced for solvation of transition states with a large charge development, resulting in a decrease in $\Delta S^\ddagger$ (Ref. 156) upon solvation of the starting substrate, and influences the diastereoselectivity of the reaction due to a strong change in entropy.^{179,183} Desolvation of a charged nucleophile before the formation of the transition state can lead to both a sharp increase in $\Delta S^\ddagger$ (Refs 156 and 195) and a decrease in this parameter.^{51,53} depending on the reaction type.

The formation of an intermediate complex between a neutral nucleophile and a base^{113,114,120} or between a substrate and a nucleophile^{57,66,67,121,135–137,162} has a substantial effect on the activation parameters and the reaction mechanism. Hence, the problem of the effect of complexation between the reagents on the energetics and mechanisms of BNR has attracted considerable interest.^{219–229}

* * *

In conclusion, there is nowadays a large body of data on the energetics of bimolecular nucleophilic reactions in solution. In the present review, an attempt was made to generalise the results of investigations in this field. The necessity of systematisation is dictated by a rapid increase in the number of studies aimed at refining the theoretical views of the energetics of nucleophilic reactions in organic chemistry and biochemistry.

This review has been written with the financial support of the Division of Chemistry and Materials Science of the Russian Academy of Sciences (Programme of Fundamental Research 'Theoretical and Experimental Studies of the Nature of Chemical Bonding and Mechanisms of Important Chemical Reactions and Processes', Project No. 4.1.11).

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^a — *Russ. Chem. Bull., Int. Ed. (Engl. Transl.)*

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^d — *Russ. J. Phys. Chem. (Engl. Transl.)*

^e — *Theor. Exp. Chem. (Engl. Transl.)*

^f — *Kinet. Catal. (Engl. Transl.)*

Oximes as reagents

A I Mikhaleva, A B Zaitsev, B A Trofimov

Contents

I. Introduction	797
II. Acidity of oximes	798
III. N- and O-nucleophilicity of the oxime function	801
IV. Nucleophilic attack on the C=N bond of oximes	808
V. Dehydration	816
VI. The Beckmann rearrangement	817
VII. Reaction of oximes involving substituents	818
VIII. Conclusion	819

Abstract. Data on the chemical properties of oximes and their derivatives widely used in the synthesis of different nitrogen-containing acyclic and heterocyclic compounds are systematised and analysed. The polyfunctional nature of oximes is emphasised and their uniqueness as the reagents for directed organic synthesis in the presence of bases is shown. The bibliography includes 332 references.

I. Introduction

Oximes have found their application in organic synthesis back in the 19th century¹ and as analytical reagents, in the beginning of the 20th century.^{2,3} At present, oximes surpass carbonyl compounds and alcohols in both the diversity of reactions and the extent of their application in synthetic chemistry. The oxime function can rather easily be introduced into an organic molecule. This may involve oximation of a carbonyl group with hydroxylamine, nitrosation of hydrocarbons, reduction of nitro compounds, oxidation of amines, oxidative ammonolysis, *etc.* At the same time, the oxime function is readily transformed into such important groups as carbonyl, amino, nitro and cyano groups and can also serve as a convenient protective group.

All compounds that contain the oxime fragment, which represents a pharmacophore group, exhibit diverse biological activities.^{4–11} For example, oximes of the furan and thiophene series and their ethers possess vasorelaxant, antispasmodic, seda-

tive, antidepressant, tranquillising, anticonvulsive, analgesic, anti-inflammatory, cytotoxic, anticancer, antiviral and bactericidal properties.⁴ These derivatives are also recommended as insecticides, fungicides, pesticides, herbicides, protozoacides and plant growth regulators.⁴ A wide spectrum of biological activity was revealed for oximes of the pyridine,⁵ indole,⁶ pyrrole⁷ and quinoline series.¹¹ Oximes of α,β -unsaturated ketones are known as insecticides,⁸ vasorelaxants⁹ and antimicrobial agents.¹⁰

A recently published series of comprehensive reviews^{4–7,11} devoted to the chemistry and biological activity of oximes of heterocyclic ketones generalises the latest achievements in this field. They provide information on the development of most typical, classical reactions of oximes and the discovery and elaboration of novel or specific transformations characteristic of certain classes of compounds. The present review does not discuss the papers cited in this series; however, it cannot be considered as an exhaustive supplement to this series. The purpose of our survey is to generalise (using typical examples) and systematise new information on the most typical chemical reactions of oximes, based on the structural peculiarities of the oxime group and its nearest environment. Attention is paid to the reactions that proceed in the presence of bases. In the analysis of the published material, this aspect seems to be important, because it focuses attention on the multifacet nature of reactivity of oximes and oximate anions. Traditionally, these compounds are considered as the objects of the Beckmann rearrangement that takes place in the presence of acids.

Oximes (**A**) and their tautomers, NH-nitrones (**B**) and the corresponding anions can exist in various tautomeric and resonance forms (Scheme 1), which allows one to call them 'chemical chameleons'. The following properties of oximes in the presence of bases can be mentioned: (1) OH- and CH-acidity; (2) O- and N-nucleophilicity; (3) the possibility of the nucleophilic attack on the C=N bond; (4) dehydration; (5) various transformations of substituents (including their migration).

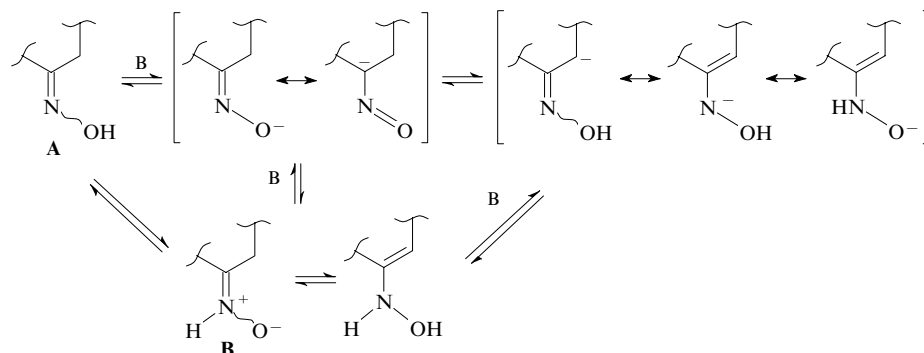
To make systematisation and analysis of base-promoted reactions of oximes easier, it seemed reasonable to assign them to one of the types listed. However, such an assignment is not always unambiguous, because many reactions of oximes simultaneously manifest several sides of their multifacet reactivity.

A I Mikhaleva, B A Trofimov A E Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, ul. Favorskogo 1, 664033 Irkutsk, Russian Federation. Fax (7-3952) 39 60 46, tel. (7-3952) 42 24 09, e-mail: mikh@irioch.irk.ru (A I Mikhaleva), tel. (7-3952) 42 44 11, e-mail: boris_trofimov@irioch.irk.ru (B A Trofimov)
A B Zaitsev Stockholm University, Svante Arrhenius 12/A-6, SE-10691 Stockholm, Sweden. Fax (46) 815 49 08, e-mail: zaitsev@organ.su.se (A B Zaitsev)

Received 13 July 2005

Uspekhi Khimii 75 (9) 884–912 (2006); translated by T Ya Safonova

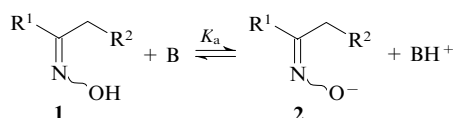
Scheme 1



B is a base.

II. Acidity of oximes

On treatment with bases, oximes (**1**) undergo deprotonation to give oximate anions (**2**).



R¹, R² = H, Alk, Ar, Het.

Oximes that contain hydrogen atoms in the α -position relative to the oxime function exhibit sufficiently high CH-acidity together with OH-acidity. Moreover, coordination of a transition metal with an oxime group results in activation of the β -C–H bond.

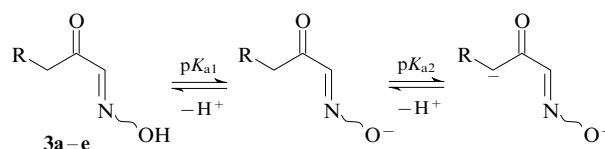
1. OH-Acidity

Studies of acid–base properties of mono- and dioximes of diketones are associated with their wide use in analytical chemistry. OH-Acidity of oximes and its correlation with their configuration was the subject of several studies.^{12–27}

Table 1 shows the data on the acidity of certain oximes. The pK_a values depend on the effect of substituents at the oxime function.

The values of the acidity constants of dioximes of α -diketones are in the ranges of 10.4–10.8 (for the first hydroxyl group) and 11.9–12.4 (for the second hydroxyl group).^{16–21}

A substantial increase in the oxime acidity is observed for α -oxo aldioximes **3a–e**.²² For these compounds, pK_{a1} changes from 8.30 (for oxime **3a**) to 6.54 (for **3e**), the latter oxime being among the most acidic oximes known.



R = H (**a**), MeS (**b**), MeSO (**c**), MeSO₂ (**d**), Me₂S⁺ (**e**).

It should be noted that the acidity of poly(acrolein oximes) is independent of their molecular mass and the content of oxime units; moreover, the pK_a (9.8)²⁸ value is lower than that of the monomer, acrolein oxime (10.61).²⁹

Table 1. Acidity constants of certain oximes.

Oxime	pK _a	Ref.
	11.48	13
	9.38	13
	9.76	14
	9.05	12
	9.94, 11.49	26
	10.29, 11.91	27
	10.68, 11.92	26

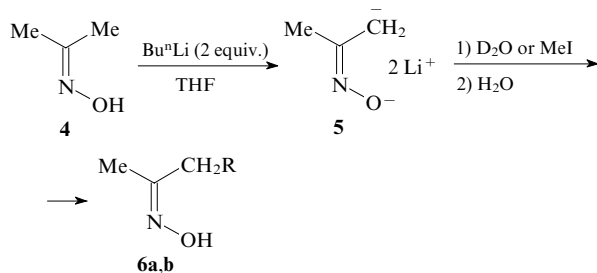
2. CH-Acidity

a. α -CH-Acidity (reactions of oxime carbanions)

The above-mentioned α -oxo aldioximes **3** exhibit sufficiently high CH-acidity, namely, pK_{a2} = 12.23 (for compound **3c**), 11.10 (**3d**), 10.55 (**3e**).²² In the general case, the electron-acceptor nature of the C=N–OH function enhances the mobility of the α -hydrogen atoms, which makes it possible to synthesise the corresponding C-anions of oximes (or of their esters) under the action of organometallic compounds.^{30–32} This reaction is widely used in organic synthesis for the formation of new C–C bonds.

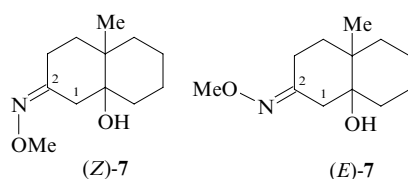
Generation of C-anions often faces a problem of low solubility of dimetallated oximes, which can be solved by different methods. Thus Ensley and Lohr³³ proposed to carry out aldol condensation with lithiated *O*-tetrahydropyranyloximes as carbanions, which can be prepared using only one equivalent of lithium diisopropylamide (LDA). Gawley *et al.*³⁴ employed cuprates of oxime ethers for 1,4-addition to cyclohexenone. These reagents are synthesised by treating the corresponding oxime ethers with potassium diisopropylamide followed by their reaction with the Cu₂Br₂·Me₂S complex. This approach allows one to enhance the efficiency of carbanion generation as compared with LDA.

Stereochemistry of oxime metallation was the subject of several studies.^{35–38} Thus, being treated with two equivalents of butyllithium, acetone oxime (**4**) exclusively forms *syn*-dianion **5**, methylation and deuteration of which leads to products **6a,b**, respectively.³⁵



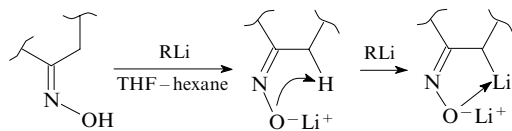
$\text{R} = \text{Me}$ (**a**, 73%), D (**b**, 100%).

Being treated with NaOH , the *Z*-isomer of *O*-methyloxime of a decalone derivative with a tertiary hydroxyl group **7** undergoes dehydration more readily as compared with the *E*-isomer.³⁶ This is explained by the higher rate of anion formation from compound (*Z*)-**7** upon proton abstraction from position 1. In this case, the ratio of *syn*- and *anti*-anions in the deprotonation product is 95 : 5.



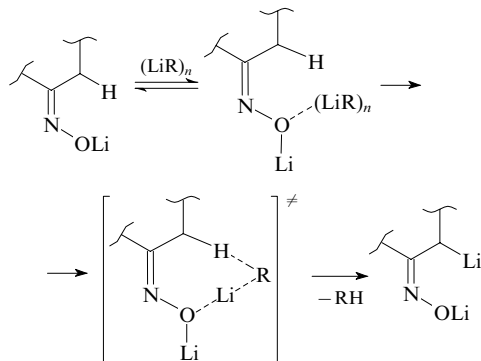
The assumption of the higher mobility of the *syn*-hydrogen atoms as compared with the *anti*-hydrogen atoms was confirmed also for deuteration (D_2O , -60°C) of a metallation product of *O*-methyl dibenzyl ketoxime with lithium isopropylcyclohexylamide in ether.³⁶

Ketoxime dianions with lithium cations can exist in the free state at 20°C for several hours; moreover, neither the equilibrium between *syn*- and *anti*-forms nor the isomerisation of dianions are observed even at elevated temperatures.³⁸ This is associated with the enhanced stability of *syn*-dianions due to the formation of chelate structures with an alkali metal. It is assumed that the formation of dilithio derivatives occurs stepwise, namely, the lithium salt is converted into a soluble dilithio derivative under the action of the second equivalent of butyllithium.



$\text{R} = \text{Bu}^n, \text{Bu}^s$.

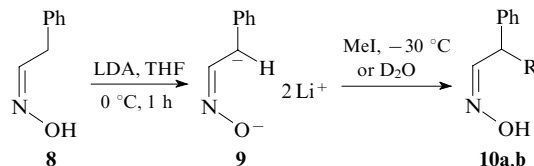
However, systematic studies of metallated compounds that contain heteroatoms capable of forming complexes with lithium made it possible to assume a different mechanism of selective *syn*-lithiation.³⁹ An organolithium compound is preliminarily coordinated by the oxygen atom of the oxime function, which is followed by the transfer of lithium to the α -carbon atom. Thus, selective



syn-metallation is due to the combined effect of kinetic and thermodynamic factors.

Stabilisation of *syn*-anions is also explained³⁵ by their partly aromatic nature. It is assumed that in a system containing six π -electrons, attractive interaction arises between the α -carbanionic site and the oxygen atom, which selectively stabilises the *syn*-form.

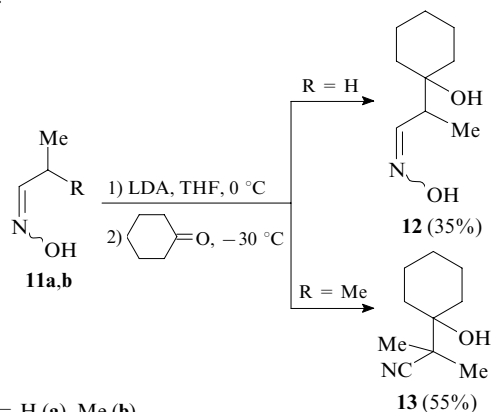
LDA was used as a base for the generation of a *syn*-dianion of aldoloxime **8**.³⁹



$\text{R} = \text{Me}$ (**a**, 86%), D (**b**, 100%).

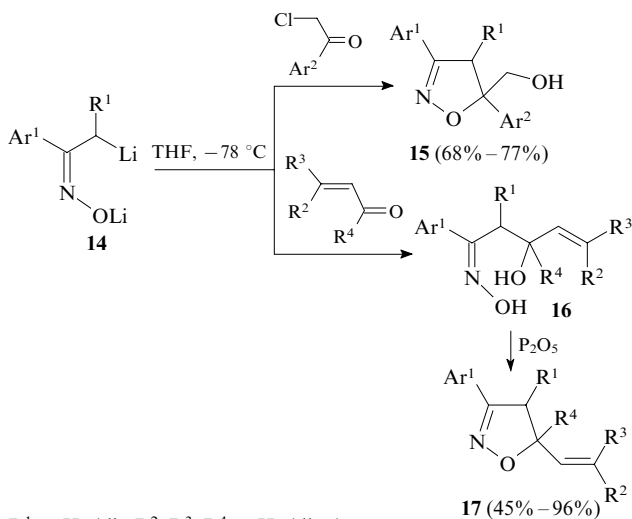
Z-Configuration of the starting oxime, which is not isomerised under mild conditions of lithiation, favours the formation of *syn*-dianion **9**. This is confirmed by high yields of methylation (**10a**) and deuteration (**10b**) products.³⁹

Propanal oxime carbanion (**11a**) was used as a methylene component in the condensation with cyclohexanone to yield aldol **12**. However, in the case of isobutyraldehyde oxime (**11b**), condensation together with dehydration of the oxime led to nitrile **13**.³⁹



$\text{R} = \text{H}$ (**a**), Me (**b**).

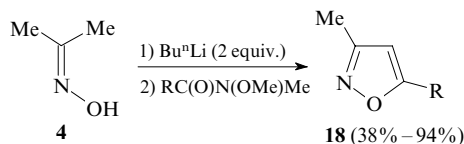
Oxime C-anions react with different electrophiles including carbonyl compounds. As the result of intramolecular dehydration of the adducts of these reactions, namely, alcohols, they are heterocyclised into isoxazole derivatives. Thus, when treated with α -chloroacetophenones under very mild conditions, dilithio derivatives of alkyl aryl ketoximes **14** form isoxazolines **15**.



$\text{R}^1 = \text{H}, \text{Alk}$; $\text{R}^2, \text{R}^3, \text{R}^4 = \text{H}, \text{Alk}, \text{Ar}$.

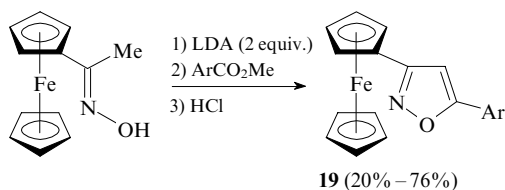
However, their reactions with α,β -unsaturated aldehydes and ketones lead to acyclic 1,2-adducts **16**. The latter are cyclised into 5-vinylisoxazolines **17** under the action of P_2O_5 .⁴⁰

Numerous of 5-alkyl-3-methylisoxazoles **18** were synthesised from the dilithio derivative of acetone oxime (**4**) and *N*-methoxy-*N*-methylamides of carboxylic acids (the Weinreb amides).⁴¹

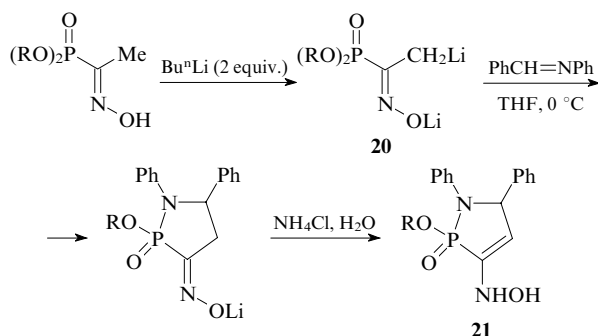


R = Alk, cyclo-Alk, Ar.

Reactions of dilithiated acetylferrocene oxime with methyl benzoates afford (5-arylisoxazole-3-yl)ferrocenes **19**.⁴²



A Schiff base was used as the electrophile in reactions with oxime dianions. Thus starting from α -oxophosphonate derivatives **20** and benzylideneaniline, 2-alkoxy-3-hydroxyamino-2-oxo-1,5-diphenyl-1,2-azaphosphol-3-enes **21** were synthesised (yields 10%–30%).⁴³



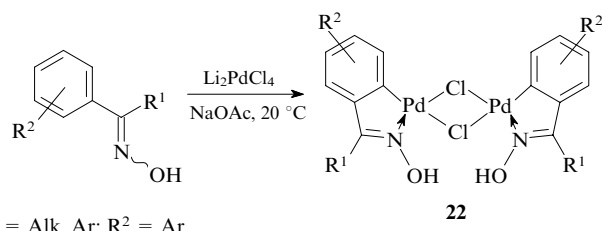
R = Et, Prⁿ, Buⁿ.

Information on oxime 1,4-dianions and their cyclisation can also be found in Refs 44–46.

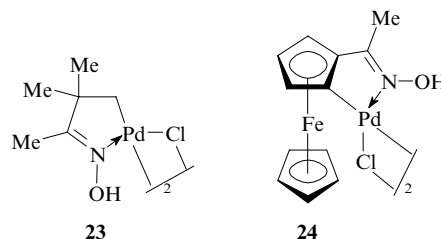
b. β -CH-Acidity (cyclopalladation)

Mono- and dioximes capable of chelation are good ligands for complexes with transition metal cations. This property forms the basis for the wide use of oximes as analytical reagents for different metals, namely, nickel, copper, cobalt, iron, palladium, platinum, manganese, rhodium, rhenium, molybdenum, *etc.*⁴⁷ In contrast to 'hard' lithium cations, transition metal cations coordinate preferentially to the nitrogen atom of the oxime group. Such an interaction is most likely a result of donating of electrons from the occupied d-orbitals of the metal to the lowest unoccupied molecular orbitals (LUMO) of the C=N bond, which leads to π -binding and additional stabilisation of the complex as a whole.

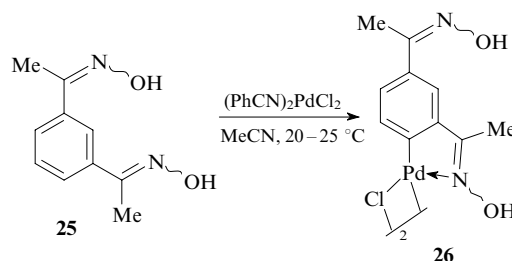
Coordination of a palladium atom to the oxime nitrogen atom favours the activation of the β -C–H bond. Thus cyclopalladation of oximes of aromatic ketones in the presence of bases results in the formation of bis(palladazole) system **22**, which is surprisingly stable in air and in aqueous medium.^{48–54} This process is usually carried out at room temperature by treating an oxime with lithium tetrachloropalladate (Li_2PdCl_4) in methanol in the presence of sodium acetate as the base.



Analogously, pinacolone and acetylferrocene oximes yielded palladium complexes **23** and **24**.⁵⁴



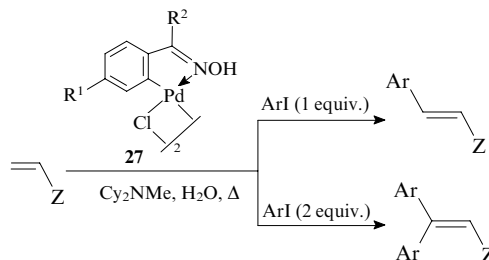
It should be mentioned that in the absence of a base in the reaction of 1,3-diacetylbenzene dioxime (**25**) with palladium(II) bis(benzonitrile) dichloride in acetonitrile cyclopalladation occurs, which involves only one oxime group to yield a dimeric complex **26**.⁵⁴



The CH-acidity of *syn*- α -methyl (or methylene) groups is not manifested in cyclopalladation, in contrast to lithiation reactions.

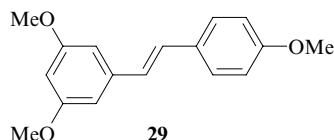
At present, complexes of the type **22** are actively studied as the catalysts of different cross-coupling processes⁵⁵ (including the Heck,^{56,57} Suzuki,^{58–60} Stille,⁵⁶ Ullmann,⁵⁸ Sonogashira^{61,62} and Glaser⁶² reactions). They are effective in both organic^{54,56,58,61,62} and aqueous^{57,59,60} media. Palladium and rhenium oxime complexes are also used as catalysts in the aza-Heck reaction.⁶³ In addition, terminal alkynes have recently been acylated with acid chlorides in the presence of such systems.⁶⁴

Controlled mono- and diarylation of α,β -unsaturated carbonyl compounds by aryl iodides was carried out using cyclopalladated 4-hydroxyacetophenone oxime (**27**) as the catalyst.⁵⁷ The yields of the reaction products were high (up to 98%).



$R^1 = \text{OH}, R^2 = \text{Me}$ (**27**); Z = CO_2Bu^t , C(O)NMe_2 , CN, C(O)Me ;
Ar = Ph, 4-ClC₆H₄, 4-FC₆H₄, 4-MeOC₆H₄.

Palladacycles **27** and **28** ($R^1 = \text{Cl}, R^2 = 4\text{-ClC}_6\text{H}_4$) proved to be efficient catalysts in the synthesis of methylated resveratrol (**29**) and its analogues,⁶⁵ which exhibit high antineoplastic activity.



Cross-coupling of the corresponding styrene with *p*-iodomethoxybenzene is carried out in the presence of methylcyclohexylamine and tetrabutylammonium bromide in aqueous dimethylamine (or in water) at 120 °C in air or under microwave irradiation. The reaction is highly regiospecific, *viz.*, stilbene **29** and its analogues are obtained in virtually quantitative yields.

Thus, under the action of strong bases, oximes acquire α -CH-acidity, while in the presence of palladium cations aryl ketoximes acquire β -CH-acidity of the aryl substituent. This allowed the development of a convenient method of synthesis of *ortho*-substituted aromatic compounds based on the catalytic version of cyclopalladation.

III. N- and O-nucleophilicity of the oxime function

Nucleophilicity of oximes is their most important chemical property that manifests itself most clearly in basic media. The oxime function contains three nucleophilic reaction sites, *viz.*, N, O and C atoms. The neutral molecule usually plays the role of an N-nucleophile, while an anion (oximate) plays the role of a strong O-nucleophile (due to the α -effect^{12, 13, 66–68}). Nucleophilicity of the carbon atom is determined by the contribution of a nitroso tautomer into the equilibrium.

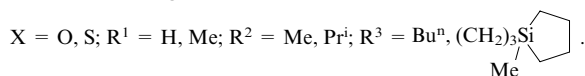
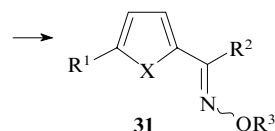
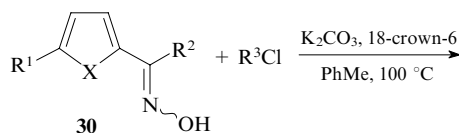
1. Reactions with electrophiles in the presence of bases

The N–O-selectivity of reactions of oximes with electrophiles depends on their structural features, the reagent nature and the reaction conditions. As a rule, the implementation of one or another reaction pathway can be rationalised within the framework of the theory of hard and soft acids and bases. The material of this section is arranged according to the type of the electrophilic agent. Reactions of oximes with alkyl halides, oxirane, bifunctional electrophiles, acylating agents and organoelement halides, which occur under different conditions, are considered.

Substitution of oximate ions for a halogen atom was studied in sufficient detail for various classes of organic substances. Having no intention to comprehensively survey the literature on this issue, we merely show the most typical examples of such reactions.

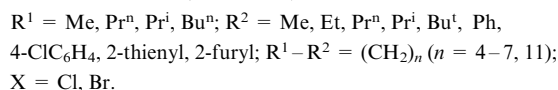
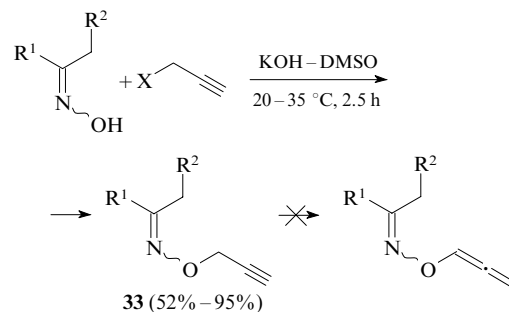
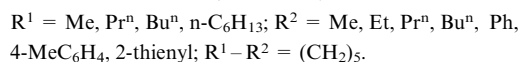
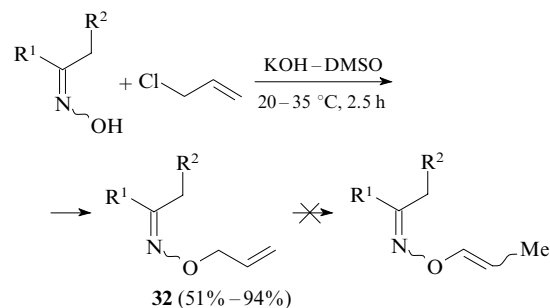
O-Alkyl(aryl)oximes can be obtained from the corresponding oximes and organyl halides in alkaline medium.^{69, 70} Alkylation of oxime salts (oximates) with alkyl halides often involves not only the oxygen atom but also the nitrogen atom (the manifestation of N-nucleophilicity). The direction of the reaction depends on the structure of substituents in the reagents and the solvent polarity. The nature of the alkali metal cation and the halogen (*e.g.*, in benzyl halides^{69, 70}) affects little the ratio of the substitution products. The dependence of the direction of alkylation on the oxime configuration was the subject of several studies.^{71–74} It was shown⁷¹ that the reaction of (*E*)-benzaldoxime with alkyl halides preferentially yields the *O*-alkylation products, while *Z*-isomer gives the *N*-alkylation products (nitrones).

Regioselectivity of *O*-alkylation of oximes can be increased by carrying out the reaction in a two-phase system. Under conditions of phase-transfer catalysis in the presence of K₂CO₃, furyl and thienyl ketoximes **30** were alkylated at the oxygen atom; the yields of products **31** were 15%–83%.⁷⁵



O-Butyl-, *O*-allyl-, *O*-(2-chloroethyl)oximes and *O,O'*-methylene dioximes were prepared from the corresponding halides and oximes in a two-phase system (NaOH, Bu₄NBr).⁷⁶ The alkylation of *E,E*-dioximes of 1,2-diketones, such as dimethylglyoxime, with dichloromethane under the conditions of phase-transfer catalysis (K₂CO₃, 18-crown-6), results in methylene dioximes and 21-membered heteromacrocycles, the oxime fragments in which are sequentially linked by methylene bridges.^{77, 78}

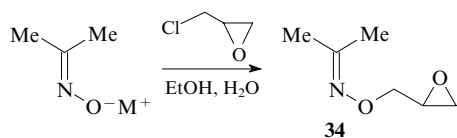
Oximate anions generated in the KOH–DMSO system substitute readily a halogen atom in allyl and propargyl halides to form the corresponding *O*-allyl- (**32**) and *O*-propargylketoximes (**33**).⁷⁹



It should be noted that no expected shift of the multiple bond to the oxygen atom to form prop-1-enyl and allenyl ethers was observed (for acid–base rearrangements of *O*-propargylketoximes in *N*-alkenylacrylamides, see Section IV.1). The fundamental reasons for the inertness of *O*-allyloximes as regards prototropic isomerisation were analysed by quantum-chemical methods.⁸⁰

Earlier, *O*-allylketoximes were obtained⁸¹ in a reaction of ketoximes with allyl halides in the presence of alkali metal hydroxides in polar aprotic solvents (*N*-methylpyrrolidone, dimethylacetamide, DMF).

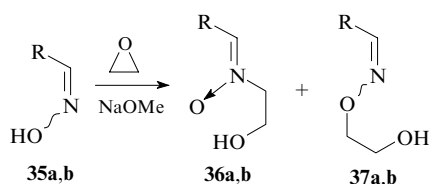
Condensation of sodium or potassium salts of acetone oxime (**4**) with epichlorohydrin in aqueous ethanol produced *O*-glycidyl-oxime **34**.⁸²



M = Na, K.

Cyclisation of γ -chloroximes^{83,84} and γ -sulfonyloximes⁸⁵ into 1,2-oxazines in the presence of bases proceeds as an intramolecular nucleophilic substitution with involvement of oximate anions as the *O*-centred nucleophiles.

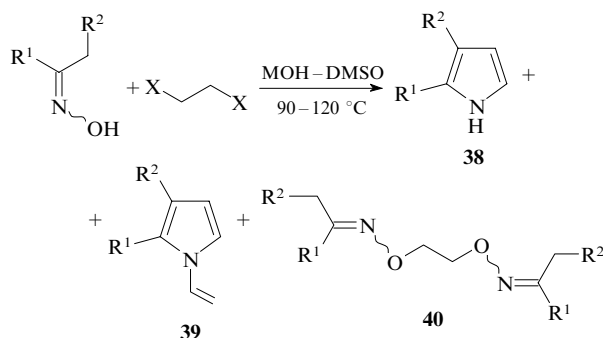
As in the reactions with alkyl halides, the direction of oxime reactions with oxirane depends first of all on the oxime configuration. Thus alkylation of the *E*-isomer of benzaldehyde 35a with oxirane yields the *N*- (36a) and *O*-substitution (37a) products in a ratio of 1 : 5.^{72,73} *Z*-Isomers of oximes of benzaldehyde (35a) and furfural (35b) give preferentially nitrones 36a,b (36a : 37a = 6 : 5, 36b : 37b = 10 : 1).⁷⁴



R = Ph (a), 2-furyl (b).

Alkylation of acetone oxime (4) with oxirane leads to the *O*-alkylation product, namely, acetone *O*-(2-hydroxyethyl)oxime in quantitative yield,⁷² whereas *Z*-oxime of 2-acetylpyridine is not alkylated with this reagent even under drastic conditions.⁷⁴ *O*-(2-Hydroxyalkyl)oximes are also prepared under the action of oxiranes in the presence of secondary amines.^{86,87}

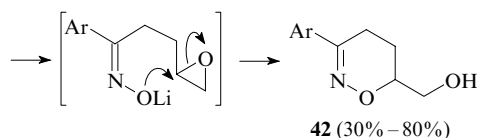
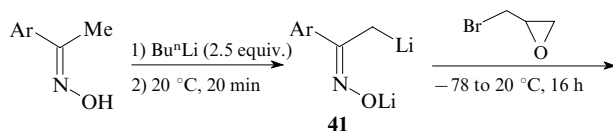
The one-pot synthesis of pyrroles 38 and 39 by the Trofimov reaction^{88–90} (see Section IV.2.b) from ketoximes and dihaloethanes (synthetic equivalents of acetylene) in superbasic media leads in certain cases to the substitution of oximate anions for a halogen atom. As a result of this process, side products, namely, ethylene glycol diethers of ketoximes 40 (*E,E*-, *E,Z*- and *Z,Z*-isomers) are formed; their content in the mixture can reach 47%.



R¹ = Me, Et, Prⁿ; R² = H, Me, Et, Prⁿ, Prⁱ; R¹–R² = (CH₂)₅;

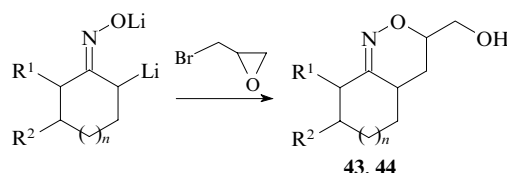
X = Cl, Br; M = Li, Na, K.

A regiospecific reaction of dilithiated oximes 41 with epibromohydrin produces 6-hydroxymethyl-5,6-dihydro-4*H*-1,2-oxazines 42.⁹¹



Ar = Ph, 2-MeC₆H₄, 3-MeC₆H₄, 4-MeC₆H₄, 3-MeOC₆H₄, 4-MeOC₆H₄, 1-naphthyl, 2-naphthyl.

Under similar conditions, epibromohydrin reacts with dithio derivatives of cycloalkanone and tetralone oximes to afford the corresponding bicyclic 1,2-oxazines 43 and their condensed tricyclic analogues 44.⁹¹

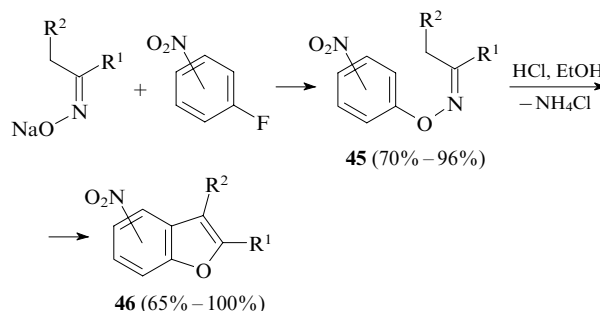


43: R¹ = R² = H: *n* = 1 (38%), 2 (51%), 3 (49%), 7 (52%);

44: R¹–R² = benzo, *n* = 1 (48%).

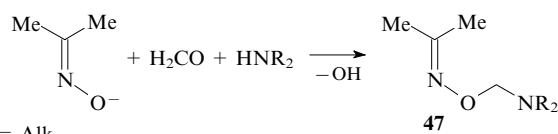
It should be noted that the acyl group in *O*-acyloximes is easily replaced by an *O*-alkyl group upon treatment of the substrate in a phase-transfer system alkyl halide–KOH–18-crown-6–benzene.⁹²

Substitution of a fluorine atom in an aromatic ring under the action of sodium oximates is described.⁹³ *O*-Aryloximes 45 formed are converted into benzofurans 46 upon refluxing with HCl in anhydrous ethanol.



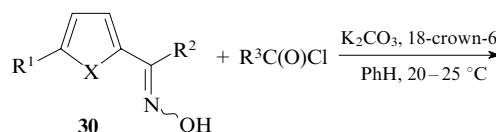
R¹, R² = Alk.

O-Aminomethyloximes 47 were synthesised⁹⁴ by the Mannich condensation.[†] The same products are formed upon alkylation of oximes with aminomethyl halides.

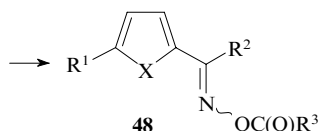


R = Alk.

Acylation of oximes can be effected under different conditions. For example, in benzene in the presence of solid K₂CO₃ and 18-crown-6, *O*-acylated derivatives 48 are formed from 2-furyl and 2-thienyl ketoximes 30; this involves no Beckmann rearrangement.⁹⁶

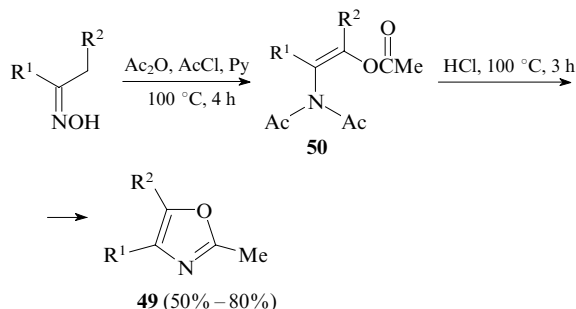


[†] The Mannich reaction with aldoximes is known⁹⁵ to involve the α -carbon atom.



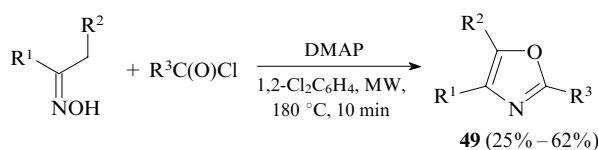
X = O, S; R¹ = H, Br; R² = Me, Et, Prⁱ; R³ = Me, Et, Bu^t, Ph.

If the acylation agent represents a mixture of Ac₂O and AcCl, then ketoximes are converted into oxazoles **49** in the presence of pyridine. The reaction proceeds *via* β-acetoxy enamides **50**.⁹⁷



R¹ = Me, Bn, Ph; R² = Me, Ph; R¹–R² = (CH₂)₄, (CH₂)₂CHMeCH₂.

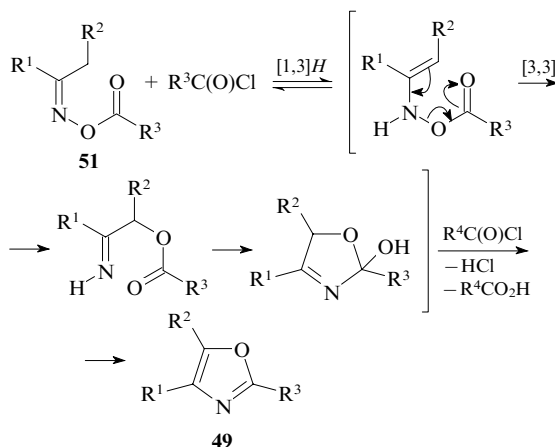
Recently, it has been shown⁹⁸ that the acylation of ketoximes with carboxylic acid chlorides in the presence of organic bases under conditions of microwave activation (150 W) also affords oxazoles **49**.



R¹ = Me, Et, Prⁱ, Ph, 4-BrC₆H₄; R² = Me, Ph; R¹–R² = (CH₂)₄;
R³ = Bu^t, Ph, 4-MeOC₆H₄, 4-CF₃C₆H₄, BnOCH₂, PhCH=CH;
DMAP is dimethylaminopyridine.

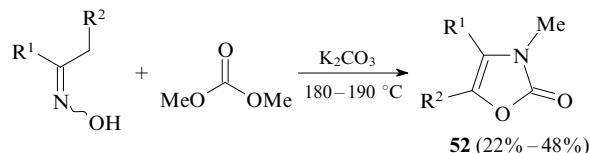
This process also occurs in the absence of microwave irradiation; however, the yields of oxazoles are substantially lower. For example, the yield of oxazole **49** (R¹ = Me, R² = Ph, R³ = 4-CF₃C₆H₄) is 43% *versus* 62% with microwave activation.⁹⁸

The cyclisation mechanism was not discussed in Ref. 98. However, since no intermediates of the type **50** were detected, the transient formation of *O*-acylketoximes **51** seems to be the most likely. The consecutive 1,3-prototropic shift and [3,3]-sigmatropic rearrangement are similar to the mechanism of pyrrole synthesis *via* *O*-vinyloximes by the Trofimov reaction (see Section III. 2.b).



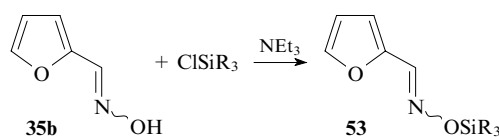
R¹–R⁴ = Alk.

The reaction of aliphatic and aromatic ketoximes containing α-methylene groups with dimethyl carbonate in the presence of K₂CO₃ leads to 4,5-disubstituted 3-methyloxazolin-2-ones **52**.⁹⁹ Presumably, the reaction involves the [3,3]-sigmatropic rearrangement and the role of dimethyl carbonate is the initial N-methylation of oximes.



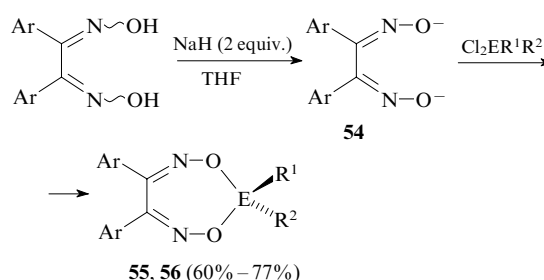
R¹ = Me, Et, Prⁿ, Ph; R² = Me, Et, Ph; R¹–R² = (CH₂)_n (n = 4, 5).

In the presence of tertiary amines, furfural oxime **35b** reacts with trialkylchlorosilanes to give *O*-silyl ethers **53**.¹⁰⁰ This is a typical example of nucleophilic substitution at the silicon atom where oximes play the role of O-centred nucleophiles.



R = Alk.

Recently,¹⁰¹ O,O'-centred dianions of vicinal dioximes **54** have been used for the synthesis of 7-membered silicon- (**55**) and tin-containing (**56**) heterocycles. The reaction occurs as the nucleophilic substitution of chlorine atoms in the corresponding dichlorides.

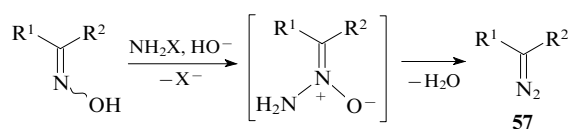


Ar = 4-XC₆H₄ (X = H, Me, Cl, MeO);

E = Si (**55**): R¹ = Me, Buⁿ, Ph; R² = Me, Buⁿ, Ph, Cl;

E = Sn (**56**): R¹ = R² = Me, Buⁿ, Ph.

In this Section, it is appropriate to mention the conversion of oximes into diazoalkanes **57** under the action of N-electrophiles, namely, chloroamine or hydroxylaminosulfonic acid (the Forster reaction).^{102, 103} In the first stage of this reaction, oximes act as N-nucleophiles.



R¹, R² = H, Alk, Ar; X = Cl, OSO₃H.

Various diazo compounds were synthesised by this method.^{103–108} Table 2 shows the most interesting of them (including diazomethane).

Thus, using the substitution reactions involving oximes as O- and N-nucleophiles, it is possible to synthesise various *O*-organoyloximes, nitrones and diazo compounds, which are valuable intermediates in organic synthesis. The selectivity of these reactions can be controlled by varying the substituents in oximes and electrophilic agents and changing the oxime configurations and experimental conditions.

Table 2. Oximes in the Forster reaction.¹⁰²

Oxime	Diazo compounds	Yield (%)
Formaldoxime	$\text{H}_2\text{C}=\text{N}_2$	75
3-Hydroxyiminocamphor		70
2-Hydroxyimino-1-tetralone		57
α -Hydroxyiminonopinone		85
2-Hydroxyimino-3,3-diphenyl-1-indanone		65

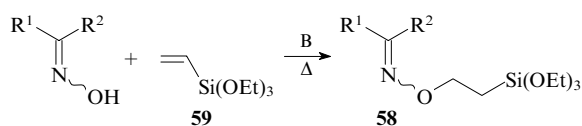
2. Nucleophilic addition of oximes to unsaturated systems

a. Reactions with alkenes

Bases catalyse the addition of oximes to electron-deficient alkenes. The catalysts are usually represented by alkali metal hydroxides^{109,110} and alkoxides,¹¹¹ quaternary ammonium salts.¹¹⁰ However, the reaction proceeds most smoothly in the presence of triphenylphosphine:¹¹² in some cases, adducts **58** were obtained in quantitative yield.

R ¹	R ²	X	Yield (%)
Bu ^t	H	SO ₂ Ph	89
Cy	H	SO ₂ Ph	88
Styryl	H	SO ₂ Ph	90
4-NO ₂ C ₆ H ₄	H	CO ₂ Et	85
3-NO ₂ C ₆ H ₄	H	CO ₂ Et	80
	H	CN	80
	H	SO ₂ Ph	95
3-HSC ₆ H ₄	H	SO ₂ Ph	92
3-Py	H	SO ₂ Ph	88
Et	Me	SO ₂ Ph	84
Ph	Me	SO ₂ Ph	87
4-MeSO ₃ C ₆ H ₄	H	SO ₂ Ph	96
	Me	CO ₂ Et	30
	Me	SO ₂ Ph	84

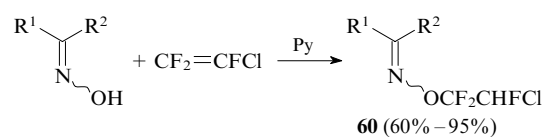
Under the action of bases, oximes add to trialkoxy(vinyl)silanes **59** to form the corresponding *O*-alkylated derivatives **58** [$\text{X} = \text{Si}(\text{OEt})_3$].¹¹³



$\text{R}^1 = \text{Alk}$; $\text{R}^2 = \text{H, Alk}$; $\text{B} = \text{AlkONa, AlkSNa, NaNH}_2$, etc.

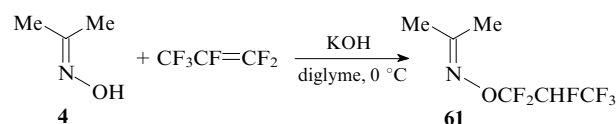
Different nitrogen bases were used as the catalysts in the reactions of oximes with polyfluoroalkenes. Thus *O*-chlorofluoro-

ethyloximes **60** were synthesised in high yields from chlorotri-fluoroethylene in the presence of pyridine.¹¹⁴

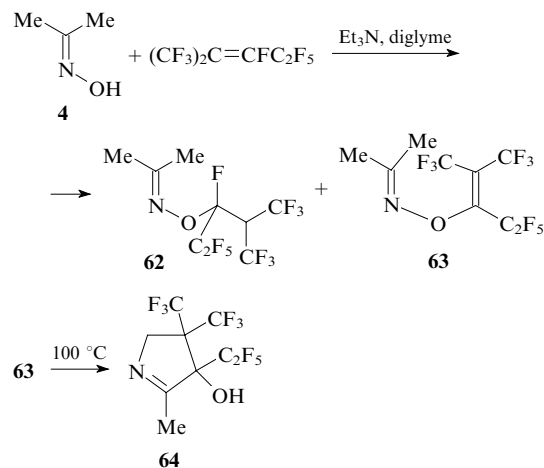


$\text{R}^1, \text{R}^2 = \text{Alk, Ar}$.

Acetone oxime (**4**) reacts with perfluoropropylene to form acetone *O*-hexafluoropropyl oxime (**61**).¹¹⁵

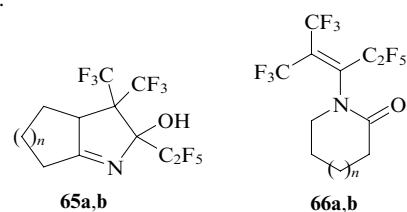


However, the reaction of acetone oxime (**4**) with perfluoro-2-methylpent-2-ene (dimer of perfluoropropylene) in the presence of triethylamine proceeds in a more complicated fashion. In addition to adduct **62**, the reaction gives the product of formal replacement of one of fluorine atoms, namely, compound **63**, which is rearranged upon heating into 4-hydroxy-2-methyl-5,5-bis(tri-fluoromethyl)-4-pentafluoroethyl-1-pyrroline (**64**).¹¹⁵



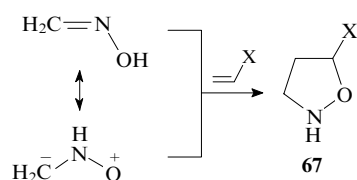
It should be mentioned that this rearrangement exactly corresponds to a proved stage of the Trofimov reaction, *viz.*, the [3,3]-sigmatropic shift in *O*-vinylloximes, which leads to the formation of, first, hydroxypyrrolines and, then, pyrroles.

The addition of oximes to alkenes can also occur in the absence of bases upon heating of the reactants. Thus thermolysis of a mixture of perfluoro-2-methylpent-2-ene and cycloalkanone oximes produced pyrrolines **65** and the Beckmann–Chapman rearrangement products, namely, *N*-perfluoroalkenyllactams **66**.¹¹⁶



$n = 1$ (a), 2 (b).

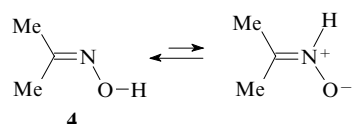
1,3-Dipolar cycloaddition of formaldoxime with electron-deficient alkenes is shown¹¹⁷ to afford 5-substituted isoxazolidines **67**. This reaction pathway is attributed to the fact that it is the mesomeric form of formaldoxime, *i.e.*, betaine, with a positive charge on the oxygen atom and a negative charge on the carbon atom that is involved in cyclisation.



X = CN, CO₂Me.

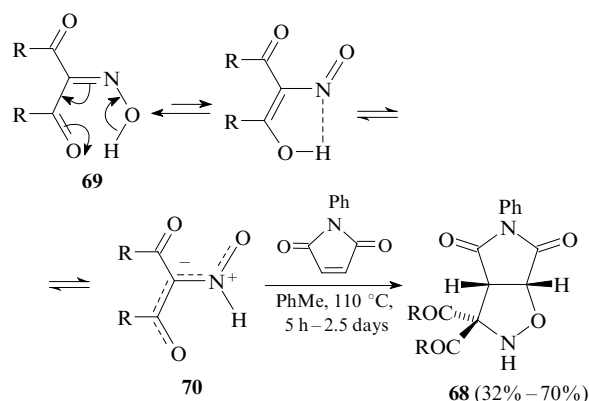
This transformation is an unusual example of [2 + 3]-cycloaddition of nitrones with the change in polarity ('Umpolung').

It is known^{118–121} that oximes can be thermally isomerised into nitrones as a result of the 1,2-prototropic shift.



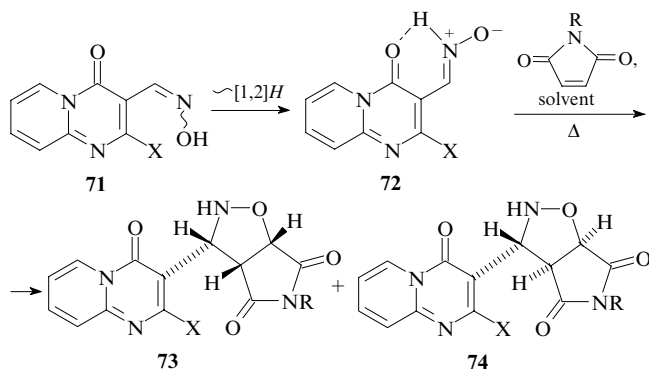
The fact that oximes react with alkenes in the form of NH-nitrones is also confirmed by the synthesis of isoxazolidines **67**. The mechanism of addition can be either intermolecular (as in the above example) or intramolecular.^{122–136}

Up to recently, information on the use of oximes in the NH-nitrone form in the intermolecular addition to dipolarophiles was limited to a few studies.^{117,120} Thus it was reported¹²⁰ that cycloadduct **68** is formed in the reaction of oxime **69** (or, more exactly, its NH-nitrone tautomer **70**) with *N*-phenylmaleimide.



R = OMe, OEt; R–R = CH₂CM₂CH₂.

The prospects of studying the isomerisation of oximes into NH-nitrones with the aim of generating NH-1,3-dipoles and their synthetic application are evident. Recently, it has been reported¹³⁷ on a successful addition of oximes of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehydes **71** in their nitrone form **72** to the activated double bond of *N*-substituted maleimides. The yields of diastereomeric isoxazolidines **73** and **74** depend on the



X = pyrrolidin-1-yl, morpholin-1-yl, NBn₂, OEt;

R = Me, Ph; solvent is PhH, EtOH, MeCN.

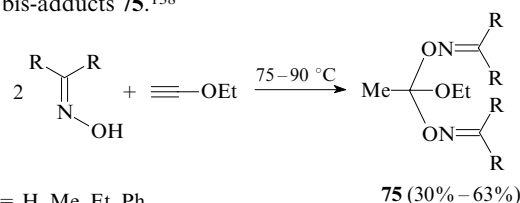
structure of the reactants and the reaction conditions and amount to 66%–82%.

Thus, in the synthesis *O*-organyloximes, the nucleophilic addition of oximes to electron-deficient alkenes is an alternative to the nucleophilic substitution involving oximate anions. This reaction can follow a synchronous mechanism (like cycloaddition), which opens up an easy way to the synthesis of pyrrolines and isoxazolidines that contain reactive functional groups. These hydrogenated azoles are promising building blocks in organic synthesis. It should be stressed that, in the latter case, the reaction takes place in the absence of a base, *i.e.*, oximes play the role of non-ionised nucleophilic reagents.

b. Reactions with alkynes

Like other electrophilic reagents, alkynes can attack an oxime molecule at both oxygen and nitrogen atoms. However, the fate of intermediates differs in many aspects and depends on various factors. Reactions of nucleophilic addition of acetylene derivatives to oximes usually lead to *O*-vinyl ethers. However, examples of heretocyclisation of intermediates formed as a result of the alkyne attack on the N-nucleophilic site are also documented.

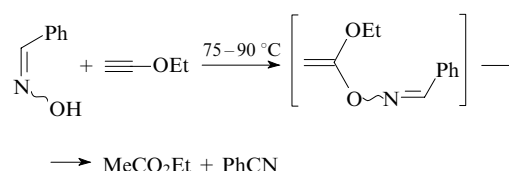
The reactions of oximes with ethoxyacetylene on moderate heating in the absence of catalyst result in regiospecific formation of bis-adducts **75**.¹³⁸



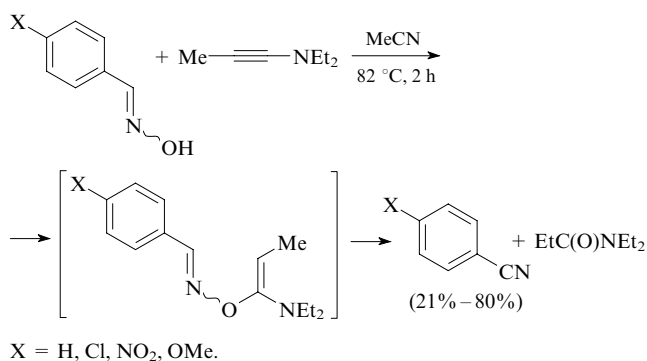
R = H, Me, Et, Ph.

75 (30%–63%)

Under similar conditions, aromatic aldoximes (both *syn*- and *anti*-isomers) sometimes give dehydration products, *viz.*, nitriles and ethyl acetate, together with the addition products.¹³⁸ For example, *syn*- and *anti*-benzaloximes form benzonitrile in the reaction with ethoxyacetylene. This reaction route was explained¹³⁸ by decomposition of intermediate monoadducts, which, however, could not be isolated.



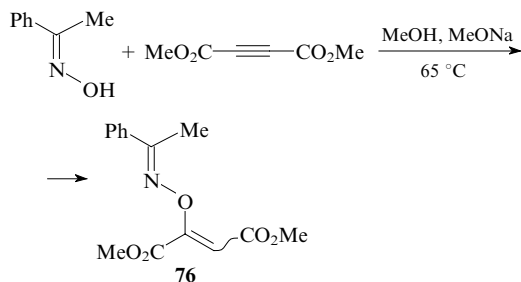
Substituted benzonitriles were also prepared in the reaction of benzaloximes with 1-(*N,N*-diethylamino)propyne.¹³⁹



X = H, Cl, NO₂, OMe.

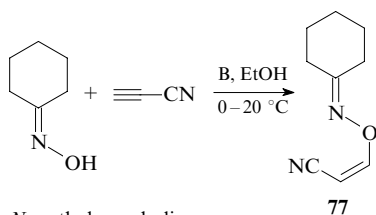
The yields of products depend on the configuration of the starting oxime. The low yield of benzonitrile (X = H, 21%) in the case of *Z*-benzaloxime is probably due to steric factors.

The reaction of acetophenone oxime with dimethyl acetylenedicarboxylate in the presence of sodium methoxide leads to *O*-adduct **76** in quantitative yield.¹⁴⁰



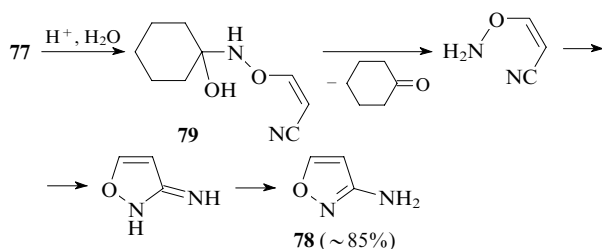
Compound **76** was obtained as a mixture of *cis*- and *trans*-isomers (1 : 2, according to the ^1H NMR data).

Cyanoacetylene adds to cyclohexanone oxime in a mixture of ethanol and *N*-methylmorpholine (5 : 2 by volume) at 0–20 °C to yield β -cyclohexylideneiminoxyacrylonitrile (**77**).¹⁴¹

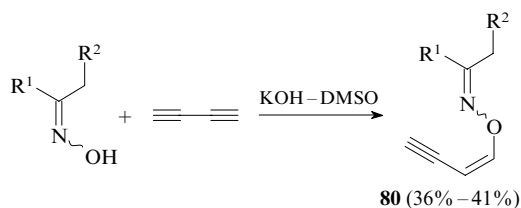


B is *N*-methylmorpholine.

Mild acid hydrolysis of the synthesised compound **77** converts it into 3-aminoisoxazole **78** and regenerates the ketone.¹⁴¹ This suggests high susceptibility of such *O*-vinyl oximes to the electrophilic addition of water to the C=N bond to form intermediates **79**.

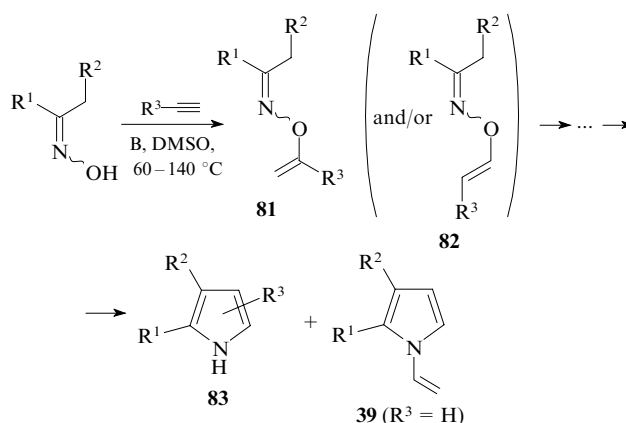


Oximes react with diacetylene in DMSO in the presence of catalytic amounts of KOH at temperature not exceeding 60 °C, which leads to the (*Z*)-*O*-ethynylvinyl derivatives **80**.^{142, 143}



$\text{R}^1, \text{R}^2 = \text{Alk.}$

Whereas oxime adducts to activated alkynes are formed even in the presence of weak bases (e.g., triphenylphosphine-catalysed reaction of oximes with ethyl propiolate¹⁴⁴), the vinylation of oximes with acetylene occurs only in superbasic media (e.g., in the KOH–DMSO system), which enhance the nucleophilicity of oximate anions. Under such conditions, oximes add to acetylene and its alkyl and aryl derivatives to form *O*-vinyl oximes **81** or **82**. This process represents the first stage of the Trofimov reaction,^{88, 145–156} which leads to pyrroles **83** and *N*-vinylpyrroles **39** (the latter are formed in the excess of acetylene).

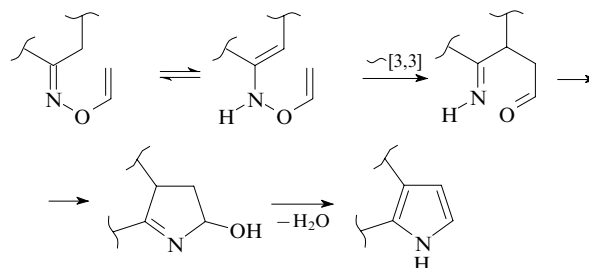


$\text{R}^1, \text{R}^2 = \text{Alk, Ar, Het}$; $\text{R}^3 = \text{H, Alk, Ar}$;
B are alkali metal hydroxides or alkoxides.

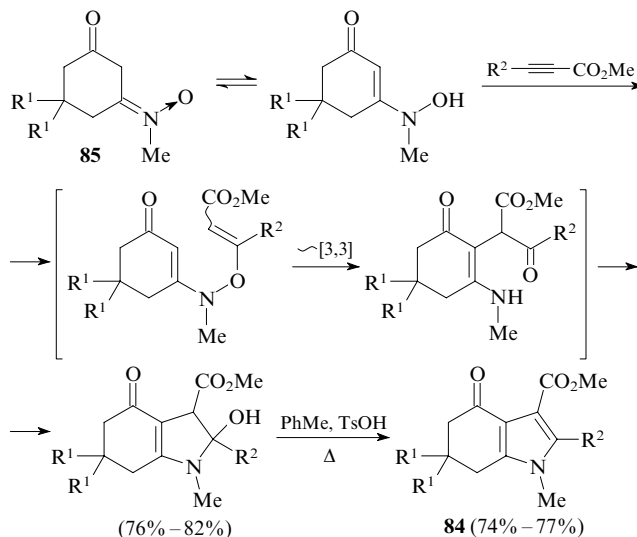
The yields of pyrroles depend on the structure of starting ketones and usually amount to 50%–70%; in certain cases, they can be nearly quantitative. The prerequisite for this reaction is that a ketoxime had an α -methyl or methylene group relative to the oxime function. If an oxime has both groups, then the methylene group is involved, as a rule, in the pyrrole ring formation.^{88, 147, 149, 156–170}

In the absence of α -methylene groups in the oxime molecule [e.g., in methyl (het)aryl, methyl *iso(ter)*alkyl, diaryl, aryl hetaryl ketoximes], intermediate *O*-vinyl ketoximes can be isolated.^{88, 147, 149, 156–169, 171, 172} Isopropyl (het)aryl ketoximes were used for the synthesis of 3*H*-pyrroles, which are difficult to synthesise.¹⁷³

O-Vinyl oximes **81** and **82** easily rearrange into pyrroles upon heating in the KOH–DMSO system^{88, 147, 149, 167} or in pure DMSO.^{174, 175}



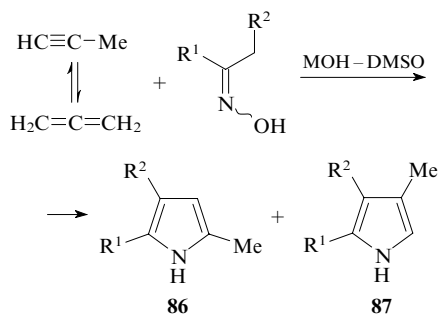
Recently, a similar reaction scheme was used for the synthesis of 4-oxo-4,5,6,7-tetrahydroindoles **84** from nitron **85**.¹⁷⁶



$\text{R}^1 = \text{H, Me}$; $\text{R}^2 = \text{H, CO}_2\text{Me}$.

It should be noted that *O*-vinylamidoximes synthesised by the addition of amidoximes to acetylene in superbasic media do not undergo the [3,3]-sigmatropic rearrangement that would lead to the formation of the desired imidazoles.¹⁷⁷

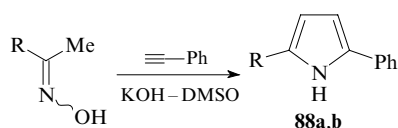
The reaction of ketoximes with the simplest homologue of acetylene, *i.e.*, propyne, its isomer allene and their mixture was studied¹⁷⁸ in the MOH–DMSO system. In all the cases (at ordinary and elevated pressures, at different temperatures and reaction times), 5- (**86**) and 4-methylpyrroles **87** are formed.



$\text{R}^1 = \text{Me}, \text{Pr}^i, \text{Bu}^i, \text{Ph}, 2\text{-furyl}, 2\text{-thienyl}; \text{R}^2 = \text{H}, \text{Me};$
 $\text{R}^1-\text{R}^2 = (\text{CH}_2)_4; \text{M} = \text{K}, \text{Cs}.$

Under these conditions, easy prototropic isomerisation of propyne to allene and *vice versa* occurs. The result of the reaction depends substantially on the ketoxime structure, being determined not only by electronic factors, but also by steric factors. Thus the more branched is the substituent at the oxime function, the larger the fraction of 4-substituted pyrrole **87**. This synthesis of pyrroles, which involves the use of a propyne–allene mixture, *i.e.*, a large-scale waste of pyrolysis of hydrocarbons into acetylene, extends significantly the scope of this reaction for the synthesis of 4- and 5-methylpyrroles with various substituents in positions 2 and 3 accessible.

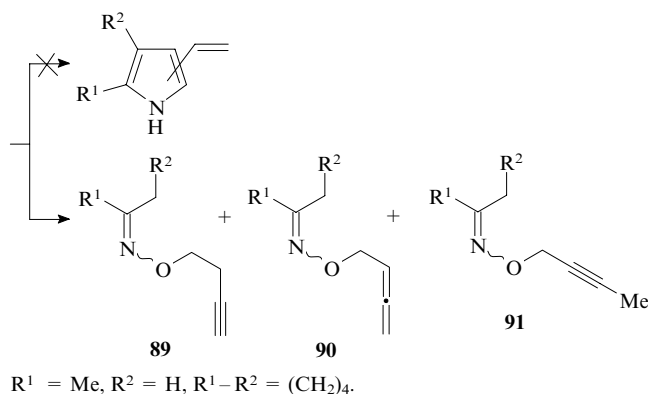
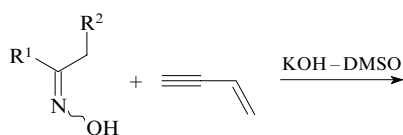
The reaction of oximes of acetone and acetophenone with phenylacetylene carried out under conditions of the Trofimov reaction produced 2-phenylpyrroles **88a,b**.¹⁷⁹



$\text{R} = \text{Me}$ (**a**), Ph (**b**).

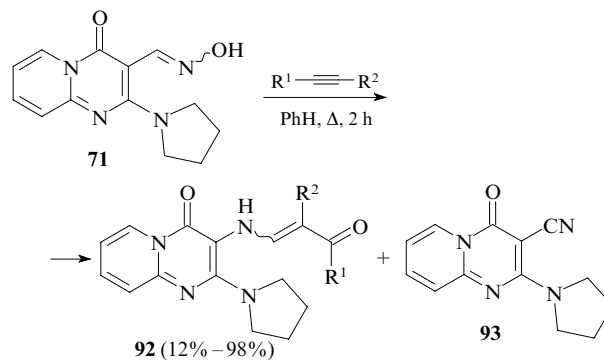
Thus, the reaction of ketoximes with acetylene allows one to easily obtain pyrroles with alkyl, aryl and hetaryl substituents as well as different systems annelated with the pyrrole ring. This reaction makes an almost unlimited series of *N*-vinylpyrroles available. These compounds, on the one hand, contain a convenient protective *N*-vinyl group which can easily be removed^{180,181} and, on the other hand, represent good building blocks for the synthesis of pyrrole derivatives and monomers with wide synthetic potentials.

As in the case of reactions with diacetylene (see above), no pyrroles are formed in the reaction of ketoximes with vinylacetylene in systems MOH–DMSO ($\text{M} = \text{K}$ or Li). This reaction produces only mixtures of *O*-butynyl and *O*-butadienyl ketoximes **89–91** (yield < 50%).¹⁸²



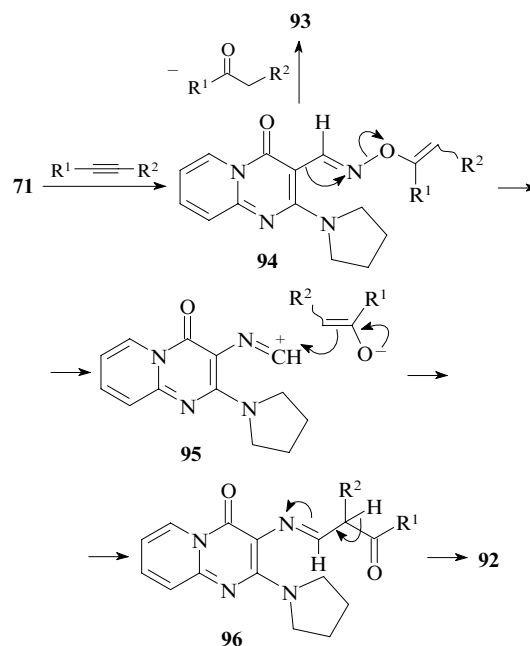
$\text{R}^1 = \text{Me}, \text{R}^2 = \text{H}, \text{R}^1-\text{R}^2 = (\text{CH}_2)_4.$

Recently, information on the nucleophilic addition of heterocyclic oxime **71** to dimethyl acetylenedicarboxylate, dibenzoylacetylene and methyl propiolate has appeared.¹³⁷ The reaction proceeds on refluxing the reactants in benzene for 2 h. In place of expected *O*- or *N*-adducts, enamines **92** and traces of nitriles **93** were isolated.

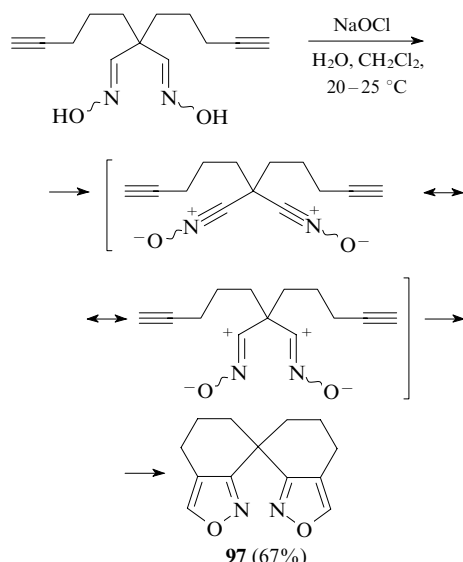


$\text{R}^1 = \text{R}^2 = \text{CO}_2\text{Me}, \text{C}(\text{O})\text{Ph}; \text{R}^1 = \text{H}, \text{R}^2 = \text{CO}_2\text{Me}.$

The formation of enamines **92** is explained by the *O*-nucleophilic attack of oxime **71** on the triple bond. *O*-Vinylloxime **94** formed undergoes decomposition along the Beckmann rearrangement path to give carbocation **95** and an enolate; these react to afford imine **96**. Rearrangement of the latter leads to enamine **92**, while nitrile **93** is formed as a result of elimination of the ketone from *O*-vinylloxime **94**.

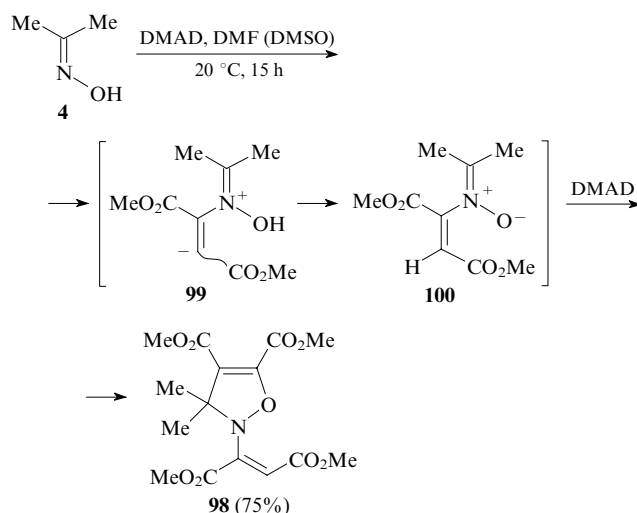


Synthesis of the first spirocyclic bis(isoxazole) **97** as a racemate is described.¹⁸³ This cyclic bis(*O*-vinylloxime) represents a C_2 -symmetric chiral ligand used in enantioselective catalysis. Intramolecular cyclisation of diacetylenic dialdoxime occurs under the action of 5% aqueous NaOCl. According to the researchers cited, the reaction yields bis(nitrile oxide). However, another possible mechanism includes the primary *O*-nucleophilic attack of the oxime function on the triple bond followed by oxidation of intermediates. Resolution of this racemate into optical isomers was accomplished by column chromatography on a chiral stationary phase.



Summarising, we show several examples of reactions of oximes with acetylene derivatives that involve an electrophilic attack on the nitrogen atom.

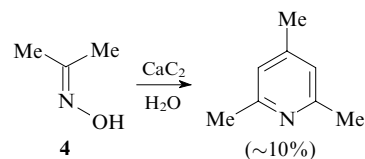
Thus acetone oxime (**4**) adds to dimethyl acetylenedicarboxylate (DMAD) to form a cyclic product, namely, functionalised 4,5-isoxazoline **98**.^{184–186}



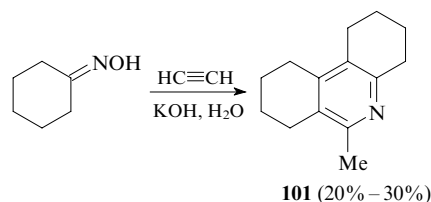
Presumably, the addition of oxime to the $C\equiv C$ bond produces a zwitterionic intermediate **99**, *i.e.*, the oxime plays the role of an uncharged nucleophile. Intramolecular transfer of a proton in the intermediate **99** results in the formation of nitrone **100**. The latter enters 1,3-dipolar addition with the second molecule of dimethyl acetylenedicarboxylate to yield isoxazoline **98**, which is the 1:2 adduct.

It should be noted that in some cases the data on the reactions of oximes with acetylenes conflict with one another. For instance, the results of a publication¹⁸⁷ describing synthesis of simplest *O*-vinylloximes by vinylation of oximes with calcium carbide in an

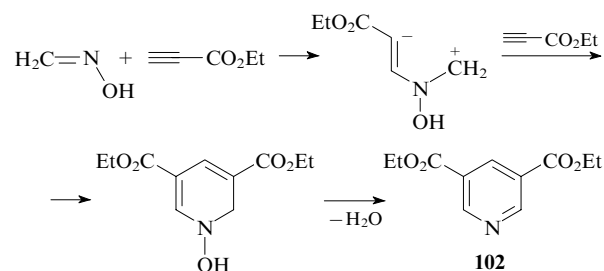
aqueous medium at 200–220 °C were checked in another study¹⁸⁸ and were not confirmed. Under these conditions, instead of *O*-vinylloximes, pyridines were obtained in low yields.^{88, 189}



In the presence of KOH, cyclohexanone oxime reacts with unsubstituted acetylene to form 6-methyl-1,2,3,4,7,8,9,10-octahydrophenanthridine (**101**) in a yield of up to 30%.⁸⁸ However, the conditions of this reaction were not optimised by the authors.



3,5-Diethoxycarbonylpyridine **102** was synthesised in a reaction of formaldoxime with ethyl propiolate.¹¹⁷ Here, the hydroxyl group of oxime remains inert with respect to the triple bond and the nitrogen atom plays the role of a nucleophilic centre. The reaction proceeds on refluxing the reactants in 50% aqueous methanol; no intermediate adduct was isolated.

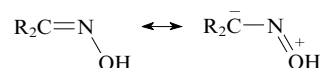


Reactions of α -chlorooximes^{190, 191} and α -amido-oximes^{192, 193} with acetylenes are also documented. However, since these compounds may be considered as the derivatives of hydroxamic acids (acid chlorides and amides), their reactions are beyond the scope of our survey.

IV. Nucleophilic attack on the $C=N$ bond of oximes

Being treated with bases, oximes not only undergo deprotonation, which enhances their nucleophilicity, but are also subjected themselves (especially, oxime ethers) to a nucleophilic attack on the nitrogen atom. Thus, competition often exists between the roles that an oxime plays as the nucleophilic reagent and as the object of a nucleophilic attack.

The presence of an oxygen atom adjacent to the $C=N$ double bond that can exert both negative inductive and positive mesomeric effects reduces the basicity of the nitrogen atom as compared with imines and decreases the positive charge on the carbon atom, making the latter less susceptible to the nucleophilic attack. For instance, the higher resistance of oximes against hydrolysis as compared with imines is explained¹⁹⁴ by the participation of the oxygen atom in charge delocalisation.



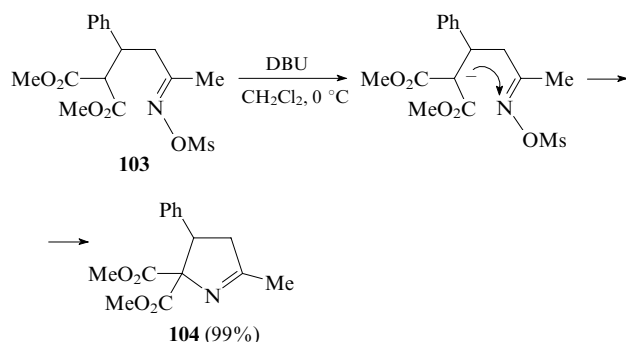
On the other hand, the electronegative nature of the oxygen atom favours nucleophilic substitution at the nitrogen atom of the oxime function.

1. Intramolecular nucleophilic substitution at the nitrogen atom

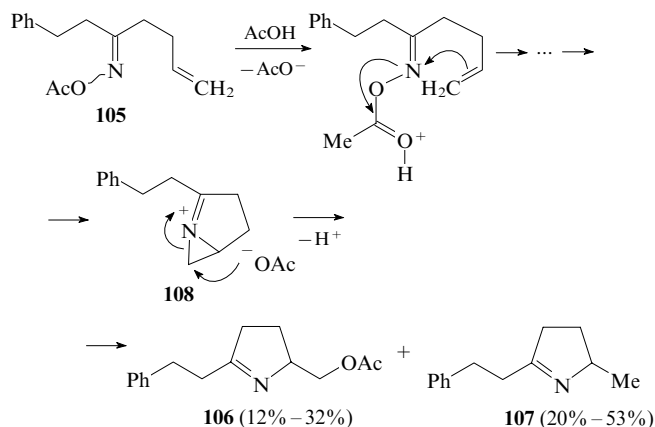
a. Heterocyclisation of oxime derivatives into azoles

Oximes with a nucleophilic site in the side chain and the N–O bond activated by the introduction of an acceptor substituent at the oxygen atom undergo intramolecular nucleophilic substitution to afford 5-membered nitrogen-containing heterocycles.[‡]

Thus *O*-mesyloxime **103**, which has an activated methine group in the γ -position with respect to the oxime function, is converted quantitatively into pyrroline **104** upon its treatment with a strong organic base, namely, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).^{196, 197}



Heating of *O*-acetyloxime of γ,δ -unsaturated ketone **105** (the ratio of *Z*- and *E*-isomers is $\sim 1:1$) in an acidic medium in the presence of hydrogen donors (AcOH, cyclohexa-1,4-diene, dioxane) under reflux for 6 h leads to a mixture of 2-acetoxymethyl-3,4-dihydro-2*H*-pyrrole **106** and 2-methyl-3,4-dihydro-2*H*-pyrrole **107**, which are formed by different mechanisms.¹⁹⁸ The reaction was assumed to proceed *via* a cationic intermediate **108**.

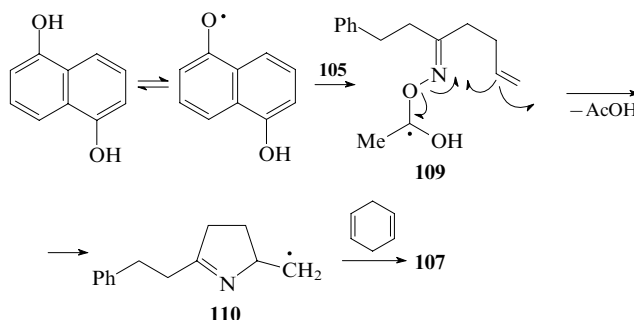


However, since 2-methylpyrroline **107** could not be formed according to a nucleophilic substitution mechanism, it was assumed¹⁹⁸ that an additional pathway of radical cyclisation exists.[§]

[‡] During preparation of this review for publication, one more review¹⁹⁵ appeared, which is devoted to the use of intramolecular nucleophilic substitution at the oxime nitrogen atom for the synthesis of various nitrogen heterocycles and contains partially the material presented in this section.

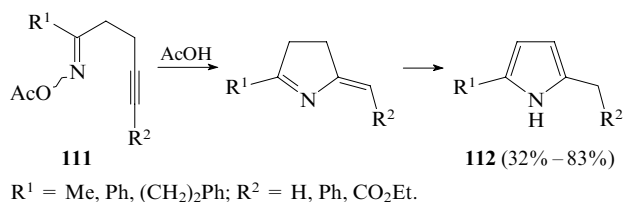
[§] Although homolytic reactions of oximes are not considered in a special Section, it seemed reasonable to present the scheme of the radical mechanism. Studies of the synthesis of pyrrolines by photochemical cyclisation of *O*-acetyl- and *O*-methyloximes of γ,δ -unsaturated ketones were continued in a recent publication.¹⁹⁹

The possible mechanism was confirmed in experiments carried out in toluene-*d*₈ in the presence of free-radical traps such as hydroquinone and naphthalene-1,5-diol. The sequence of transformations that involve naphthalene-1,5-diol is as follows:¹⁹⁸



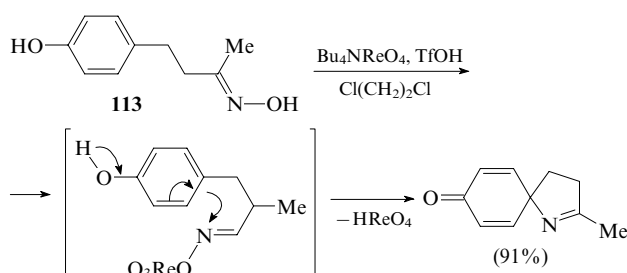
The transfer of an electron from naphthalene-1,5-diol to oxime **105** leads to the formation of radical **109**, which cyclises to form pyrroline radical **110**. The latter splits a hydrogen atom from cyclohexa-1,4-diene to form pyrroline **107**.

Under similar conditions (AcOH, hydroquinone, cyclohexa-1,4-diene, dioxane, reflux, 6–24 h), *O*-acetyloximes **111**, which contain alkyl substituents, cyclise to pyrroles **112**.¹⁹⁸

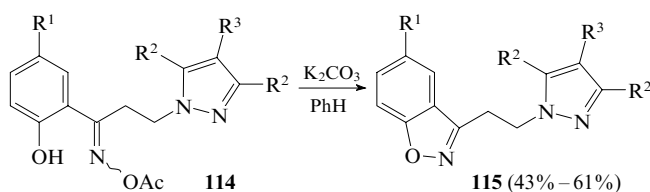


$R^1 = \text{Me, Ph, (CH}_2\text{)}_2\text{Ph}$; $R^2 = \text{H, Ph, CO}_2\text{Et}$.

The direction of heterocyclisation of phenols depends on the mutual arrangement of the hydroxyl group and the side-chain oxime fragment. Intramolecular nucleophilic substitution of the S_N2 type at the nitrogen atom is observed in the reaction of ketoxime **113** with tetrabutylammonium perhenate in the presence of trifluoromethanesulfonic acid (TfOH). Here, the phenolic substituent plays the role of a nucleophile.²⁰⁰

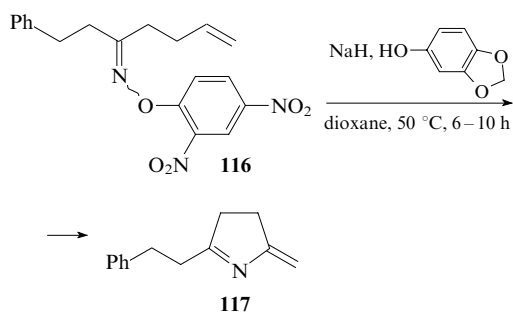


Examples of an intramolecular nucleophilic attack of a phenoxide ion on the nitrogen atom in an acetylated oxime function are known²⁰¹. Thus the treatment of *O*-acetyloximes **114** with potassium carbonate in benzene leads to benzoisoxazoles **115**.

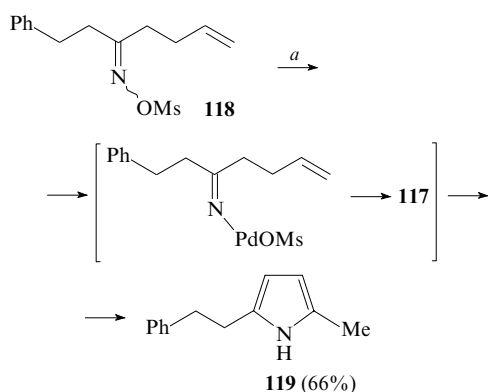


$R^1, R^2, R^3 = \text{H, Alk.}$

Reduction of *O*-2,4-(dinitrophenyl)oximes of γ,δ -unsaturated ketones **116** in the presence of a radical trap (3,4-methylenedioxyphenol) leads to cyclisation to pyrrolines **117**.²⁰²

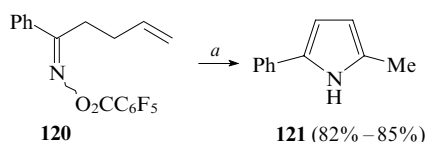


As a result of the aza-Heck intramolecular reaction, *O*-methylsulfonyloxime **118** is converted into pyrrole **119**, the yield of the expected Beckmann rearrangement products being 10% (see below, Section VI).²⁰³



(a) Pd(OAc)₂ (10 mol.%), P(*o*-Tol)₃ (30 mol.%), Et₃N, DMF, 80 °C, 0.5 h.

The use of *O*-acyloximes increases the regioselectivity of the process. Thus, irrespective of its configuration, *O*-pentafluorobenzoyloxime **120** undergoes Pd(0)-catalysed cyclisation to pyrrole **121**. The high yield of the product was explained by the absence of side Beckmann rearrangement.²⁰³



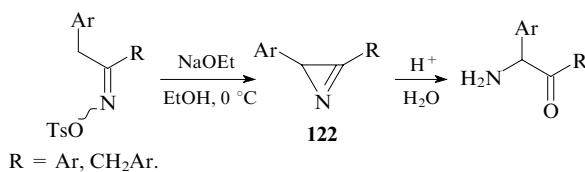
(a) (1) Pd(PPh₃)₄ (3 mol.%–10 mol.%), Et₃N, DMF, 80 °C, 1 h;
(2) Me₃SiCl, CH₂Cl₂, 20 °C, 0.5 h.

This version of the aza-Heck reaction is a simple approach to the synthesis of 2,5-disubstituted pyrroles provided oximes of the types **118** and **120** are available. Surveys^{195, 204} show several more examples of such cyclisation and also discuss relevant publications^{205–211} describing intramolecular nucleophilic substitution reactions at the oxime nitrogen atom that involve unsaturated substituents and proceed under the action of, *e.g.*, Ni(0)²¹⁰ and copper salts.^{211–217} Similar reactions that lead to quinoxalines and 2*H*-dihydropyrroles were considered.²¹⁸

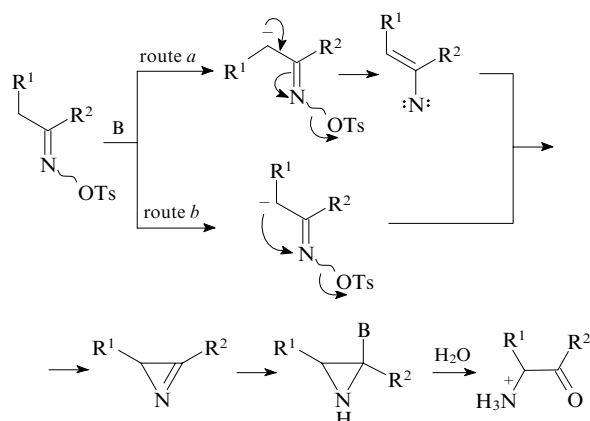
b. The Neber rearrangement

The mechanisms of the Neber and the Hoch–Campbell reactions (see Section IV.1.c) assume the formation of intermediate azirines as the key stage. Intramolecular nucleophilic substitution of the groups at the oxime nitrogen atom is realised by a carbanion, which is generated as a result of the abstraction of an α -proton under the effect of bases. It thus seems reasonable to discuss these reactions in the Section devoted to the nucleophilic attack on the C=N bond.

The Neber rearrangement^{84, 219–229} represents a transformation of ketoxime sulfonates into α -amino ketones in the presence of bases. In certain cases, intermediate azirines **122** were isolated from the reaction mixtures.^{226–229}

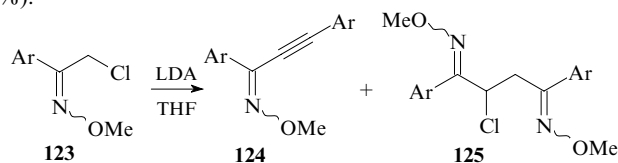


Two possible mechanisms of the rearrangement were proposed,^{227, 230} namely, the nitrene mechanism (route *a*) and the anionic mechanism (route *b*).



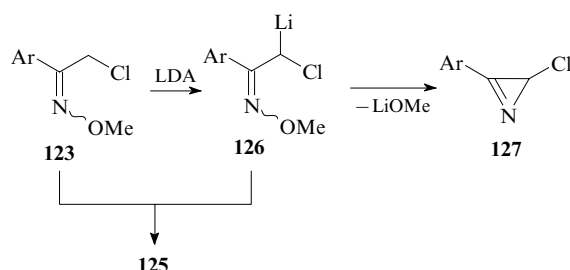
The mechanism of the Neber rearrangement was also considered in other studies.^{231, 232} The use of chiral quaternary ammonium salts as the phase-transfer catalysts allowed preparation of optically active amino ketones (*ee* reaches 70%).²³² This suggests that the reaction follows the anionic route *b*, because the route *via* nitrenes should lead to the loss of stereochemical information transferred in the deprotonation of oxime upon the action of a chiral base.

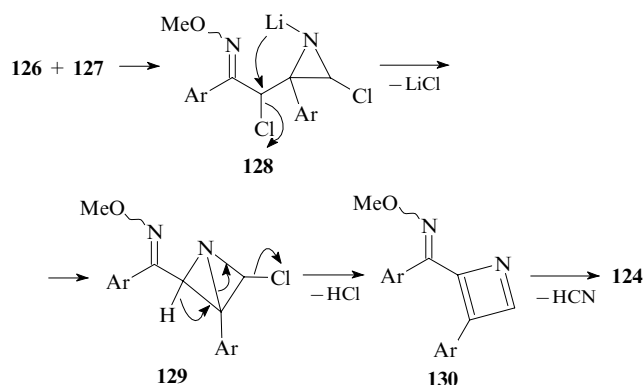
The reaction of *O*-methyloximes of substituted α -chloro acetophenones **123** with LDA leads to *O*-methyloximes of 1,3-diarylpopyn-1-ones **124** and bis(*O*-methyloximes) of 1,4-diketones **125** (in certain cases, *e.g.*, for Ar = Ph, their yield reaches 38%).²³³



Ar = Ph, 4-MeOC₆H₄, 4-BrC₆H₄, 2-naphthyl.

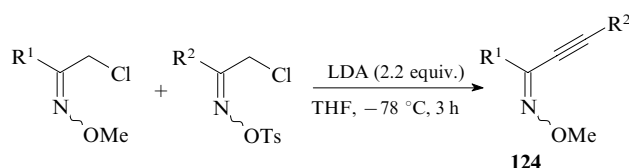
Bisoximes **125** are formed in the reaction of the starting substrate with its lithiation product **126**, while alkynyloximes **124** are formed as a result of several rearrangements *via* chloroazirines **127**.





It was assumed²³³ that, first, aziridine **128** is formed from chloroazirine **127** and its lithium derivative **126**, which is followed by a two-step fragmentation of the intermediate 1-aza-2-chlorobicyclo[1.1.0]butane **129**. Its dehydrochlorination with ring-opening yields unstable azacyclobutadiene **130**, which decomposes into alkyloxime **124** and HCN. In certain experiments (e.g., for Ar = 4-ClC₆H₄), the addition of MgBr₂ to the reaction mixture substantially increases the yield of alkyloximes **124** (from 19% to 70%), which at best reaches 81%.

In reactions of two different α -chlorooximes one of which has a good leaving group (TsO, EtCO₂) at the nitrogen atom, cross-coupling occurs.²³³ As a result, alkyloximes **124** with different substituents are formed. If an oxime has no bulky groups (e.g., *tert*-butyl), the reaction proceeds stereoselectively.



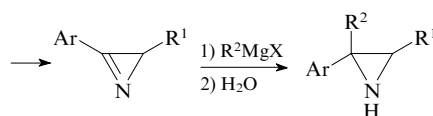
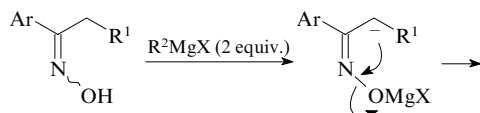
R ¹	R ²	Yields of compounds 124 (%)	Ratio Z : E
Me	Ph	57	> 95 : 5
Bu ^t	Ph	63	62 : 38
cyclo-C ₅ H ₉	Ph	73	> 95 : 5
n-C ₈ H ₁₇	Ph	69	> 95 : 5
Ph	4-ClC ₆ H ₄	73	94 : 6
4-MeOC ₆ H ₄	Ph	68	> 95 : 5
4-ClC ₆ H ₄	Ph	65	> 95 : 5

The Neber rearrangement was used for the synthesis of compounds that can influence the cardiovascular system,^{234,235} exhibit antipsychotic activity²³⁶ and are potential histamine antagonists (H₂).²³⁷

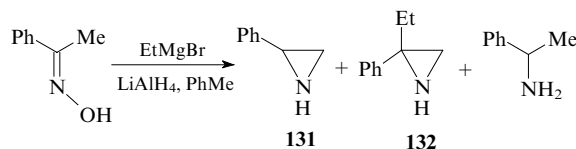
c. The Hoch–Campbell reaction

Hoch²³⁸ and Campbell^{239–242} have independently discovered that, when treated with Grignard reagents, ketoximes afford aziridines in the yields varying from low to moderate. Later, this reaction was used in the synthesis of various compounds of this class.^{101, 108, 243–248} Upon hydrolysis, the aziridine ring opens to yield amino alcohols.²³⁹

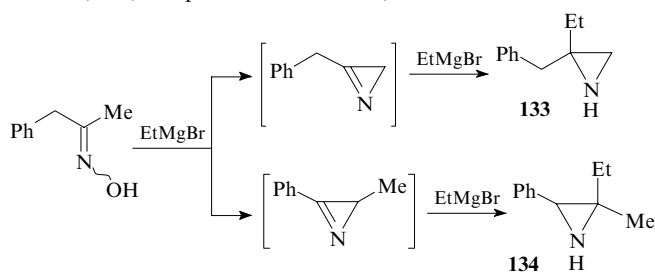
Formally, the Hoch–Campbell reaction is similar to the Neber rearrangement, because it involves a nucleophilic attack of a carbanionic centre on the oxime nitrogen atom.²¹⁹



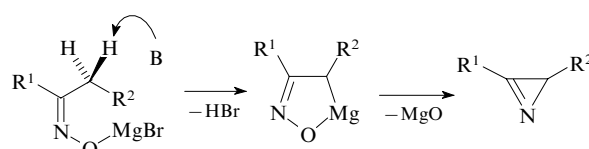
A mixture of aziridines **131** and **132** with α -phenylethylamine in the 64 : 1 : 35 ratio was isolated upon the reaction of acetophenone oxime with EtMgBr in the presence of LiAlH₄. The formation of aziridine **131** confirms the role of azirines as the intermediates in this reaction.²⁴⁹



By the example of benzyl methyl ketoxime, it was shown²⁴⁴ that the formation of an azirine ring is stereospecific in toluene. This reaction preferentially involves a substituent in the *syn*-position with respect to the hydroxyl group of the oxime function and produces aziridine **133**. However, in THF both possible isomers, *viz.*, compounds **133** and **134**, are formed.



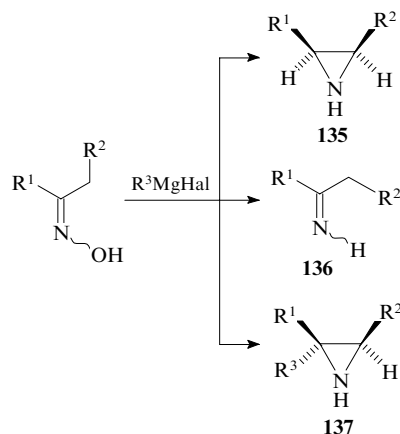
It was assumed¹⁰¹ that the cationoid Mg atom favours the proton abstraction from the *syn*-methylene group due to the intramolecular stabilisation of the carbanionic centre formed.



B = AlkMgBr.

The preferential involvement of *syn*-methylene groups in the formation of aziridines was also observed in the reaction of *O*-alkylketoximes with the Grignard reagents.³⁶ The steric effect of substituents in the azirine ring determines the stereoselectivity of the addition of an organomagnesium compound to the intermediate azirine.²⁴⁴

Three types of compounds, namely, aziridine **135**, ketimine **136** and a product of the Hoch–Campbell reaction **137**, were

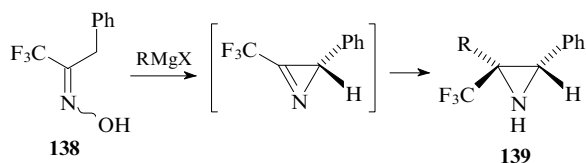


R¹, R² = Alk, Ar; R³ = Bu^t, Cy.

obtained in a reaction of a series of aliphatic and aromatic ketoximes with organomagnesium derivatives.²⁵⁰

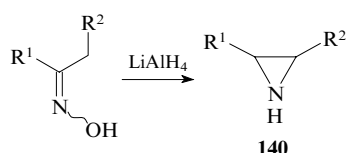
The result of this reaction depends strongly on the nature of both the oxime and the Grignard reagent used. Thus cyclohexanone oxime is converted exclusively into the Hoch–Campbell reaction products **137** [$R^1 - R^2 = (CH_2)_4$], whereas benzophenone oxime and camphor oxime form only ketimines **136**. Among all organomagnesium compounds used, isobutylmagnesium bromide showed the best results in the reductive formation of aziridine, whereas in the case of phenethyl- and 2,2-diphenylethylmagnesium bromides the reaction did not follow this pathway.

Trifluoromethylaziridines **139** were synthesised in reactions of trifluoromethyl ketoxime **138** with Grignard reagents.^{251, 252}



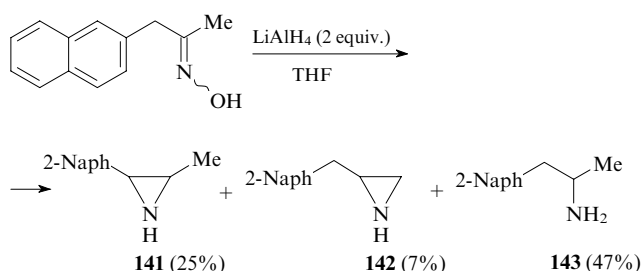
$R = \text{Alk, All.}$

Substituted aziridines **140** are formed together with amines in reactions of oximes with lithium aluminium hydride.^{253, 254} It is evident that this kind of transformation can be considered as an analogue of the Hoch–Campbell reaction.



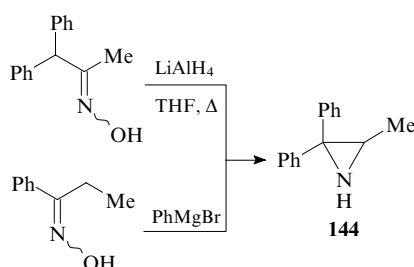
$R^1, R^2 = \text{H, Alk, Ar.}$

Reflux of a mixture of *syn*- and *anti*-isomers (1 : 4) of β -naphthylpropan-2-one oxime with 2 equivalents of LiAlH_4 in THF yields *cis*-3-methyl-2-(β -naphthyl)aziridine **141**, 2-(β -naphthylmethyl)aziridine **142** and a primary amine **143**.²⁵⁴



Naph = naphthyl.

Reduction of 1,1-diphenylpropan-2-one oxime with lithium aluminium hydride in boiling THF produces 3-methyl-2,2-diphenylaziridine **144** in 41% yield.²⁵³ Its structure was also confirmed by an independent synthesis according to the Campbell method from ethyl phenyl ketoxime and PhMgBr .²⁴¹



It was noted²⁵³ that the methyl group is involved in the formation of an aziridine ring upon the reduction of 1-alkyl-1-

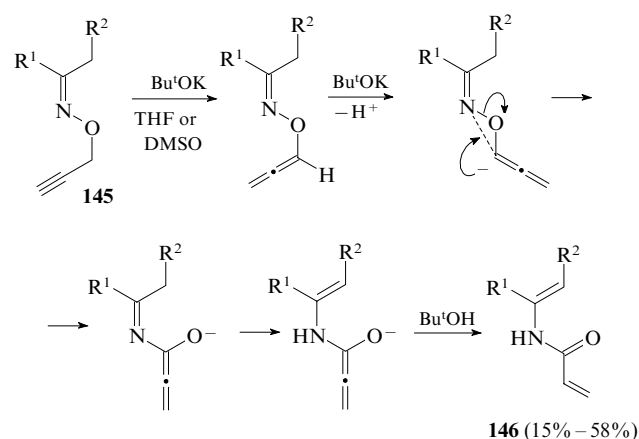
phenylpropan-2-ones with LiAlH_4 . Thus the reactions of 1-methyl-1-phenyl- and 1-ethyl-1-phenylpropan-2-ones produced, in addition to primary amines, 2-(1-phenylethyl)- and 2-(1-phenylpropyl)aziridines in 38% and 31% yields, respectively. Under similar conditions, aldoximes also form aziridines in 38% yield, whereas the attempts to obtain aziridines from *O*-tosylaldoximes by the Neber reaction failed.²¹⁹

Reduction of di(*p*-methylbenzyl) ketone oxime and its acyl derivatives with LiAlH_4 in THF proceeds stereospecifically to give *cis*-aziridines (yields > 80%).²⁵⁵ Complex hydride $\text{NaAlH}_2(\text{OC}_2\text{H}_4\text{OMe})_2$ exhibits higher selectivity, it reduces ketoximes and their ethers into substituted aziridines in high yield with only trace amounts of amines.²⁵⁵

Thus, the conversion of oximes into aziridines under the action of LiAlH_4 and related hydrides resembles the reactions with organomagnesium compounds: in both cases aziridines are the intermediates which are formed in an intramolecular nucleophilic attack of the α -carbanionic centre on the oxime nitrogen atom.²⁵⁶

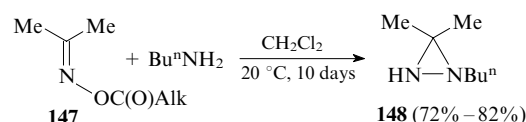
d. Miscellaneous reactions

In closing this Section, we consider two examples of the nucleophilic attack on the $\text{C}=\text{N}$ bond. Thus it is assumed that the intramolecular nucleophilic substitution at the oxime nitrogen atom is the key stage of the mechanism of strong-base-induced rearrangement of *O*-propargylketoximes **145** into *N*-1-alkenylacrylamides **146**.²⁵⁷



$R^1 = \text{Alk, Ar; } R^2 = \text{H, Alk; } R^1 - R^2 = (\text{CH}_2)_n; n = 3, 4.$

Carbon and nitrogen atoms in the $\text{C}=\text{N}$ bond manifest simultaneously their electrophilic properties in the reaction of acetone oxime esters **147** with butylamine to give diaziridine **148**.²⁵⁸



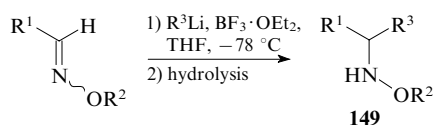
For similar acetaldoxime derivatives, the yield of diaziridine is only 16% due to the concomitant elimination of the acid AlkCO_2H .

2. Addition of organometallic compounds to the $\text{C}=\text{N}$ bond

The reaction of organometallic compounds with oximes or their ethers is of interest for the synthesis of hydroxylamines. Addition of alkyl- or phenyllithium to unprotected oximes requires a substantial excess of the organolithium compound.²⁵⁹ Moreover, the presence of active α -hydrogen atoms relative to the oxime function substantially reduces the yield of the adduct.

Lewis acids favour the reaction of organometallic compounds with the oxime group probably due to the coordination to nitrogen and oxygen atoms, which increases the positive charge on the carbon atom. Thus in the presence of 1 equivalent of $\text{BF}_3 \cdot \text{OEt}_2$,

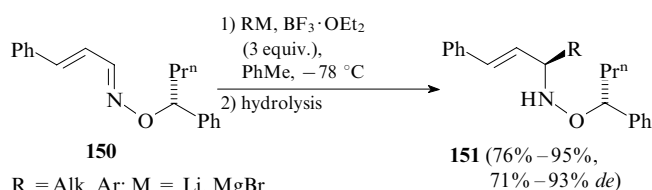
(het)aryllithium compounds add to aldoxime ethers to form *O*-alkylhydroxylamines **149** (in yields up to 64%).²⁶⁰



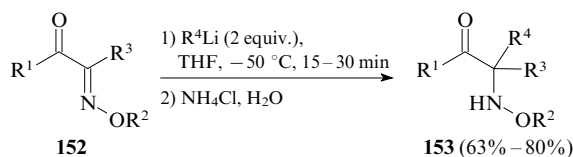
R¹ = Me, Prⁱ; R² = Me, Buⁿ; R³ = Ar, Het.

In this case, the oxime group configuration has a strong effect on the yield of the reaction product, which is substantially higher for *Z*-isomers.²⁶⁰

The addition of organolithium and organomagnesium compounds to (*R*)-*O*-(1-phenylbutyl)cinnamaloxime **150** was used as the key stage in asymmetric synthesis of α -amino acids.²⁶¹ The highest yields of adducts **151** were achieved in reactions with alkyl(or aryl)lithium.



The reaction of organolithium compounds with oximes of α -oxo carboxylic acids, their esters and amides **152** produces derivatives of *N*-hydroxy amino acids **153**.²⁶²



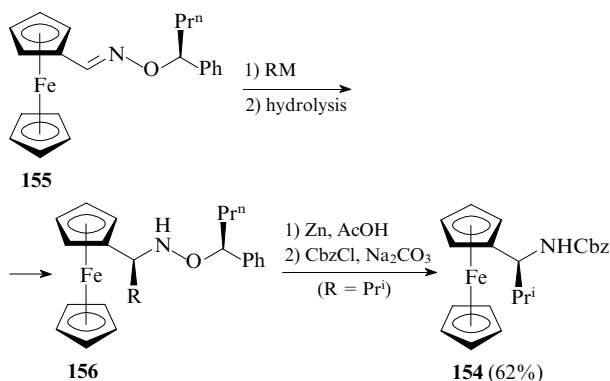
R¹ = OH, OMe, OBu^t, NMePh; R² = Bn, PhCHMe; THP;

R³ = H, Me; R⁴ = Me, Buⁿ, Bu^s, Bu^t, Ph;

THP is tetrahydropyran-2-yl.

High yields of products of this reaction were explained by the activating effect of the acceptor substituent at the oxime function. However, organomagnesium and organozinc compounds do not react with oximes **152** under these conditions.²⁶²

A series of chiral ferrocenylalkylamines (*e.g.*, compound **154**) were synthesised by diastereoselective 1,2-addition of organometallic reagents to esters of ferrocenecarbaldehyde oxime **155** containing a chiral substituent, which was followed by reduction of hydroxylamines **156** formed.²⁶³

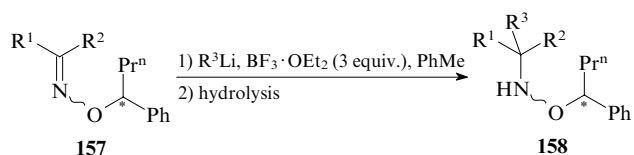


156: R = Prⁱ (85%), Buⁿ (81%), All (70%);

M = Li, MgHal; Cbz is benzyloxycarbonyl.

Recently, an asymmetric synthesis of α -amino acids, which is based on diastereoselective addition of organolithium compounds (2-furyllithium, phenyllithium, vinylolithium) to (*R*)- and (*S*)-*O*-(1-

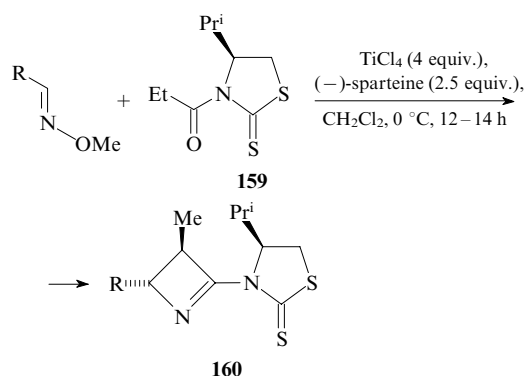
phenylbutyl)oximes **157** was carried out.²⁶⁴ The corresponding hydroxylamines **158** were obtained with high diastereoselectivity (the configuration of the new chiral centre is given first).



R ¹	R ²	R ³	Yield (%)	de (%) (configuration)
Pr ⁱ	Me	2-furyl	31	52 (<i>R,S</i>)
4-BrC ₆ H ₄	Me	2-furyl	14	> 95 (<i>R,S</i>)
4-BrC ₆ H ₄ CH ₂	H	2-furyl	40	83 (<i>S,R</i>)
Pr ⁱ	H	Ph	38	95 (<i>R,S</i>)
Bu ^t	H	Ph	31	> 98 (<i>R,S</i>)
EtMe ₂ C	H	Ph	32	> 98 (<i>R,S</i>)
Pr ⁿ	H	H ₂ C=CH	87	84 (<i>R,S</i>)
Pr ⁱ	Me	H ₂ C=CH	54	> 95 (<i>S,R</i>)
H ₂ C=CH(CH ₂) ₂	H	H ₂ C=CH	77	94 (<i>R,S</i>)
Cy	H	H ₂ C=CH	74	92 (<i>S,S</i>)
Ph	H	H ₂ C=CH	46	98 (<i>S,S</i>)

Reductive cleavage of the N–O bond in hydroxylamines **158**, followed by a series of successive transformations produces *N*-substituted amino acids and their esters.²⁶⁴

O-Methyloximes add chlorotitanium enolate of *N*-propionylthiazolidine-2-thione **159** to form azetine **160**.²⁶⁵

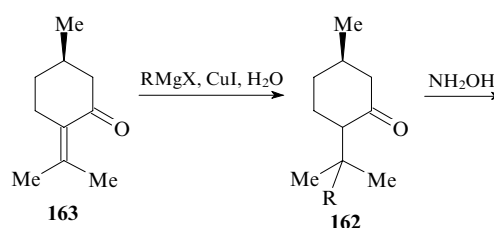


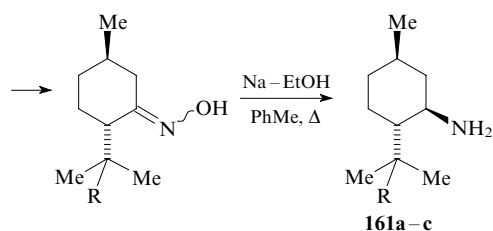
R = Cy, Ph, styryl, 1-naphthyl, 2-thienyl.

3. Reduction of oximes

Depending on the reagent nature, the reduction of oximes may produce amines, hydroxylamines or alcohols. As a rule, alkali metals or complex metal hydrides are used as the reducing agents. The key stage of this reaction is the transfer of a hydride ion or an electron to the antibonding orbital of the C=N bond to form an N-anion or a radical anion. Below, different types of reagents used in the oxime reduction are considered.

Oximes are smoothly reduced with sodium in liquid ammonia to form amines.²⁶⁶ Optically pure menthylamine (**161a**), (–)-8-methylmenthylamine (**161b**) and (–)-8-phenylmenthylamine (**161c**) were prepared from the available menthone (**162**, R = H) and (+)-pulegone (**163**) by reduction of the corresponding oximes with the Na–ethanol system in refluxing toluene.²⁶⁷

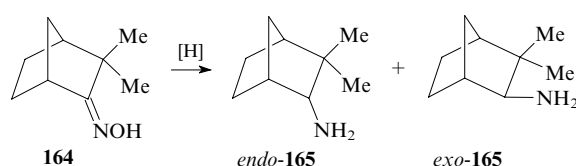




R = H (**a**, 59%), Me (**b**, 67%), Ph (**c**, 93%).

Refluxing of ketoximes in THF in the presence of LiAlH_4 usually leads to aziridines in addition to amines (yields up to 47%).^{253,255} TiCl_4 or FeCl_3 additives to lithium aluminium hydride make the process more selective in the case of oximes of chroman-4-one, acetophenone and benzophenone. The corresponding amines were obtained in 60%–70% yields.²⁶⁸

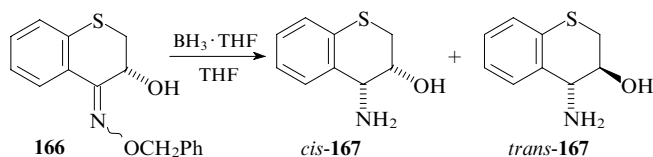
A search for reagents for the reduction of camphenylone oxime **164** was carried out²⁶⁹ with the aim of preparing *endo*-2-camphenylamine **165**.



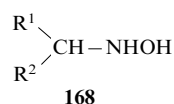
Systems LiAlH_4 –THF (product **165** is formed in 72% yield, the ratio *endo*:*exo* = 5 : 3), NaBH_4 – TiCl_4 –glyme (76%, 100 : 0) and Na – Pr^nOH (78%, 100 : 0) have proved to be effective.

In the presence of chiral additives, the asymmetric reduction of oximes is possible. Thus a complex of lithium aluminium hydride with 3-*O*-benzyl-1,2-*O*-cyclohexylidene- α -D-glucopyranose reduces different aliphatic and aromatic ketoximes and their methyl and tetrahydropyranyl ethers to chiral amines in low or moderate optical yields.²⁷⁰ The best enantioselectivity (56% *ee*) was achieved in the reduction of methyl cyclohexyl ketoxime.

Borane and its complexes are widely used for the reduction of various oximes. For example, the possibility of stereoselective reduction of cyclic α -hydroxy *O*-benzylketoxime **166** with borane to form 1,2-aminoalcohol **167** was demonstrated.²⁷¹ The yields were in the range 68%–86%, the mixture preferentially contained the *cis*-isomer (68%–92% *de*).

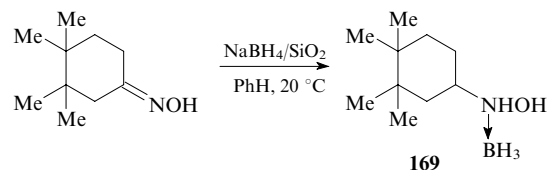


Pyridine–borane is a selective reductive system. Upon the action of this reagent, oximes are converted into substituted hydroxylamines in high yields; other functional groups (ester, nitrile, nitro groups) remaining unaffected.²⁷² Thus the pyridine–borane complex prepared by reaction of pyridine hydrochloride with sodium borohydride reduces oximes of aliphatic and aromatic ketones and of aromatic aldehydes to the corresponding hydroxylamines **168** in 74%–92% yields.²⁷³ This method can also be applied for the efficient reduction of *O*-acyl- and *O*-methyloximes.²⁷⁴

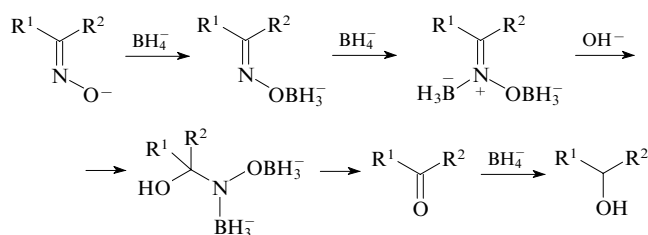


$\text{R}^1 = \text{H}$; $\text{R}^2 = \text{Ph}$, 3- $\text{NO}_2\text{C}_6\text{H}_4$, 4- CNC_6H_4 , 4- ClC_6H_4 ; $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{PhCH}_2\text{CH}_2$; $\text{R}^1 = \text{Pr}^n$; $\text{R}^2 = \text{Pr}^n$, Ph .

Sodium borohydride is also an efficient reducing agent under various conditions. For example, silica gel-supported NaBH_4 reacts with oximes at room temperature in benzene to form borane complexes of hydroxylamines **169**.²⁷⁵

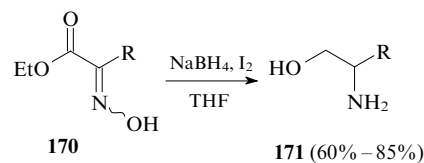


Refluxing of oximes with sodium borohydride in aqueous alkali affords alcohols formed upon reduction of the corresponding ketones.²⁷⁶



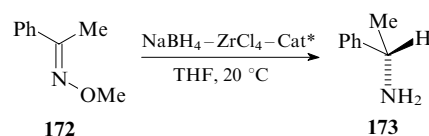
$\text{R}^1, \text{R}^2 = \text{Alk}$.

Oximes of α -oxo esters **170** are reduced with sodium borohydride in THF in the presence of I_2 , AcOH , TiCl_4 , ZrCl_4 , CoCl_2 , H_2SO_4 and Me_3SiCl to the corresponding amino alcohols **171**.²⁷⁷



R = Me, Et, Pr^i , Buⁿ, Ph.

The reduction of *O*-alkylketoximes with a system NaBH_4 – ZrCl_4 modified with chiral amino alcohols was studied.²⁷⁸ For example, reduction of acetophenone *O*-methyloxime **172** afforded (*S*)-1-phenylethylamine **173** in 89%–96% yield and optical purity of 42%–95% *ee*.

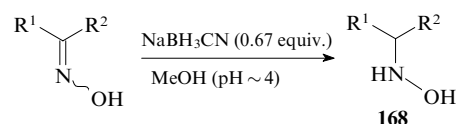


Cat* is (*S*)-valinol, 1,1-diphenyl-(*S*)-valinol, (*S*)-leucinol, (*S*)-isoleucinol.

Among amino alcohols studied, (*S*)-valinol and 1,1-diphenyl-(*S*)-valinol exhibit the highest enantioselectivity.

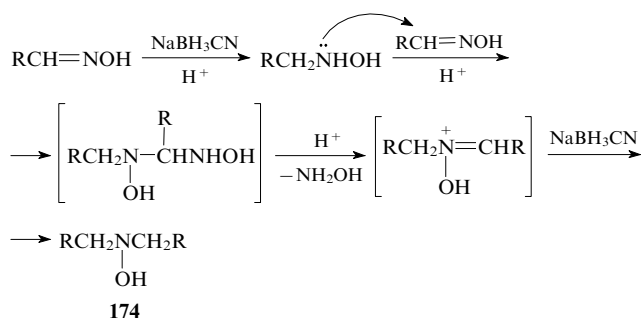
Sodium cyanoborohydride is often used as the reducing agent. Thus cyclisation of oxime ethers of 2-(3-hydroxyphenyl)ethyl ketones into the corresponding quinolines under the action of NaBH_3CN is accompanied by the formation of hydrogenated derivatives.²⁷³

Ketone oximes are smoothly reduced with sodium cyanoborohydride in weakly acidic media (pH ~4) to form the corresponding *N*-alkylhydroxylamines **168**.²⁷⁹



R ¹	R ²	Time /h	Yield (%)
Me	Et	3	73
Me	Ph	1	75
	(CH ₂) ₄	3	77
	(CH ₂) ₅	3	66

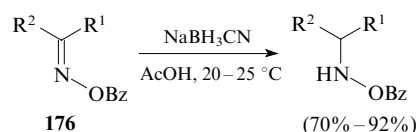
Under these conditions, aldoximes undergo reductive *N*-alkylation to form bisalkylated hydroxylamines **174**.²⁷² These products may have been formed as a result of the following sequence of reactions:



A decrease in the pH of the medium (down to ~3) allows one to substantially diminish the contribution of this process and synthesise monoalkyl derivatives **175**. The change in the reaction pathway is explained²⁷² by the acceleration of the oxime group reduction.

RCH=NOH		pH~4	$\text{(RCH}_2\text{)}_2\text{NOH}$
		pH~3	RCH_2NHOH
			175
Compound	R	Time /h	Yield (%)
174	n-C ₆ H ₁₃	3	57
	Ph	4	60
175	n-C ₆ H ₁₃	1	33
	Ph	1	79

Sodium cyanoborohydride in acetic acid reduces *O*-benzoyloximes of aliphatic ketones **176** to the corresponding *O*-benzoylhydroxylamines.²⁷⁴



R¹–R² = (CH₂)₄, (CH₂)₅, (CH₂)₂CH(Bu^t)(CH₂)₂, (CH₂)₁₁;
R¹ = Bn, R² = Me.

The reduction of ethers of oximes of aromatic aldehydes and ketones proceeds much more slowly than the decomposition of sodium cyanoborohydride under the action of acetic acid. For this reason, the reduction of the C=N bond in these compounds is ineffective under these conditions.

Triethylsilane in trifluoroacetic acid is a good alternative to sodium cyanoborohydride. This system makes it possible to reduce the above-mentioned benzoyloximes **176** (yields 73%–95%) and ethers of oximes of aromatic aldehydes to hydroxylamines.²⁷⁴

The hydrazine–Raney Ni system in aqueous or aqueous ethanolic solutions easily reduces ketoximes to the corresponding amines; under these conditions, aldoximes do not react.²⁸⁰

4. Deoximation

Deoximation is a method of conversion of oximes into carbonyl compounds. In the general case, this reaction assumes a primary attack of an O-centred nucleophile (H₂O or OH[–]) on the carbon atom of the C=N bond. Apparently, the rate of the process will increase with an increase in the electrophilicity of the carbon atom of the C=N bond or the nucleophilicity of the O-nucleophile. The formation of complexes with Lewis acids (or protonation) and the oxidation of the oxime group should enhance the former parameter, while the use of superbasic media (such as KOH–DMSO) should enhance the latter parameter. The examples shown below agree well with these assumptions.

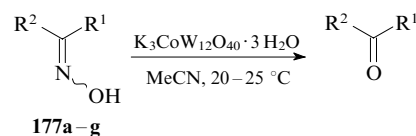
The deoximation reaction is widely used in organic synthesis and analysis, for example, in purification and identification of carbonyl derivatives.²⁸¹ Deoximation of oximes synthesised by nitrosation of active methylene groups in different organic compounds and also by condensation of nitroalkenes with aldehydes,²⁸² is the key stage in the synthesis of certain carbonyl compounds.²⁸¹ The oxime group can play a protective role and also selectively activate α-methylene groups;²⁸³ hence, the studies aimed at the conversion of oxime groups into carbonyl ones are topical. Deoximation in basic media is a less common and less efficient reaction as compared with the acid-catalysed process. However, it is of interest, first of all, as a method for synthesising carbonyl compounds from oximes that contain groups unstable in the presence of acids.²⁸¹ Oxidation of alkali metal ketoximates with, e.g., fluorochlorate, is often used for regeneration of ketones.²⁸⁴

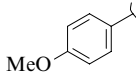
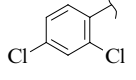
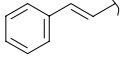
Deoximation of sodium aldoximates and ketoximates with CuCl₂·H₂O in acetonitrile proceeds much faster and, in certain cases, leads to higher yields of carbonyl compounds as compared with deoximation of neutral oximes.²⁸⁵ This is explained²⁸⁵ by the greater susceptibility of oximates to oxidation due to the higher energy of the highest occupied molecular orbital (HOMO) and larger negative charge of the oximate anion, which favour the interaction with the electrophilic centre of the oxidant.

Deoximation is sometimes a side process, e.g., in the synthesis of pyrroles from ketoximes and acetylenes in superbasic media by the Trofimov reaction.^{88, 145–156}

At present, deoximation methods are being actively studied.^{286–300} In the past two years, several new efficient methods were developed for the removal of the oxime protection under mild conditions.^{296, 301–305}

One of modern methods of deoximation is based on the use of potassium salt of cobalt-tungstic heteropolyacid K₃CoW₁₂O₄₀·3H₂O, which is an inexpensive and easily recoverable heterogeneous catalyst.²⁹⁶ The reaction proceeds in acetonitrile at room temperature, the products are formed in good yields. This method allowed the conversion of various aldoximes and ketoximes, e.g., compounds **177a–g**, into carbonyl compounds.



Compound	R ¹	R ²	Time /min	Yield (%)
177				
a		H	60	95
b		H	45	90
c		H	30	93

Compound 177	R ¹	R ²	Time /min	Yield (%)
d		H	45	86
e		Me	90	92
f			90	90
g			60	85

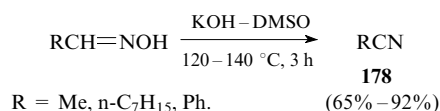
The fact that in this case the removal of the oxime protection is not accompanied by the oxidation of the liberated aldehyde function (in contrast to other reactions of oxidative hydrolysis) is an important advantage of the proposed method. Even sterically hindered camphor oxime **177g** is successfully converted under these conditions into camphor with high yield, while the oxime of α,β -unsaturated aldehyde **177c** undergoes chemoselective deoxygenation with the retention of the double bond and its configuration. It should be noted that deoxygenation of optically active oxazolidine **177d** containing an aldoxime function in the α -position with respect to the asymmetric carbon atom did not affect the chiral centre configuration.²⁹⁶

Among other recently developed deoxygenation methods, cleavage of oximes with antimony pentachloride (CH_2Cl_2 , 0 °C – room temperature, the carbonyl compound is formed in 75%–92% yields),³⁰¹ hydrolysis of oximes in the presence of iodobenzoic acid and β -cyclodextrin (room temperature, yields 82%–96%)³⁰² and oxidative hydrolytic cleavage of oximes with *N*-bromosaccharin under microwave irradiation (acetone, H_2O , 2–3 min, yields 88%–97%)³⁰³ deserve mention.

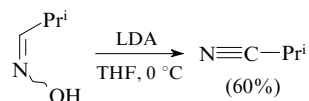
V. Dehydration

Dehydration of aldoximes, like deoxygenation, is usually carried out with acidic reagents.³⁰⁶ However, when aldoximes contain groups sensitive to acids, the conversion of aldehydes into nitriles by elimination of water from the oxime group can be accomplished in basic media, *i.e.*, via oximate anions.

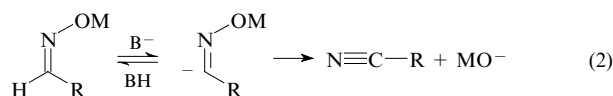
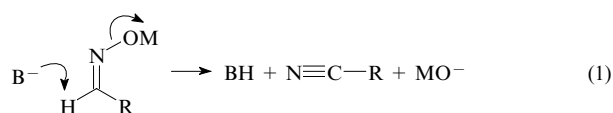
An effective synthesis of nitriles **178** by dehydration of aldoximes on heating in a superbasic system (KOH – DMSO) is described.^{88, 307}



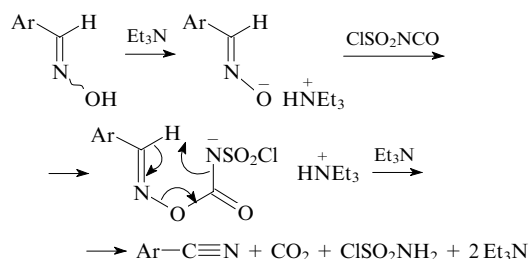
Elimination of water from aldoximes can occur under the action of such a base as LDA.³⁹



Most probably, the aforementioned elimination processes follow the E2 [reaction (1)] and/or E1cB [reaction (2)] mechanisms.



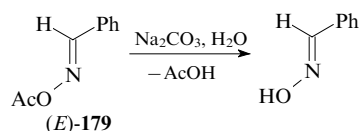
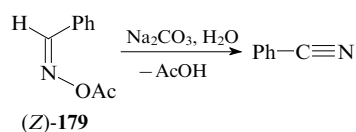
The following mechanism was proposed³⁰⁸ for the dehydration of aromatic aldoximes to nitriles with chlorosulfonyl isocyanate in triethylamine (yields 74%–87%):



In the presence of triethylamine, the elimination of water from aldoximes also occurs under the action of SCl_2 , S_2Cl_2 , Cl_3CSCl , PhSCl , PhSeCl , PhSe(O)Cl (in Et_2O or CHCl_3)³⁰⁹ or succinimide-sulfonium (in triethylamine).³¹⁰

The rate of elimination of water or alcohols (in the case of oxime ethers) depends on the configuration of the aldoxime function. Thus upon dehydration in the system $(\text{CF}_3\text{CO})_2\text{O}$ –pyridine (ratio 1 : 4, 3 h, room temperature), (*E*)-benzaloxime is transformed into benzonitrile in 38% yield, whereas for its *Z*-isomer the yield is 90%.³¹¹ For *E*-isomers, the yields increase in the presence of excess of pyridine or with triethylamine and with an increase in the reaction temperature. At high temperatures, the nitrile yield is independent of the configuration of the original oxime due to easier *E*–*Z*-isomerisation of the oxime.

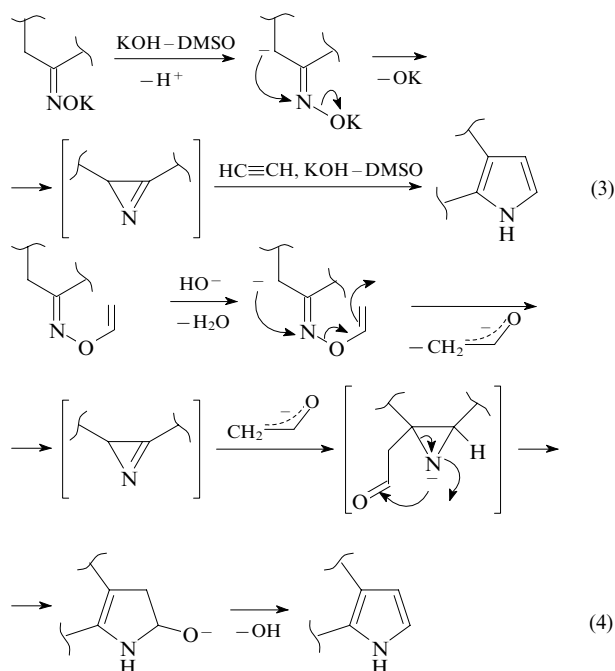
Unstable (*Z*)-benzaloxime acetate **179** obtained on treatment of the corresponding oxime with acetic anhydride readily loses acetic acid even upon slight heating in a sodium carbonate solution. At the same time, under similar conditions, the *E*-form is converted into the original oxime rather than nitrile.³¹²



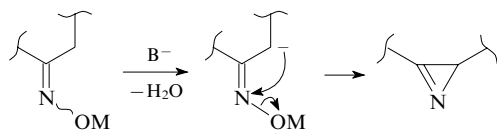
In the water–dioxane system (4 : 1, 25 °C), the base-catalysed elimination of alcohols (phenols) from substituted *O*-alkyl(aryl)-benzaloximes takes place to afford the corresponding substituted benzonitriles.³¹³ Under these conditions, the elimination rate is higher by a factor of several tens for *Z*-oximes as compared with *E*-isomers. In the case of *E*-isomers, the rate of *syn*-elimination increases when electron-withdrawing groups are present in the leaving group and/or in the aromatic substituent at the oxime function. The elimination of phenols from (*E*)-*O*-arylbenzaloximes [$\text{Ar} = \text{Ph}$, 4- $\text{NO}_2\text{C}_6\text{H}_4$, 2,4-(NO_2) $_2\text{C}_6\text{H}_3$] proceeds smoothly in 60% aqueous DMSO under the action of hydroxide anions. As a result, benzonitriles are formed in quantitative yields.³¹⁴ The examples shown above suggest that the reaction

proceeds predominantly by the E2 mechanism, which is characterised by easier *anti*-elimination.

Earlier, it was assumed^{88, 157} that the synthesis of pyrroles from ketoximes and acetylene by the Trofimov reaction includes the stage of azirine formation. In this case, either 1,3-dehydration of the ketoxime, which is followed by the reaction of azirine formed with acetylene [reaction (3)], or elimination of vinyl alcohol (as acetaldehyde) from the intermediate *O*-vinyloxime followed by the addition of acetaldehyde as the enolate anion to azirine [reaction (4)] are possible. Both pathways lead to the formation of the pyrrole ring.



Although another mechanism is currently accepted, namely, a [3,3]-sigmatropic rearrangement of *O*-vinyloximes,^{88, 145–156} it is possible that the above-mentioned pathways are also realised in certain cases (or in parallel). This is confirmed by the fact that, being treated with strong bases, ketoximes undergo 1,3-dehydration and cyclise to azirines (the Hoch–Campbell reaction, see Section IV.1.c).^{239, 315, 316}

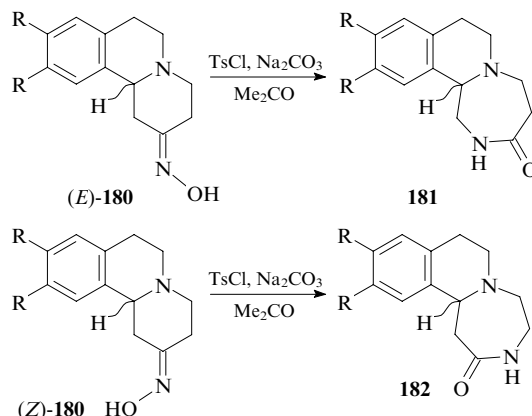


B = RMgX, LiAlH₄; M = MgX, AlH₄.

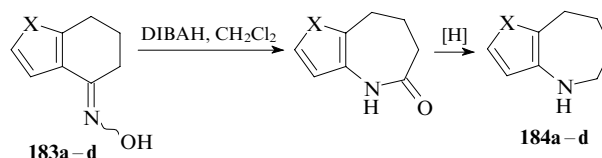
VI. The Beckmann rearrangement

The Beckmann rearrangement, *viz.*, the conversion of oximes into the corresponding amides, is traditionally considered as an acid-catalysed process.¹⁰⁸ The examples where it occurs in the presence of bases are less common; however, this is of particular preparative value for oximes with functions unstable in acidic media.

For example, the Beckmann rearrangement of *E*- and *Z*-oximes of benzoquinolizidones **180** into isomeric diazepinoisoquinolines **181**, **182** under the action of *p*-toluenesulfonyl chloride (TsCl) in the presence of Na₂CO₃ occurs with no side skeleton rearrangements typical of reactions in acidic media (yields 45%–50%).³¹⁷

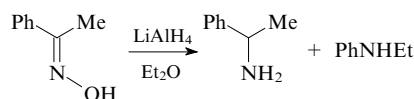


Ring expansion of the cyclohexanone oxime fragment fused to heterocycles in oximes **183a–d** under the action of diisobutyl aluminium hydride (DIBAH) results in tetrahydrofuro- (**184a**), -thieno- (**184b**) and -pyrrolo-[3,2-*b*]azepines (**184c,d**).³¹⁸ It is evident that the reaction proceeds through the reduction of an intermediate amine, namely, the Beckmann rearrangement product.

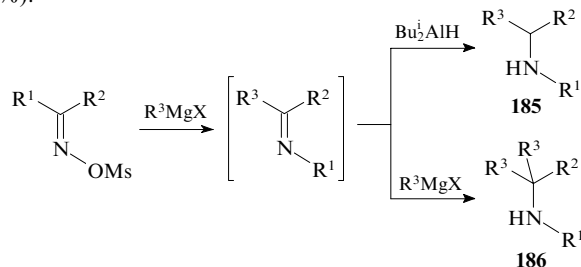


X = O (a), S (b), NH (c), NMe (d).

The reaction of acetophenone oxime with LiAlH₄ in ether produces, in addition to the expected α -phenethylamine, *N*-ethyl-aniline, a reduction product of the Beckmann rearrangement.³¹⁹

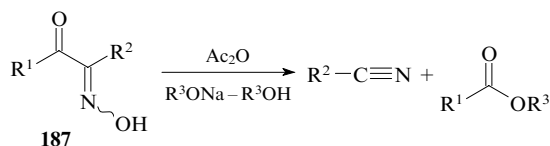


The action of organomagnesium compounds on methanesulphonates of cycloalkanone and acetophenone oximes results in the Beckmann rearrangement to give intermediate imines, which are reduced (with DIBAH) or converted (by the reaction with R³MgX) into amines **185** or **186**, respectively (yields up to 79%).³²⁰



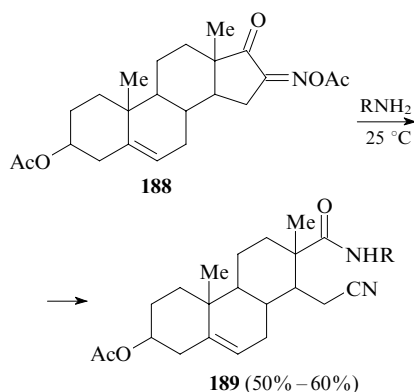
R¹ = Alk, Ar; R² = Alk; R³ = Alk, HC≡C, CH₂=CHCH₂, HC≡CCH₂; X = Cl, Br, I.

The second order Beckmann rearrangement can also proceed in the presence of bases. For example, under the action of acylating agents, monooximes of α -diketones **187** form nitriles in aqueous solutions of strong bases with elimination of carboxylic acids,³²¹ whereas in the presence of alcohols, the latter can form the corresponding esters.³²²



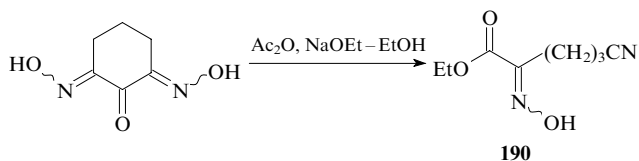
$\text{R}^1 = \text{Ph, Bn, CH=CHPh}; \text{R}^2 = \text{H, Me, Ph}; \text{R}^3 = \text{H, Me, Et}.$

Treatment of steroidal α -acetoxyimino ketone **188** with primary amines at 25 °C brings about the Beckmann rearrangement to give the corresponding amidonitrile **189**.³²³

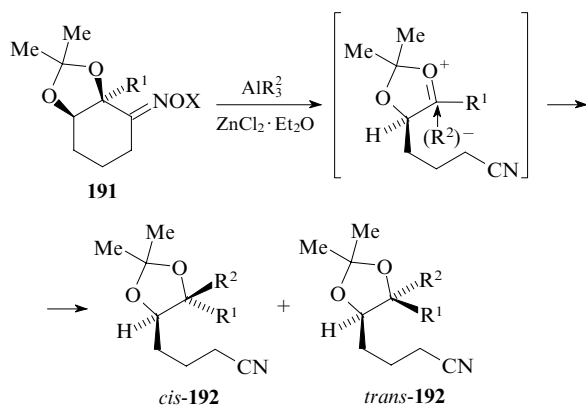


$\text{R} = \text{Pr}^n, \text{Bu}^n, \text{Bn}, (\text{CH}_2)_n\text{OH} (n = 2, 3).$

Treatment of cyclohexane-1,2,3-trione-1,3-dioxime with acetic anhydride in the NaOEt–EtOH system yields ethyl 2-hydroxyimino-5-cyanopentanoate (**190**).³²⁴

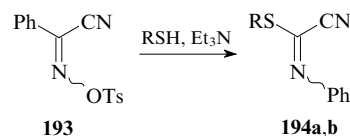


Being treated with organoaluminium compounds in the presence of ZnCl_2 , esters of oximes of 2-alkyl-2,3-isopropylidenedioxycyclohexanones **191** undergo the Beckmann fragmentation with simultaneous formation of a new carbon–carbon bond to form nitriles **192**. The latter exist as a mixture of geometrical isomers, the overall yield reaches 83%.³²⁵



$\text{X} = \text{Ac, 2,6-Cl}_2\text{C}_6\text{H}_3\text{C(O)}; \text{R}^1 = \text{H, Alk}; \text{R}^2 = \text{Alk, CH}\equiv\text{C}.$

In the presence of thiols and trimethylamine, oxime *p*-toluenesulfonate **193** is rearranged into imines **194a,b**. This transformation is similar to the Beckmann rearrangement.³²⁶

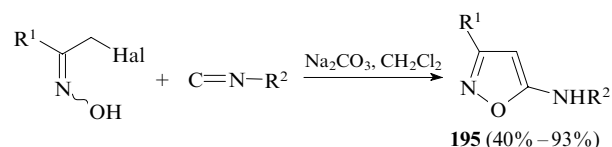


$\text{R} = \text{Et (a), Bn (b)}.$

VII. Reaction of oximes involving substituents

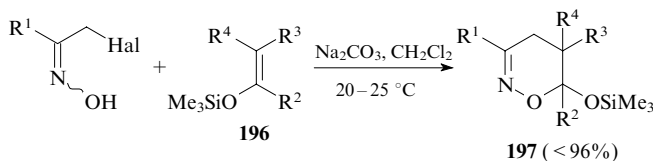
Many reactions of oximes in the presence of bases occur with simultaneous involvement of both the oxime function and the reaction centres of peripheral functional groups to give heterocyclic compounds. Below, we show several typical examples.

Oximes of α -halo ketones react with isocyanides in the presence of sodium carbonate to form 5-aminoisoxazoles **195**.³²⁷



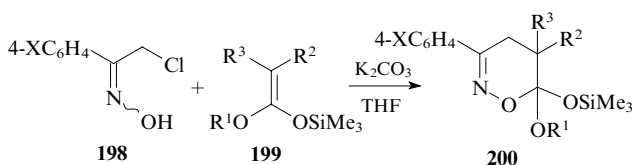
$\text{R}^1, \text{R}^2 = \text{Alk, Ar}; \text{Hal} = \text{Cl, Br}.$

Nitrosoalkenes are the intermediates in this reaction, which are converted into 5,6-dihydro-4*H*-oxazines in the presence of alkenes according to a mechanism of [4 + 2]-cycloaddition.³²⁸ For example, α -halo ketoximes react with trimethylsilyloxy alkenes **196** in the presence of Na_2CO_3 to form oxazines **197** (as a mixture of *cis*- and *trans*-isomers).³²⁹



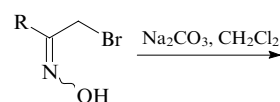
$\text{R}^1 = \text{Ph, CO}_2\text{Et}; \text{R}^2, \text{R}^3, \text{R}^4 = \text{H, Alk, OSiMe}_3.$

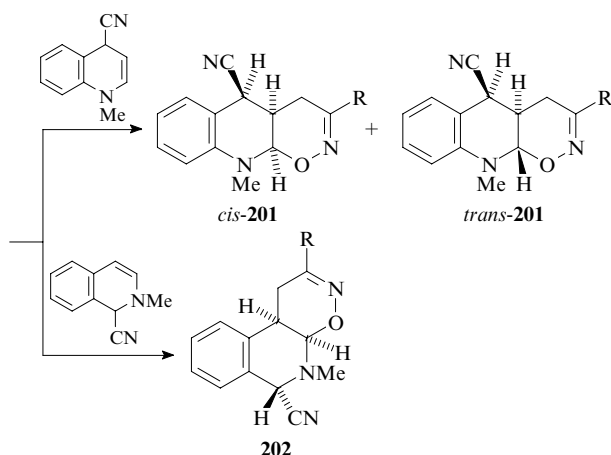
In a similar way, the reaction of oximes of substituted α -chloroacetophenones **198** with ketene silyl acetals **199** in the presence of K_2CO_3 in THF produces 6-alkoxy-3-aryl-6-trimethylsilyloxy-5,6-dihydro-4*H*-1,2-oxazines **200** in moderate yields.³³⁰



$\text{R}^1 = \text{H, Alk}; \text{R}^2 = \text{Alk, Ar}; \text{R}^3 = \text{Alk}; \text{X} = \text{H, Cl, Me, OMe}.$

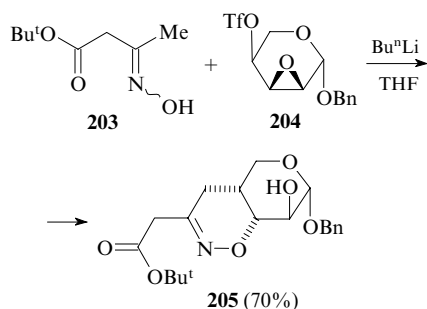
Substituted nitrosoalkenes obtained *in situ* from α -bromooximes add to dihydro(iso)quinolines to form fused oxazines **201** and **202**.³³¹





R = Ph, 4-NO₂C₆H₄, CO₂Et.

The reaction of β -keto ester oxime **203** with epoxypyranoside **204** under the action of butyllithium in THF produces oxazines **205** enantiospecifically.³³²



VIII. Conclusion

As is seen from the material shown above, oximes and their derivatives are widely used for the synthesis of amines, hydroxylamines, nitriles, amides, ketones, diazo compounds and various heterocycles (isoxazoles, isoxazolidines, benzofurans, pyrroles, pyrrolines, imidazoles, pyridines, oxazines, azirines, aziridines, diaziridines, palladacycles). In the presence of bases and competitive nucleophiles, oximes behave as real 'chemical chameleons'. Depending on substituents, reagents used and reaction conditions, they can play the role of N-, O- and C-nucleophiles, 1,3-dipoles (in the NH-nitron form), electrophiles (the objects of the nucleophilic attack on the C=N bond), selective ligands for transition metal cations and also the components of highly efficient palladium catalysts. Oximes can undergo dehydration, the Beckmann and Neber rearrangements, Hoch–Campbell and Trofimov reactions, recover aldehydes and ketones, be reduced and add organometallic compounds, etc. Such an astonishing chemical plasticity of oximes in the presence of bases makes them versatile synthons in directed organic synthesis.

We believe that systematisation and analysis of chemical properties of oximes as multifunctional nucleophilic agents, which are presented in this review, will help further unravelling of their synthetic potential.

This work was supported by the Russian Foundation for Basic Research (Project No. 03-03-32472) and the Ministry of Industry, Science and Technology of the Russian Federation (Grant NSh-2241.2003.3).

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^a — *Chem. Heterocycl. Compd. (Engl. Transl.)*

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^h — *J. Struct. Chem. (Engl. Transl.)*

Enediyne antibiotics and their models: new potential of acetylene chemistry

I A Maretina, B A Trofimov

Contents

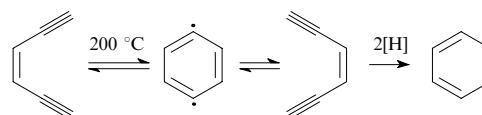
I. Introduction	825
II. Typical representatives of enediyne antibiotics	825
III. Cycloaromatisation of enediynes	829
IV. Synthesis of enediyne antibiotics and their analogues	836
V. Introduction of the enediyne fragment into other classes of organic compounds	840
VI. Conclusion	842

Abstract. Structures and chemical properties of enediynes, viz., compounds comprising a system of conjugated double and triple bonds, are surveyed. The presence of this system in the molecules of enediyne antitumour antibiotics ensures their high activity. The mechanism of biological action of enediynes is discussed based on cycloaromatisation of the enediyne chromophore resulting in highly active benzenoid 1,4-diradicals, which selectively cleave DNA. The key strategies of enediyne synthesis are analysed. The bibliography includes 291 references.

I. Introduction

The role of antibiotics in nature and in the human life can hardly be overestimated. Compounds with conjugated double and triple carbon–carbon bonds occupy a special place among them. Compounds with acetylene, vinylacetylene and acetylene–allene type systems of bonds were first found in the late 19 century in some plants and mushrooms. Since molecules containing these fragments are most often unstable, their presence in natural objects appeared unusual. However, as experimental facts have been accumulated, it turned out that compounds of this type are characteristic of the living nature, are widely represented and perform important functions, in particular, act as antibiotics, fungicides and insecticides. By the early 1970s, more than 600 natural acetylene derivatives have been isolated and studied. The studies published by that time were summarised in the fundamental monograph by Kucherov, Mavrov and Derzhinskii.¹

The first representatives of enediyne antibiotics, natural antitumour compounds, were discovered in the second half of the 20th century.^{2–6} This was preceded by a discovery by Bergman of the thermal cycloaromatisation of (Z)-3-ene-1,5-diyne systems (enediynes), which was later named after him.⁷



The diradical intermediates formed upon cyclisation of enediynes were found⁸ to attack selectively the DNA regions responsible for cell functioning.

By the end of the 20th century, the structure of the enediyne antitumour antibiotics has been studied in outline, but many important details, especially those concerning their synthesis, reactivity and the mechanism of physiological action remained unknown. Therefore, the attention of researchers to the development of new approaches to their synthesis and construction of functional models does not decline. The success in the design of enediyne systems gave a large number of synthetic analogues of known natural antibiotics of this class.

Study of the factors that influence cycloaromatisation of enediynes resulted in the development of a simple model of DNA cleavage induced by the benzenoid[†] diradicals formed (see, for example, Ref. 8). The second and third generations of enediyne antibiotics appeared, which are more active towards tumour cells than the natural products. The present review is devoted to the studies along this line carried out mainly over the last decade.

II. Typical representatives of enediyne antibiotics

1. Neocarzinostatin

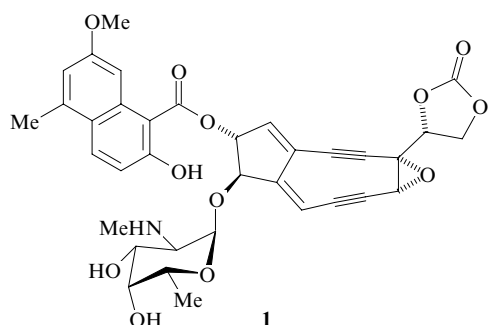
Neocarzinostatin was isolated in 1965 from the culture *Streptomyces carzinostaticus* var. F-41.² This was the first natural enediyne antibiotic to be described. This is a 1 : 1 complex of an apoprotein (a 113 amino-acid peptide) with chromophore **1**. Later, it has been shown that the chromophore component (generally designated as NCS in the modern literature on this subject) has a bicyclic dienediyne core.^{2, 8–11}

I A Maretina, B A Trofimov A E Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, ul. Favorskogo 1, 664033 Irkutsk, Russian Federation. Fax (7-3952) 39 60 46, e-mail: mironov_evgenii@mail.ru (I A Maretina), tel. (7-3952) 51 14 31, e-mail: admin@irioch.irk.ru (B A Trofimov)

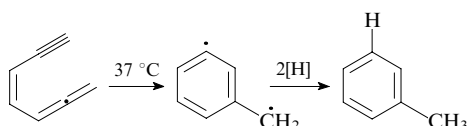
Received 10 January 2006

Uspekhi Khimii 75 (9) 913–935 (2006); translated by Z P Bobkova

[†] The systematic name of the parent compound of this diradical series is 1,4-phenylene or 1,4-didehydrobenzene; however, for compliance with the term generally used in the literature, below they are referred to as benzenoid diradicals.

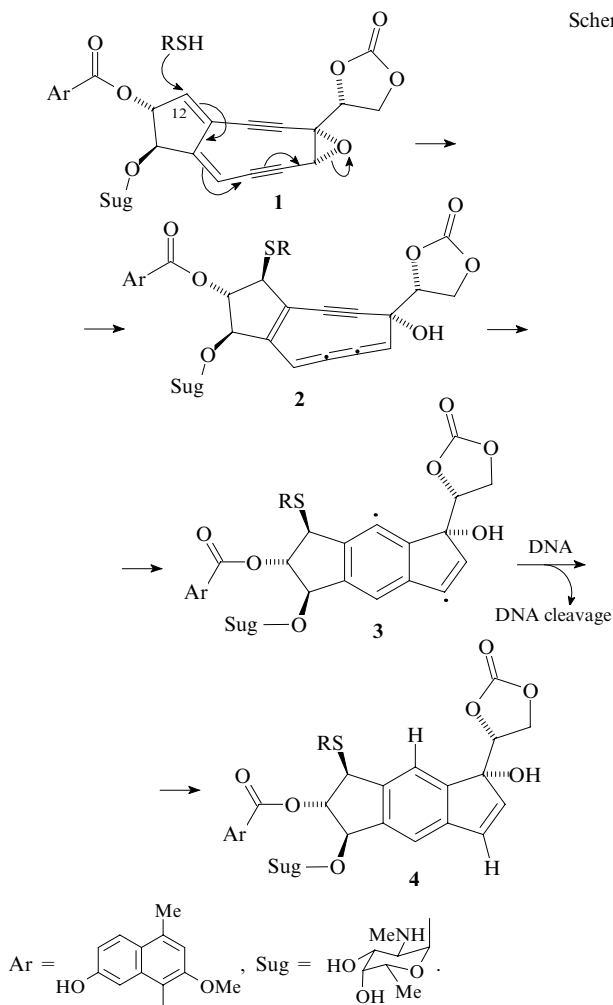


The biological activity of NCS is due to the Myers–Saito cycloaromatisation of the *Z*-enyne–allene system:⁹



The mechanism of DNA destruction by the neocarzinostatin chromophore^{2,8} is shown in Scheme 1. The cascade of reactions resulting in DNA cleavage is initiated by the specific nucleophilic attack on the C(12) carbon atom. The addition of a nucleophile (for example, a free sulfide group from the chromophore-surrounding proteins) induces bond rearrangement in the ring accompanied by oxirane opening giving rise to cumulene **2**. (In model syntheses, activation is due to an external nucleophile, for example, methyl thioglycolate.) The unstable intermediate **2** rapidly undergoes cycloaromatisation to give diradical **3**. The

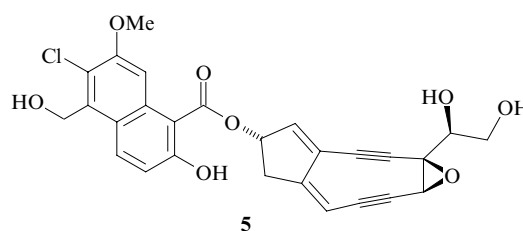
Scheme 1



latter abstracts hydrogen from DNA, thus inducing its destruction and being converted into compound **4**. The cumulene intermediate **2** is detectable in the NMR spectra at low temperatures.^{2, 12, 13}

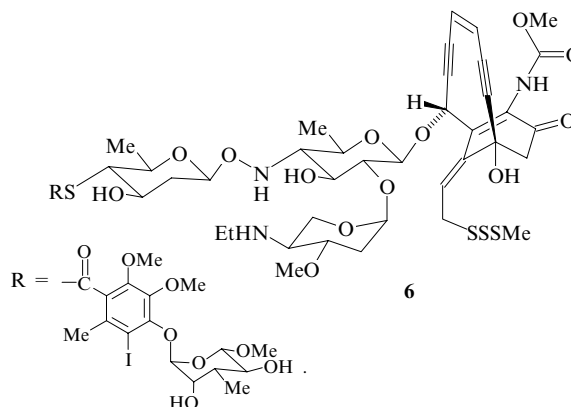
The reaction of the diradical with DNA starts with the elimination of the hydrogen atom from position C(5) of the deoxyribose fragment (the major reaction route).¹⁴ The subsequent stages result in cleavage of the DNA chain.

A unique analogue of neocarzinostatin, *i.e.*, the non-protein antibiotic N 1999 A2, which is a potent growth inhibitor for tumour cells and bacteria, was isolated from *Streptomyces* sp. AJ 9493.^{15–20} The cytotoxic properties of this analogue with respect to some types of tumours are superior to the action of neocarzinostatin. The molecule of N 1999 A2 (**5**) also contains a nine-membered enediyne ring, but, unlike neocarzinostatin, it has neither a concomitant peptide nor a sugar residue.¹⁸



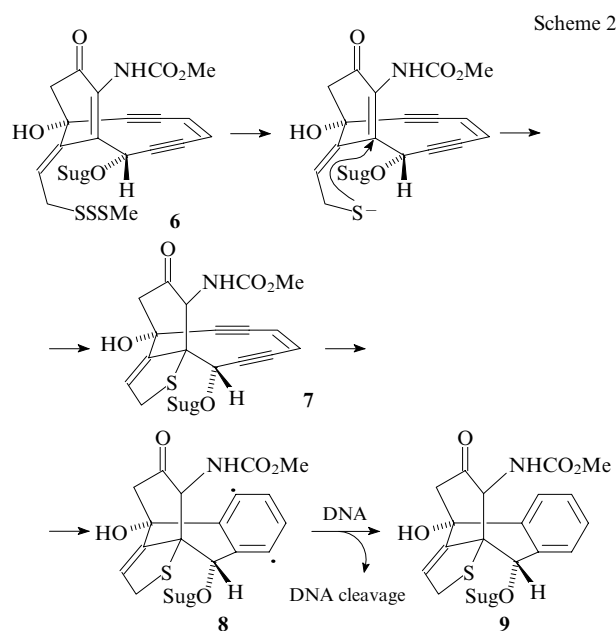
2. Calicheamicins, namenamycin, shishijimicin

Calicheamicins are a family of antibiotics isolated from *Micromonospora echinospora* ssp. *calichensis*.^{2, 21} The structure of one of them, calicheamicin γ_1^1 (**6**), is shown below.

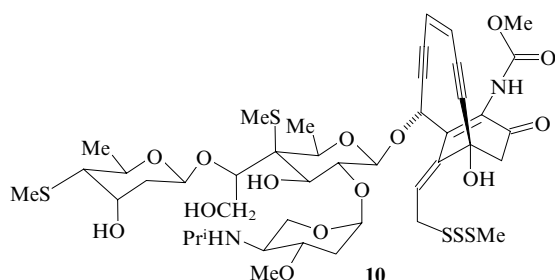


Representatives of this family of antibiotics are active with respect to Gram-positive and Gram-negative bacteria in concentrations below $1 \mu\text{g ml}^{-1}$ (Refs 2–6 and 22) and with respect to malignant tumours in concentrations of $0.15–5 \mu\text{g ml}^{-1}$. The biological activity of these compounds is manifested as selective cleavage of double-stranded DNA *in vivo*; moreover, the carbohydrate part of the molecule was found to be responsible for selective coordination to the DNA minor groove (preferably, it binds to pyrimidine-rich regions).^{3, 6, 23–29}

The calicheamicin aglycon has a rigid bicyclic core. The enediyne fragment incorporated in a ten-membered ring is able to undergo the Bergman cyclisation. The allylic trisulfide fragment activates the process (Scheme 2).^{8, 23} An attack by a nucleophile on the central sulfur atom of the trisulfide fragment gives a thiol group, which adds intramolecularly to the double bond (the Michael reaction) giving enediyne **7**, which is highly prone to cycloaromatisation to give highly reactive 1,4-benzenoid diradical **8**. This diradical abstracts a hydrogen atom from DNA, thus inducing its cleavage. The aromatic compound **9** formed upon the addition of hydrogen atoms was identified²¹ based on low-temperature NMR spectra.^{23, 30}



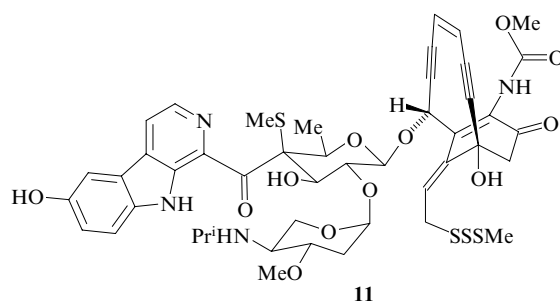
Namenamicin (**10**) is isolated from the marine ascidian *Polysyncraton lithostrotum* (Didemniidae, the Fiji Islands). From 1 kg of the frozen ascidian, one can obtain 1 mg of the antibiotic. Its structure and the cytotoxic properties are similar to those of calicheamicin and esperamicin.^{16, 31}



Namenamicin exhibits a cytotoxic activity *in vitro* with an average IC_{50} value of $\sim 3.5 \text{ ng ml}^{-1}$, an antitumour activity *in vivo* with respect to the model leukemia P388 in rats (a 40% increase in the life time at doses of 3 mg kg^{-1}) and an antimicrobial action (see below). Its lower activity with respect to DNA destruction and higher selectivity compared to that of calicheamicin are due to differences in the structure of the carbohydrate fragment.¹⁶

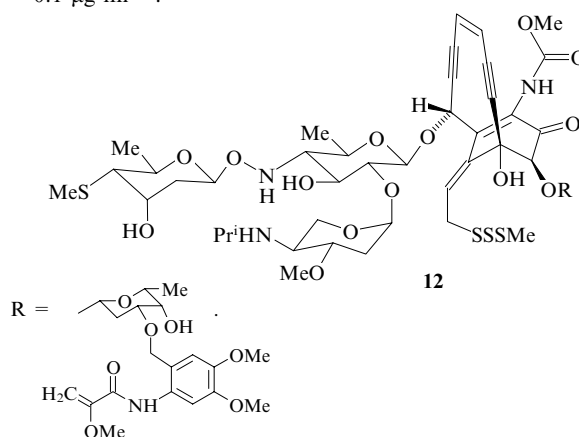
Organisms	Minimum inhibitory concentration / mg ml^{-1}		
	namenamicin	calicheamicin	penicillin G
<i>Bacillus subtilis</i>	0.03	0.00005	0.25
<i>Candida albicans</i>	0.25	0.03	> 128

Shishijimicin (**11**) can be isolated from a methanolic or ethanolic extract of ascidian.^{9, 32} Its carbohydrate moiety contains a 6-hydroxy- β -carboline fragment, while the aglycon is represented by 13-(2-methyltrisulfanylethylidene)bicyclo[7.3.1]trideca-4,9-diene-2,6-diyne-11-one derivative. This compound is much more cytotoxic than namenamicin, which is devoid of the β -carboline heterocycle.



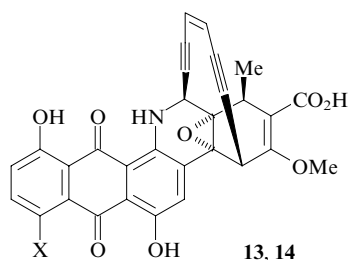
3. Esperamicins

Esperamicin is an exceptionally active broad-spectrum natural antibiotic. It was isolated from *Actinomadura verrucospora* Pto *Esperanza* in 1985.⁹ Its structure is similar to that of calicheamicin. The esperamicin molecule contains a bicyclic enediyne core. The absolute configurations of esperamicin A₁ (**12**) and calicheamicins were determined simultaneously.³³ Esperamicins and calicheamicins are the strongest known antitumour drugs. They are active against several model tumours in concentrations of $\sim 0.1 \text{ } \mu\text{g ml}^{-1}$.



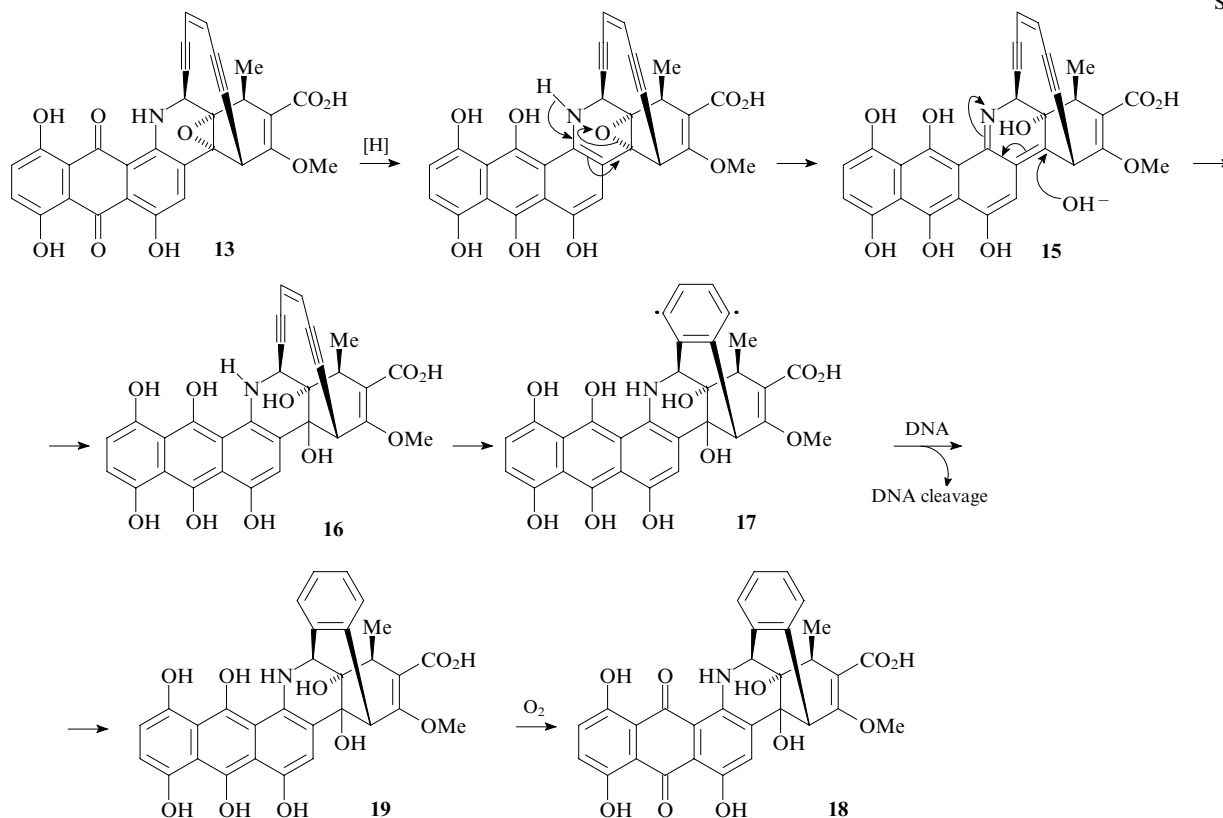
4. Dynemicins

Dynemicin A (**13**), the first discovered representative of this family of antibiotics, was isolated from *Micromonospora chersina*.^{9, 34–36} It exhibits high activity against many types of tumours and increases the life span of rats infected by leukemia P388 and melanoma B16. Its high activity is combined with low toxicity.³⁵ Yet another member of this family is deoxydynemicin (**14**) isolated from *Micromonospora globosa* MG331-hF6.²



A distinctive feature of dynemicins is the combination of a ten-membered bridging enediyne ring with an anthraquinone fragment. X-Ray diffraction analysis has shown that the anthraquinone moiety of the molecule is bevel with respect to the enediyne ring.^{36–40}

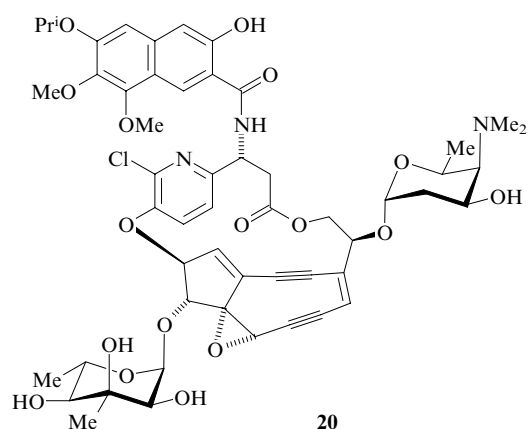
Scheme 3



The tentative mechanism of DNA cleavage under the action of dynemicin A involves initial reduction of quinone **13** (Scheme 3).^{8,9} This is followed by opening of the epoxide ring to give intermediate **15**. Under the action of a nucleophile (for example, the hydroxide anion), **15** is converted into diol **16** with an unstable polycyclic system of multiple bonds, which undergoes fast cycloaromatization to give 1,4-benzenoid diradical **17**, which cleaves DNA. The final product **18** is formed upon oxidation of polyol **19**.^{2, 41, 42}

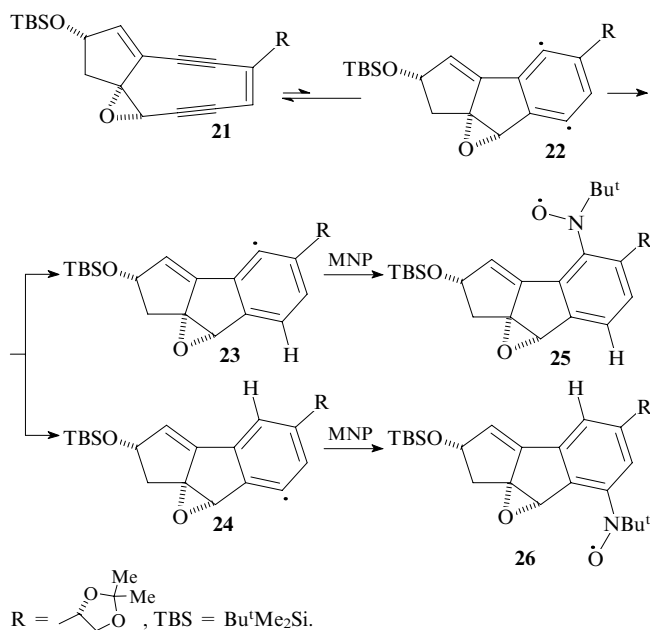
5. Kedarcidin, C-1027, maduropeptin

Studies of neocarzinostatin and the mechanism of its action demonstrated that a whole group of enediyne antibiotics represent non-covalent complexes formed by unstable chromophores and proteins that stabilise them. This resulted in the discovery of the kedarcidin,^{2, 8, 9, 43–51} C-1027^{2, 8, 9, 52–55} and maduropeptin^{2, 56, 57} chromophores. The kedarcidin chromophore (**20**) was first described in 1991.² Antitumour preparations based on kedarcidin, like many other enediyne antibiotics, are also active with respect to Gram-positive bacteria.⁴³



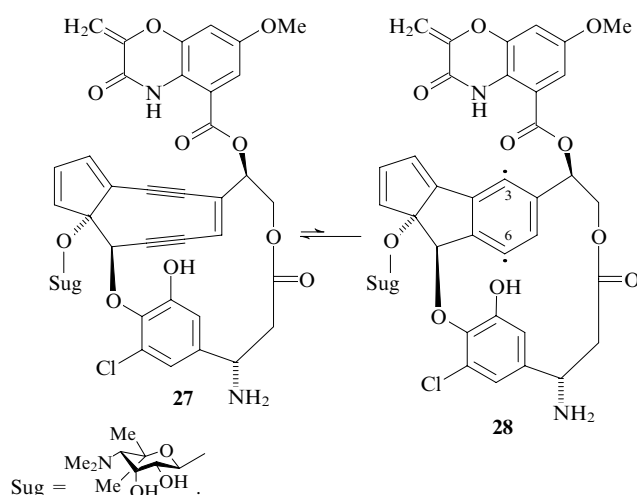
The kedarcidin apoprotein exists in a number of forms.² The main form contains 114 amino acid residues with predominance of alanine and serine. Whereas for neocarzinostatin the apoprotein:chromophore molar ratio is 1:1, in the case of kedarcidin, this ratio is equal 18:1. Cleavage of DNA by kedarcidin resembles the action of neocarzinostatin.⁴³

An analogue of the kedarcidin chromophore **21** exists as an equilibrium mixture with the cycloaromatization product, 1,4-didehydrobenzene **22**. This system was studied by the spin trap method^{58, 59} using 2-methyl-2-nitrosopropane (MNP), which allowed identification of intermediate monoradicals **23** and **24** having different reactivities.



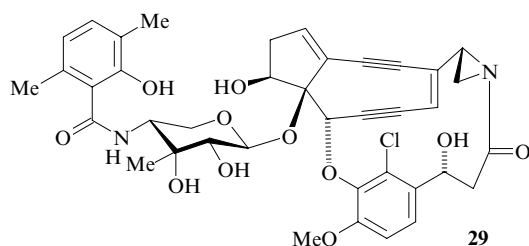
Spin adducts **25** and **26** formed in 2 : 1 ratio were characterised by EPR and mass spectrometry.⁵⁹

An exceptionally active antitumour antibiotic C-1027 containing a polypeptide and a dienediene chromophore **27** was isolated from the culture broth of *Streptomyces globisporus*.² To date, this is the most labile nine-membered enediyne chromophore.⁹ Chromophore **27** is stable only when bonded to the apoprotein. In the free state, it undergoes rapid cycloaromatisation even at room temperature.^{60–72} Unlike other representatives of this subfamily, compound **27** can be cycloaromatised without the thiol activation.⁹



A two-stage mechanism of hydrogen atom abstraction from DNA by diradical **28** was established. First, one hydrogen atom adds slowly to position 6 giving free monoradical and then the second H atom rapidly adds at position 3 to give the aromatic structure.⁷³ The radical intermediates formed upon DNA cleavage by the antibiotic C-1027 were captured by spin traps, and the spin adducts were identified by EPR spectroscopy and mass spectrometry.^{60, 73} These data provide an insight into the mechanism of antibiotic action in DNA cleavage processes.^{59, 73}

The antibiotic maduropeptin, which possesses bactericidal and antitumour activities, was isolated in 1990 from *Actinomadura madurae*.^{2, 9, 56, 57} It is a 1 : 1 complex of a water-soluble protein comprising 32 amino acids and enediyne chromophore **29**.



Maduropeptin is also capable of forming diradicals without activation.⁹

III. Cycloaromatisation of enediynes

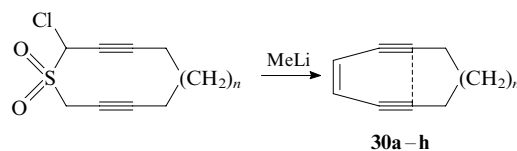
Cycloaromatisation reactions of enediynes have attracted considerable attention due to their high synthetic potential and the possible use in pharmaceutical chemistry,[‡] as indicated by numerous publications: monographs,^{2, 6} reviews^{8, 9, 74, 75} and original papers (see, for example, Refs 76–79). Below we consider the results of experimental studies and quantum-chemical simulation

‡ It was proved that the antitumour activity of natural antibiotics is directly related to their susceptibility to cycloaromatisation.^{80–90}

of enediyne systems. Note that apart from the thermal Bergman reaction, other (homolytic and heterolytic) ways to initiate cycloaromatisation are also possible.

1. Susceptibility to cycloaromatisation

The first theory that relates the susceptibility of a enediyne system to cycloaromatisation to the distance between the acetylenic bonds belongs to Nicolaou, who studied cycloaromatisation of monocyclic enediynes **30a–h**.⁹¹

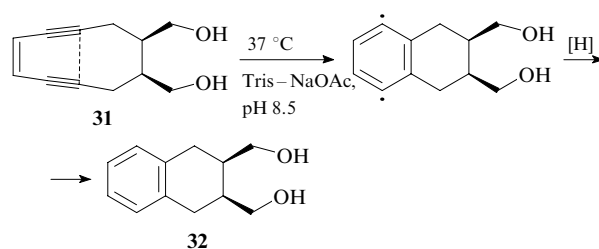


$n = 1$ (**a**), 2 (**b**), 3 (**c**), 4 (**d**), 5 (**e**), 6 (**f**), 7 (**g**), 8 (**h**).

Nine-membered cyclic enediyne **30a** ($n = 1$) has not been synthesised, but the products of its cycloaromatisation have been identified. Other compounds have been isolated in a free state. Of these, only the ten-membered enediyne **30b** undergoes cycloaromatisation at moderate temperatures, while compounds **30c–h** do not cyclise under these conditions.

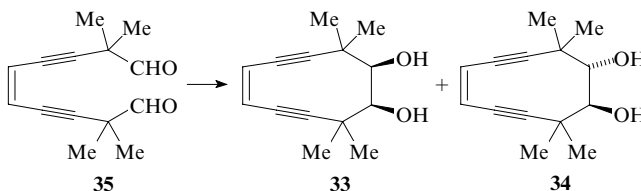
Thus, it can be seen that the ease of cycloaromatisation of the enediyne macrocycle depends on the distance between the terminal acetylenic carbon atoms. The range of 3.2–3.3 Å is critical; in this case, the reaction proceeds at a noticeable rate at moderate temperature. The transition state energy for this reaction was estimated based on calculations and kinetic data.⁹¹

In diol **31**, the distance between the terminal acetylenic atoms is equal to 3.20 Å; this compound cyclises at 37 °C. Diol **31** readily cleaves DNA, while the final product **32** does not react with DNA under the same conditions.⁹¹

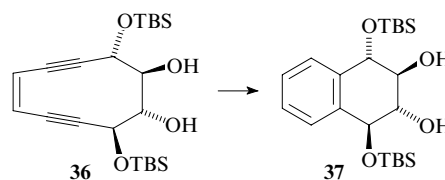


Tris = HOCH₂C(CH₂OH)(NH₂)CH₂OH.

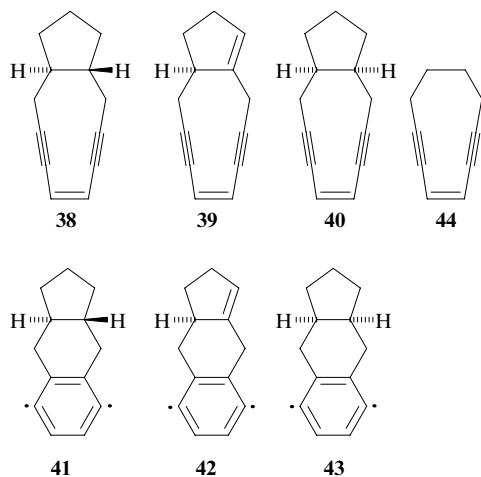
Diols **33** and **34** prepared from dialdehyde **35** cleave DNA *in vitro* (Tris – acetate buffer, pH 8.5); the half-conversion time is 4 h at 50 °C.⁹²



The synthesis of enantiomerically pure ten-membered cyclic tetrahydroenediynes from L-tartrates has been reported.^{93, 94} The introduction of silyl protecting groups allows one to control the cycloaromatisation rate in compound **36** (deprotection accelerates the process). The half-conversion time for compound **36** into product **37** is 2 h at 50 °C and pH 8.5.⁹⁴



Determination of the distance between the acetylenic bonds is the easiest method for predicting the tendency of a enediyne system to aromatisation. A more fundamental approach is to estimate the heat of formation of the diradical. For enediynes **38**–**40**, which mimic the chromophores of the calicheamicin antibiotics, the distances between the terminal carbon atoms of the acetylenic fragments and the enthalpies of formation of the respective diradicals **41**–**43** were determined by semiempirical calculations (AM1)⁹⁵

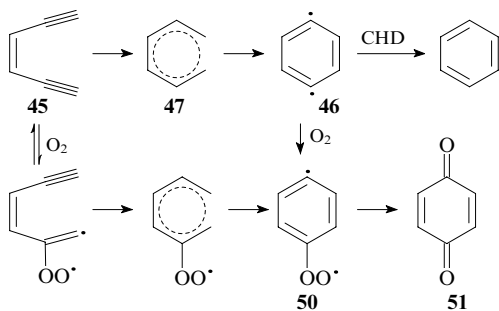


Compound	Distance / Å	Diradical	ΔH_f / kcal mol ⁻¹
38	3.24	41	48.2
39	3.09	42	40.9
40	2.98	43	38.1

The calculations predict a decrease in the susceptibility to cycloaromatisation (**40** > **39** > **38**) from the *cis*-fused to *trans*-fused bicyclic structure, which is correlated with the variation of the distance between the acetylenic carbon atoms. Compound **38** is expected to be much less reactive than the simplest ten-membered monocyclic enediyne **44**, which is cycloaromatised very slowly at 25 °C (the calculated heat of formation of the corresponding diradical is 45.2 kcal mol⁻¹).²

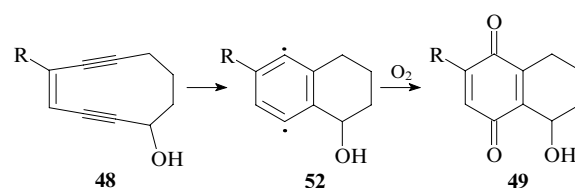
2. The diradical pathway of enediyne cyclisation

The simplest example of the Bergman cyclisation is the transformation of hex-3-ene-1,5-diyne (**45**) into 1,4-didehydrobenzene (**46**) through transition state **47** accompanied by hydrogen atom abstraction from 1,4-cyclohexadiene (CHD) to give benzene (Scheme 4).



Scheme 4

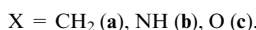
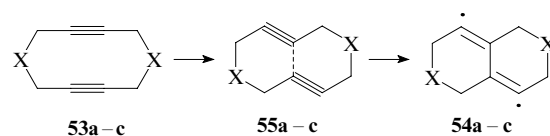
Recently, it has been found⁹⁶ that cyclisation of enediyne **48** in an aqueous medium (in the presence of traces of oxygen) gives quinone **49**, its yield being proportional to the concentration of dissolved oxygen.



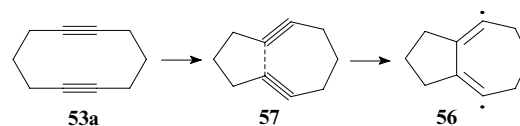
In this connection, one more radical pathway for cyclisation of enediyne **45** was proposed, involving oxidation with oxygen to give peroxide diradical **50** and then quinone **51**. The possible radical pathways of cyclisation of enediyne **45** (see Scheme 4) were studied theoretically (DFT calculations, 6-31 G* basis set).^{86,96–98} For triplet and singlet diradicals and neutral species formed during cyclisation of compounds **45** and **48**, geometry optimisation was carried out and the relative energies and reaction barriers were estimated. To take into account the solvent effects, some calculations were repeated using the polarised continuum model (PCM).

It was shown that diradical **52** cannot react with O₂ in the gas phase. The assumption of direct reaction of enediyne **48** with oxygen is also not confirmed.⁸⁶ To elucidate the nature of the intermediate diradical, gas-phase thermolysis of 1,6-cyclodecadiyne has been studied.^{99,100}

Molecular orbital calculations [CASSCF(8,8)/6-31 G*] have been carried out for the gas-phase transannular ring closure in ten-membered cyclic diynes **53a–c** to give bicyclo[4.4.0]deca-1,6-diene-2,7-diyls **54a–c**.⁹⁹



The geometries were optimised for the ground states **53a–c**, transition states **55a–c** and intermediates **54a–c**. The activation energy for the transition **53** → **54** was found to depend on the distance between the triple bonds. The transition along the route **53a** → **57** → **56** has higher activation energy than **53a** → **55a** → **54a**.⁹⁹

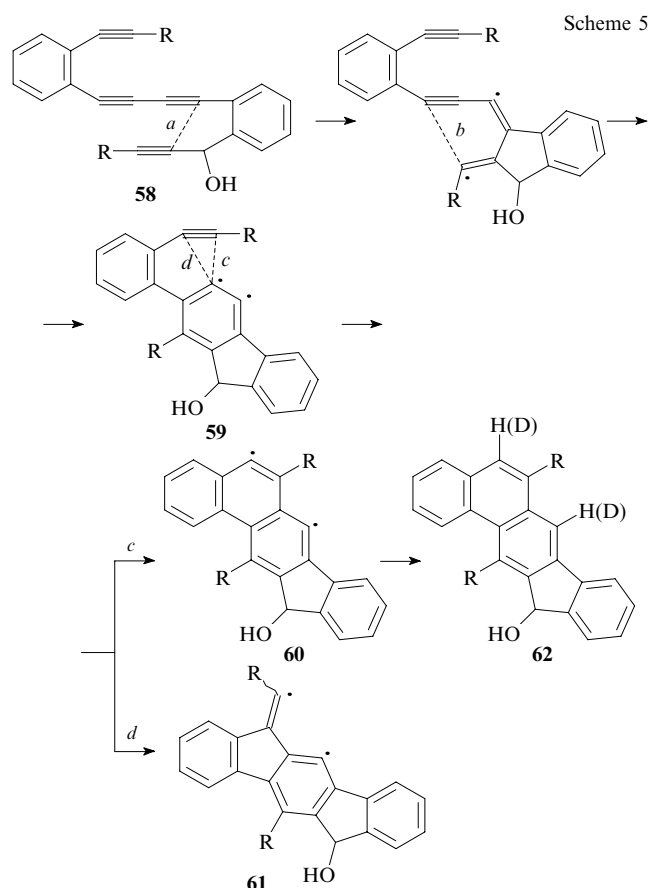


Aromatic enediynes **58** cyclise at 25 °C to give fused systems (Scheme 5).^{8,101}

Thermolysis of compounds **58** initiates the cycloaromatisation of acetylenic bonds along the pathway *a* and is accompanied by the tandem radical cyclisation along the pathway *b* to give σ,σ -dehydrobenzene diradicals **59**.¹⁰¹ Subsequently, thermal radical cyclisation of diradicals **59** (along pathway *c* or *d*) gives two types of diradicals, **60** and **61**, respectively.

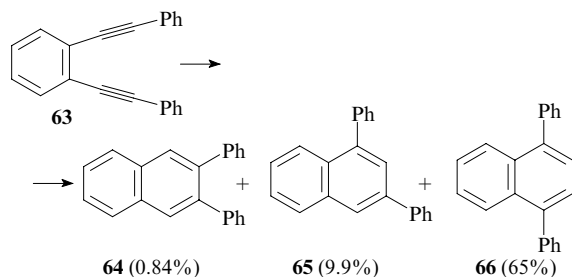
In particular, product **62** was obtained by this method in 10% yield from tetrayne **58** ($R = \text{C}\equiv\text{CSiMe}_3$). Synthesis of compounds **62** is accompanied by the formation of large amounts of by-products. Thermolysis of the same tetraacetylene in methanol-d₄ gives **62-d**₂ containing deuterium only in positions 5 and 7 (see Scheme 5).¹⁰¹

Upon thermal cyclisation (320 °C, 3 h) of 1,2-bis(phenylethynyl)benzene (**63**), the expected 1,2-diphenylnaphthalene **64** was detected in trace amounts (0.84%).¹⁰² The isomeric naphtha-



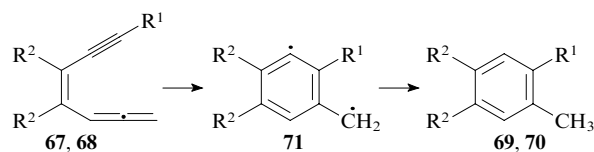
R = H, SiMe₃, Ph, C≡CSiMe₃.

lenes **65** and **66** resulting from migration of the phenyl groups were the major cyclisation products.



Analysis of the thermodynamics of these transformations is carried out using quantum-chemical calculations (DFT). Cycloaromatisation of these enediynes in the presence of tellurium proceeds under mild conditions.¹⁰³

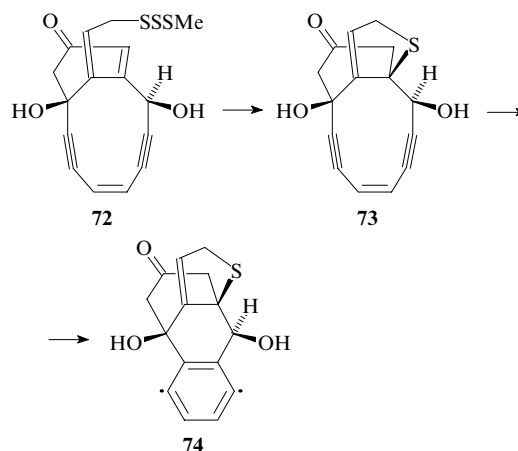
Cyclisation of allene enynes **67** and **68** into benzene (**69**) and naphthalene (**70**) compounds occurs at 50–100 °C through diradicals **71**.^{50, 104, 105}



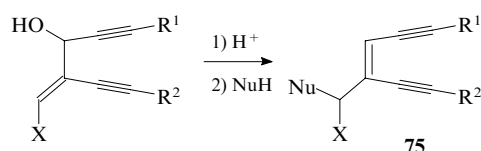
R¹ = H, Alk, Ph; R₂² = H₂ (**67**, **69**), (CH)₄ (**68**, **70**).

To elucidate the reaction mechanism, quantum-chemical calculations were carried out, and the geometric parameters of radicals **71** and thermodynamic parameters of their formation reactions were determined.¹⁰⁴

As noted above, an important feature of natural enediynes is the fact that some chemical reactions convert them from a stable form (e.g., **72**) into a reactive form (**73**), which is rapidly converted into benzenoid diradical (**74**).^{106–109}

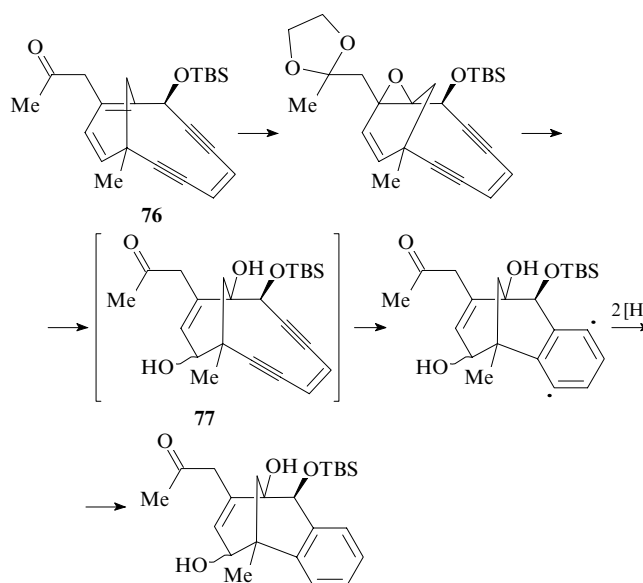


The synthesis of *cis*-enediynes **75** by acid-catalysed rearrangement of 1,2-dialkynylprop-2-en-1-ols in the presence or in the absence of nucleophilic reagents (alcohols or thiols) can serve as an example of chromophore activation through isomerisation of double bonds.¹¹⁰

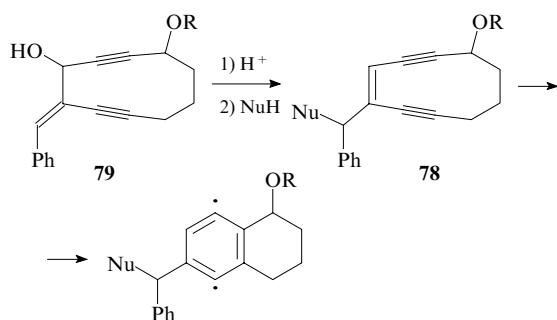


X = H, Ar; Nu = OH, OMe, SMe; R¹ = CH₂SPh; R² = (CH₂)₄OMe.

The activation of the enediyne bond system in compound **76**, which mimics calicheamicin, through the rearrangement of multiple bonds, resulting in structure **77** more prone to cycloaromatisation, was studied experimentally and by quantum-chemical calculations.¹¹¹ The diradical formed in the cycloaromatisation of enediyne **77** is converted upon reduction into the corresponding ketodiols in a high yield.



Cycloaromatisation of the 10-membered highly strained enediyne **78**, prepared from thermally stable precursor **79**, has been carried out.^{112, 113}



Nu = OH, OEt; R = anthraquinone-2-carbonyl.

Acid-catalysed dehydration of alcohol **79** affords allylic intermediate, which is attacked by the nucleophile exclusively on the γ -carbon atom to give enediyne **78** prone to cycloaromatisation.^{114–116} The same allylic rearrangement presumably takes place on heating alcohol **79** in a weakly basic medium in the presence of DNA.¹¹⁷

The formation of reactive enediynes upon allylic rearrangement obviously underlies the mechanism of action of the maduropeptin^{118, 119} and kedarcidin⁵⁸ chromophores.

3. Electrophilic activation of the cyclisation

As an alternative to the C(1)–C(6) cyclisation of enediynes such as *o*-bis(2-phenylethynyl)benzene (**63**), which proceeds through diradical **80**, C(1)–C(5) cyclisation proceeds through diradical **81** to yield benzopentafulvenes (Scheme 6).¹²⁰

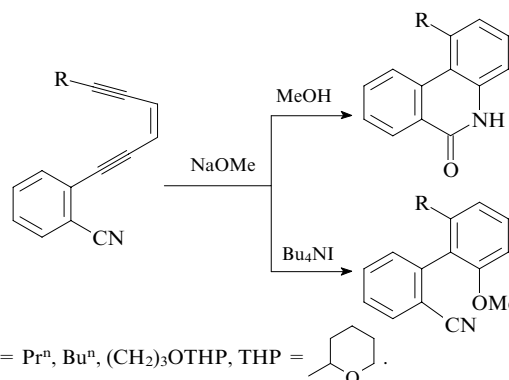
The energy barrier to the formation of naphthalene diradical **80** is rather high (40 kcal mol^{–1}, according to UBS-B3LYP/6-31G* calculations). It was found that, unlike the homolytic reaction resulting in naphthalene derivatives, the reaction of the

enediyne **63** with bromine results in fulvene **82**.¹²⁰ The cyclisation of compound **63** induced by bromine proceeds through cation **83**.

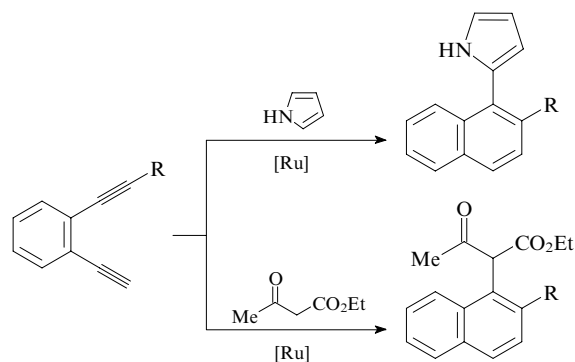
4. Cyclisation under the action of nucleophiles

Cyclisation of non-functionalised enediynes along the diradical pathway and through electrophilic addition gives benzene derivatives and functionalised fulvenes, respectively.¹²¹ Base-induced aromatisation of enediynes (the Bergman anionic cyclisation) can be used for functionalisation of the benzene nucleus by nucleophiles.^{122–124}

A general method for the preparation of functionalised aromatic compounds from enediynes has been developed; the key stage of the method is cycloaromatisation of the enediyne fragment induced by nucleophiles.¹²² Depending on the reaction conditions and the substrate structure, either benzo[*c*]phenanthridinone or biaryls are formed. If the methoxide anion attacks the nitrile function, cycloaromatisation resulting in phenanthridinones takes place. If the attack is directed on the acetylenic C(2) atom of the enediyne system, biaryls are formed.¹²²

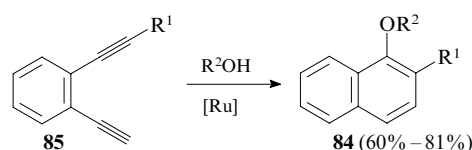


The cyclisation of enediynes with a terminal acetylene group induced by neutral nucleophiles (water, alcohols, aniline, acetylacetone, pyrroles, dimethyl malonate) and catalysed by the ruthenium complex [TpRu(PPh₃)₂(MeCN)₂PF₆] [Tp is hydrotris(pyrazol-1-yl) borate] can serve as a general method for the synthesis of functionalised benzenes and naphthalenes.

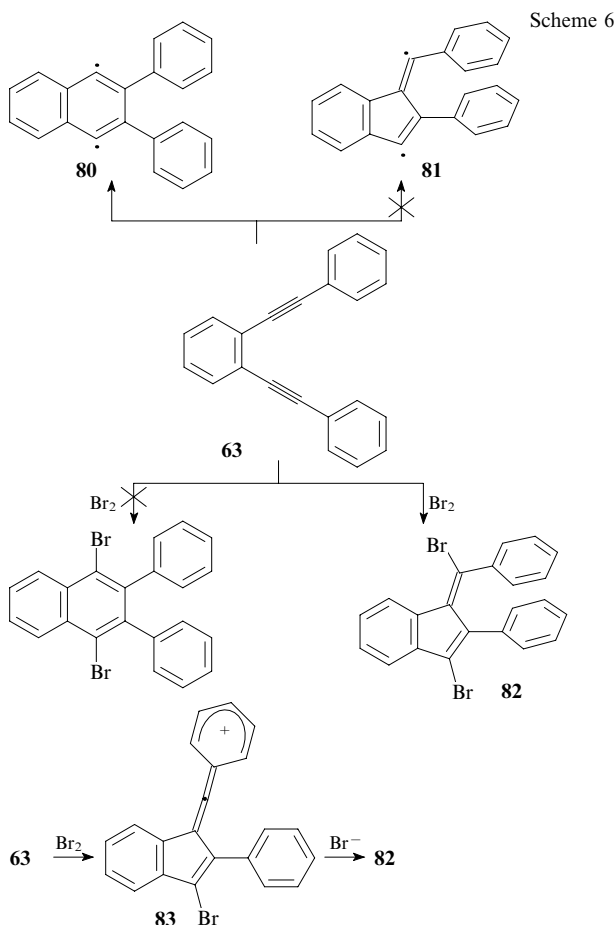


R = H, Me; [Ru] = [TpRu(PPh₃)₂(MeCN)₂]PF₆.

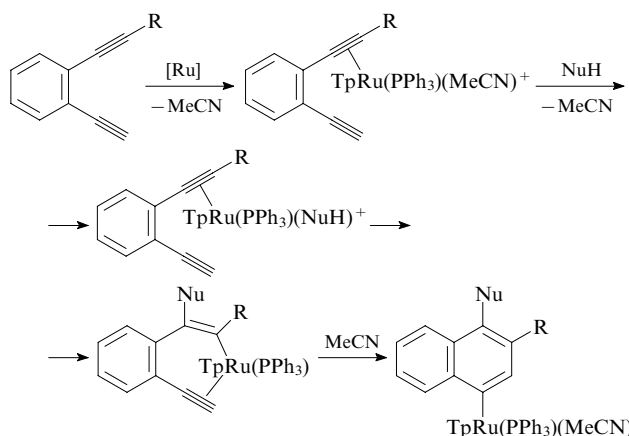
In particular, this method was used to prepare 1-alkoxy-2-substituted naphthalenes **84** by treatment of enediynes **85** with water or an alcohol (*n*-butyl, isobutyl or *tert*-butyl alcohol).¹²¹



R¹ = H, Me, Et; R² = H, Buⁿ, Buⁱ, Bu^s, Bu^t.

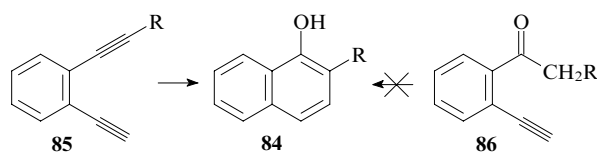


In this case, the addition of nucleophiles to the substituted triple bond and spontaneous cyclisation of the enediyne system take place in the coordination sphere of ruthenium.^{121, 125–128}



Presumably, the reaction involves vinylruthenium and vinylideneruthenium intermediates.¹²¹

This type of enediyne cycloaromatisation is quite unusual, because electrophilic metal complexes can catalyse hydration of terminal alkynes **85** to ketones **86**.¹²⁹ It was shown that the latter are not intermediates of cycloaromatisation, because they do not form naphthols under the conditions studied.¹³⁰

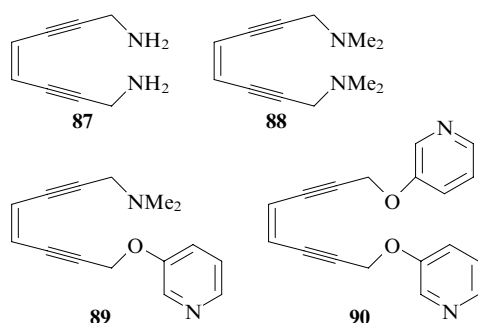


5. Cycloaromatisation of heteroatomic enediynes

It is expedient to consider the cycloaromatisation of enediynes containing heteroatoms taking nitrogen-containing derivatives as examples, as they attract most interest.^{131–133}

a. Acyclic nitrogen-containing enediynes

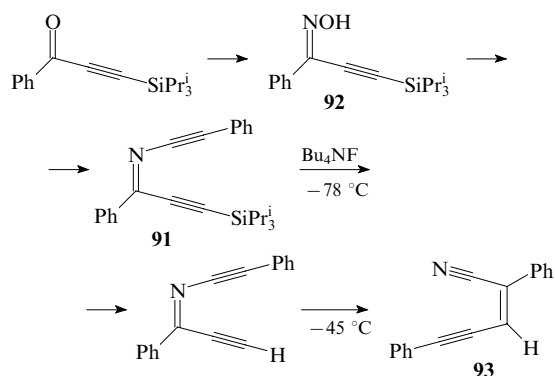
The thermal cyclisation of enediynes **87–90** in the presence of CHD is affected by steric factors.^{131–133}



This is believed¹³¹ to be caused by hindered rotation of substituents about the acetylene groups of the enediyne fragment. Enediyne **88** cyclises only at 186 °C, whereas the cyclisation temperature for 3-hydroxypyridine derivative **90** is 149 °C, which is attributable to the easier rotation of substituents. The cycloaromatisation temperature of 1,6-bis(3-pyridyl)hex-3-ene-1,5-diyne in which the pyridine rings are directly bound to the acetylene groups increases to 195 °C.

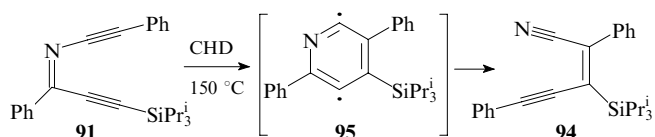
b. C,N-Dialkynylimines (aza-enediynes)

The replacement of the sp² carbon atom of an enediyne by a nitrogen atom results in C,N-dialkynylimines **91**. These compounds are synthesised from acetylenic ketoximes **92**.¹³⁴



Deprotection of the acetylene fragment in compound **91** destabilises the molecule, and rearrangement takes place at –45 °C giving rise to β-phenylethynylacrylonitrile derivative **93** (yield 89%).¹³⁵

Thermolysis of protected aza-enediyne **91** (heating in chlorobenzene in the presence of 20 equiv. of CHD in a sealed tube at 150 °C for 3 days) resulted in 2,5-diphenyl-3-triisopropylsilyl-pent-2-en-4-ynenitrile (**94**) (yield 35%).¹³⁵

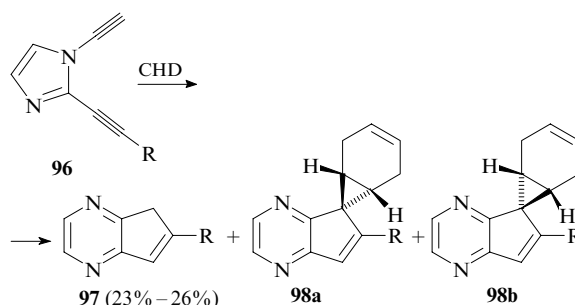


The reaction proceeds presumably *via* 2,5-didehydropyridine intermediate **95** (the aza-Bergman cyclisation), which undergoes fast ring opening (the retro-aza-Bergman cyclisation).¹³⁵ Di-radical intermediates have not been isolated, although GC/MS analysis detected the formation of pyridine type products upon the thermolysis of aza-enediynes in acidic media.¹³⁵

The synthesis and transformations of dialkynyldiazenes (diaz-enediynes) that possess antitumour action have been described.¹³⁶

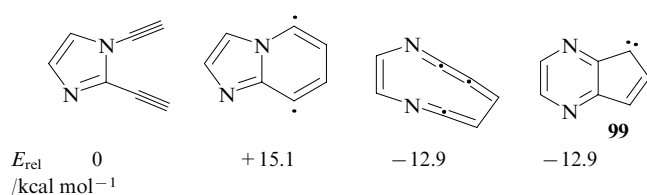
c. Hetarenediynes

The Bergman-type thermal cyclisation of 1,2-dialkynylimidazoles **96** (heating in a sealed tube with CHD at 75–100 °C for 2–4 days) gives, in addition to 5*H*-cyclopentapyrazine (**97**), spirobicyclo[4.1.0]heptane-7,5-5*H*-cyclopentapyrazines **98a,b**.^{137, 138}

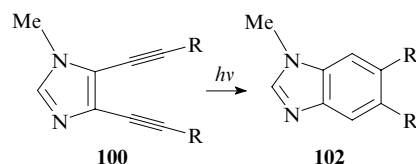


R = H, Alk, Ar.

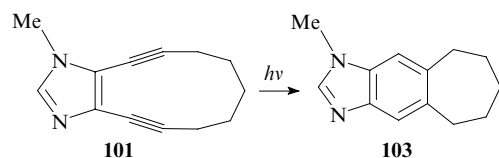
Quantum-chemical calculations (B3LYP/6-31G*) of the relative energies of the possible intermediates of this process indicate that cyclopentapyrazinecarbene intermediates **99** are most favourable.¹³⁸



The photoinduced (irradiation with a 450 W lamp) cyclisation of a number of 1-methyl-2,3-diethynylimidazoles **100** and their macrocyclic analogue **101** to give benzimidazoles **102** and **103** has been studied.^{139, 140}



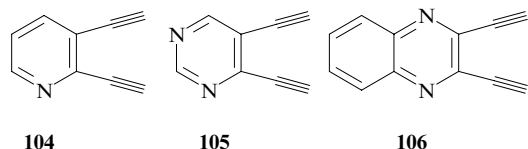
R = Me, Buⁿ, Ph.



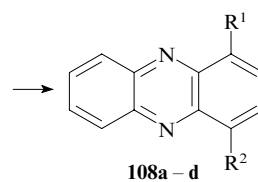
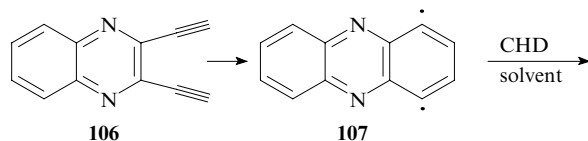
The cycloaromatisation products **102** are formed in good yields. Bicyclic compound **101** cleaves plasmid DNA at low temperatures.¹⁴⁰

Although the distance between the terminal acetylene atoms is the major factor affecting the cyclisation of enedynes,^{141, 142} electronic effects also play a role.^{143–145}

The influence of the electronic factors and the medium on the cyclisation of hetarenediynes **104–106** has been studied.¹⁴³



It was shown that the presence of the electron-deficient hetarene fragment decreases the activation energy of the reaction.¹⁴⁶ Using cyclisation of 2,3-diethynylquinoxaline (**106**) as an example, it was shown that the reaction kinetics depends appreciably on the nature of the solvent (acetonitrile, methanol, benzene, dioxane, carbon tetrachloride, THF); the half-conversion time may vary from 361 to 16 min.¹⁴³ Cyclisation in each solvent was carried out both in the presence and in the absence of CHD (*i.e.*, either CHD or the solvent served as the hydrogen source). The removal of CHD from the reaction mixture did not exert pronounced influence on the structures and yields of the cyclisation products. Less polar solvents ensured higher yields of the cyclisation products. In most solvents, phenazine **108a** was formed as the major product, while in benzene and carbon tetrachloride, the products formed in the reaction of diradical **107** with the solvent (**108b–d**) predominated.¹⁴³

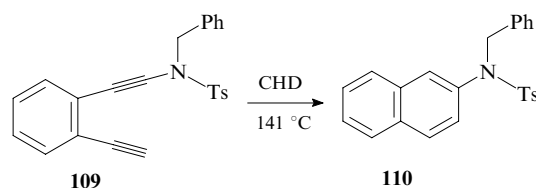


R¹ = R² = H (**a**), Ph (**b**), Cl (**c**); R¹ = , R² =  (**d**).

Solvent	Half-life /min	Cyclisation products	Yield (%)
Acetonitrile	361	108a	7
Methanol	312	108a	2
Benzene	96	108b	58
Dioxane	60	108a	15
CCl ₄	14	108c	81
THF	16	108a + 108d	36, 9

d. Enediyne sulfonamides

A study of the thermal cyclisation of *N*-benzyl-*N*-(2-ethynylphenyl)ethynyl-*p*-toluenesulfonamide (**109**) (141 °C, benzene: CHD = 2:1) to naphthalene derivative **110** has shown that the half-conversion time of this compound (44 min) is much shorter than that for the parent compound of the series, 1,2-diethynylbenzene.¹⁴⁷ This is indicative of the activating effect of the sulfonamido group on the cyclisation; simultaneously, this group decreases the hydrolysability of the ynamine fragment.¹⁴⁸

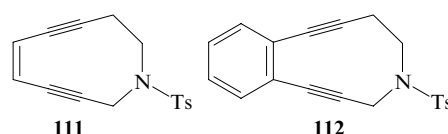


Ts = SO₂C₆H₄Me-4.

This example confirms once again the general trend, namely, that σ-withdrawing substituents at the terminal acetylenic carbon atom of an enediyne increases the susceptibility of the compound to cycloaromatisation.

The synthesis and reactivity of cyclic enediyne sulfonamides are considered in a number of publications.^{149–153}

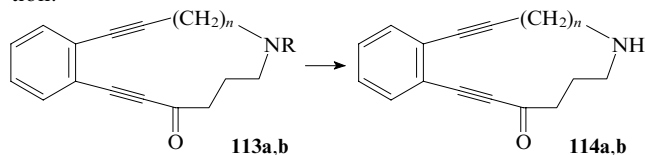
Enediyne sulfonamides have certain advantages as regards cycloaromatisation over the carbon and sulfur analogues. In particular, the presence of a short C–N bond (1.47 Å), which is shorter than the C–C (1.54 Å) or C–S (1.81 Å) bonds in the corresponding analogues, results in a decrease in the distance between the terminal acetylenic carbon atoms. Indeed, in sulfonamide **111** this distance is only 3.24 Å,⁹¹ *i.e.*, corresponds to the critical distance that ensures easy cyclisation.



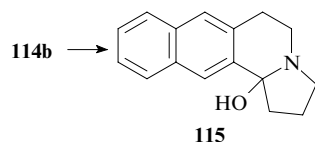
Heterocyclic compound **111** slowly undergoes cycloaromatisation even at 25 °C in CDCl₃ to give tetrahydroisoquinoline.¹⁵² In acetonitrile, its half-life at 23 °C is 72 h, which implies an activation energy of 18 kcal mol⁻¹.

Cycloaromatisation of sulfonamide **112** occurs at 62 °C with a half-life of 52 h. Its low reactivity compared to that of enediyne **111** was attributed to less pronounced resonance energy stabilisation of the transition state and to different degrees of pyramidalisation of the nitrogen atom.¹⁵²

N-Deprotection of the 12-membered enediyne **113a** results in a quite stable cyclic amino ketone **114a**. Meanwhile, its 13-membered homologue, amino ketone **114b**, proved to be unstable, being rapidly converted into cycloaromatisation product **115**.¹⁵³ In this case, the Bergman cyclisation is stimulated by the parallel transannular cyclisation involving the amine and carbonyl function.

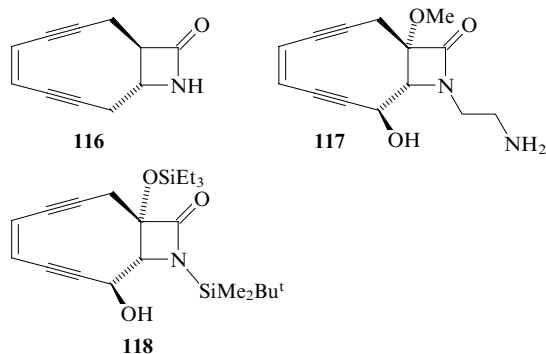


R = SO₂C₆H₄NO₂-4; n = 1 (a), 2 (b).



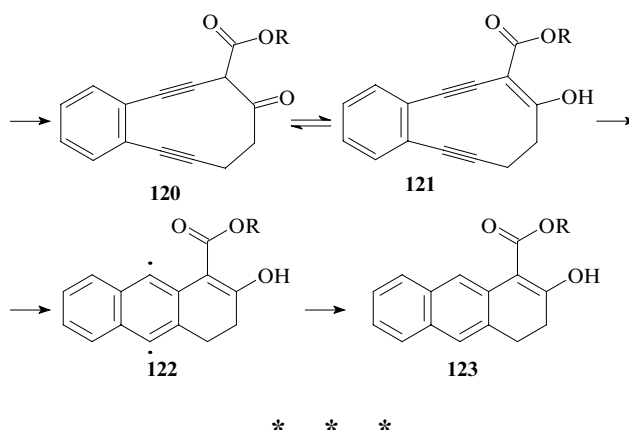
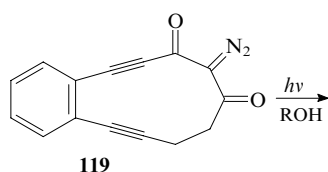
e. Lactenediynes

This is the name for ten-membered enediynes fused to β -lactam.^{154–156} The presence of *trans*-fused rings in the molecules of compounds **116–118** makes them rather thermostable. Cycloaromatisation is initiated by β -lactam ring opening.¹⁵⁵ N-Protected compound **118** is unable to cleave DNA, however after deprotection, the enediyne becomes reactive.¹⁵⁵ The parent compound of the series of substituted lactenediynes, bicyclic compound **116**, easily undergoes cycloaromatisation (the half-conversion time is 36 h at 30 °C).¹⁵⁴



f. Cyclic enediynes with a diazocarbonyl fragment

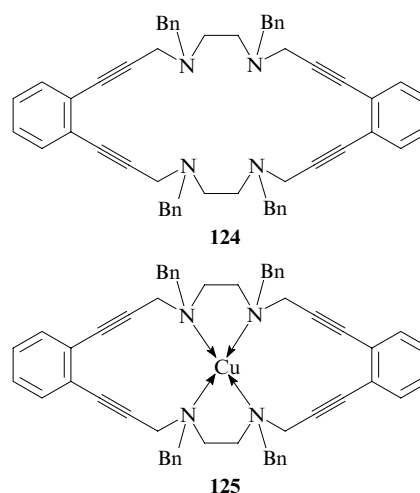
Irradiation of 11-membered enediynes with a diazo- β -dicarbonyl fragment results (through the Wolf rearrangement) in reactive ten-membered structures. Indeed, photolysis of enediyne **119** induces its rearrangement into oxo ester **120**,¹⁵⁷ which is in equilibrium with enol **121**. The latter undergoes fast cycloaromatisation to give reactive diradical **122**, which is converted into dihydroanthracene **123** in the presence of hydrogen donors. These reactions served as the basis for the development of a new concept of activation of enediyne antibiotics based on photochemical transformations of functional groups adjacent to the enediyne chromophore.



It is impossible to cover all types of cycloaromatisation of heteroatomic enediynes in a brief review. Note only that along with nitrogen-containing enediyne compounds, compounds with other heteroatoms adjacent to the enediyne system, in particular a sulfur atom, are also under study.^{158–160}

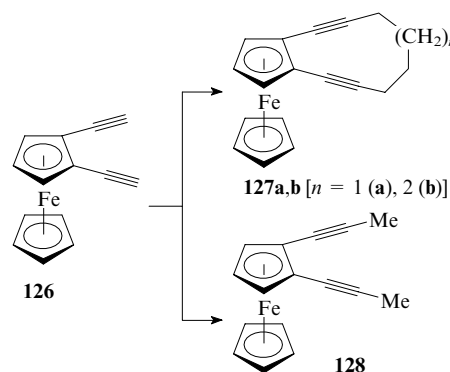
6. Metal complex enediynes

The thermal cycloaromatisation of enediynes is affected by complexation. For instance, the formation of a complex of enediyne **124** with copper decreases the distance between the acetylenic carbon atoms; as a result, the cycloaromatisation temperature for complex **125** is 70° lower than that for the starting ligand **124**.¹⁶¹

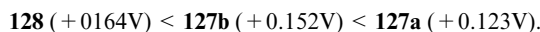


Synthesis of a number of enediyne macrocyclic ligands and their complexes with copper and zinc salts and DSC estimation of their relative reactivities towards cycloaromatisation have been reported.¹⁶²

Deprotonation of diethynylferrocene (**126**) with butyllithium and treatment of the resulting dianion with diiodobutane (or diiodopentane) results in enediyne complexes **127a,b**.¹⁶³



Methyl derivative **128** was prepared in a similar way. One can observe a correlation between the ring strain in compounds **127a,b** (based on *ab initio* calculations) and their susceptibility to electrochemical oxidation:



A similar trend can be followed in the variation of their ionisation potentials in both the liquid and gas phases.¹⁶³

IV. Synthesis of enediyne antibiotics and their analogues

Total syntheses of enediyne antibiotics and their analogues cannot be described within the limits of this paper; therefore, we only briefly consider the general approaches.

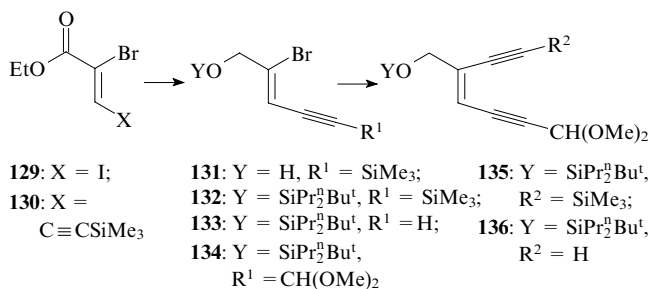
The Sonogashira cross-coupling of vinyl or aryl dihalides with terminal acetylenes catalysed by Pd(0) or Cu(I) complexes is used most often to prepare enediynes.¹⁶⁴ Good results are obtained in the Pd(0)-catalysed reaction of (*Z*)-1,2-bis(trimethylstannyl)-ethenes with iodoalkynes (the Stille cross-coupling).^{165, 166} A large number of methods of *cis*-enediyne synthesis are based on the introduction of a double bond into 1,5-diyne systems. These are based on reductive elimination¹⁶⁷ and acid-catalysed¹⁶⁸ and base-catalysed¹⁶⁹ elimination of alcohols or diols,¹⁷⁰ the Diels–Alder reaction¹⁷¹ and rearrangements of allylic alcohols.^{116–118, 172} Numerous studies along this line are devoted to the synthesis of the neocarzinostatin chromophore^{2, 51, 173–176} and its analogues.^{177, 178}

Typical strategies for the construction of enediyne system are described in brief below.

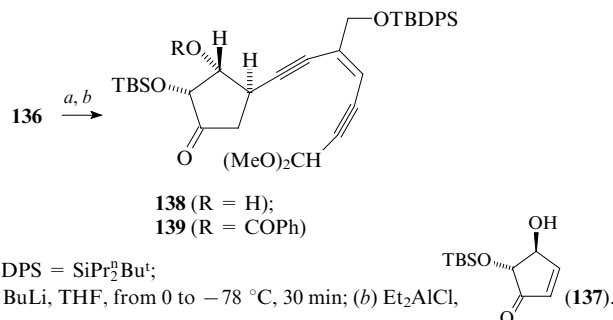
1. Construction of the bicyclic dienediyne system

The functionalised bicyclic system of enediyne antibiotics can be constructed by aldol condensation.^{179, 180} In the synthesis of NCS chromophore- and kedarcidin-related systems, dihydroxylated cyclopentenone often serves as the starting structural block.^{181–184} Early approaches to the synthesis of the bicyclic nucleus of NCS have been described by Myers *et al.*^{185, 186} A recent paper by Hiram and co-workers¹⁸⁷ presents an advanced approach to the construction of the molecule of this chromophore based on the convergent synthetic scheme. In some syntheses, cobalt carbonyls have been used to protect triple bonds.^{42, 188–190}

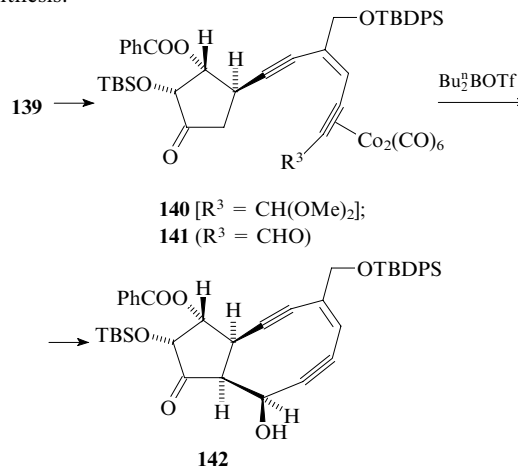
A typical synthesis of a bicyclic enediyne system includes: (i) construction of the enediyne fragment from simple starting compounds; (ii) its conjugate addition to the enone to form a cyclopentene fragment; (iii) closure of the second ring by aldol reaction.¹⁸⁰ Bromoiodoethylene **129** obtained from ethyl propiolate is coupled with trimethylsilylacetylene, and the resulting enyne ester **130** is reduced to alcohol **131**. The protection of the hydroxy group by *tert*-butylchlorodipropylsilane (compound **132**) and deprotection of the acetylene function yield terminal alkyne **133**. Compound **133** is converted into acetal **134**. This is followed by cross-coupling with trimethylsilylacetylene in the presence of Pd(II) to give compound **135** and by removal of the TMS-protection, which results in enediyne **136**.¹⁸⁰



Conjugate addition of enediyne **136** to enone **137** is carried out via the alkynylaluminium derivative.¹⁸⁰ The yield of product **138** is 51%.



The elaboration of adduct **138** requires benzoate protection (conversion into compound **139**) and protection of one triple bond with cobalt carbonyl to give complex **140** (84%).¹⁹¹ Acetal **140** is transformed into aldehyde **141**; its cyclisation (on treatment with di-*n*-butylboryl triflate and triethylamine) yields enediyne **142** (yield 75%). This route ensures high stereoselectivity of enediyne synthesis.



Most of chromophores of the enediyne antibiotics contain a ten-membered ring.^{2, 4} Some studies dealing with the construction of the bicyclic core of enediyne antibiotics are directed at preparation of larger rings (as they are formed more easily) followed by their contraction. A classical example of this approach has been demonstrated by Mayer and Sondheimer,¹⁹² who were the first to use electrocyclicalisation to form diradicals.

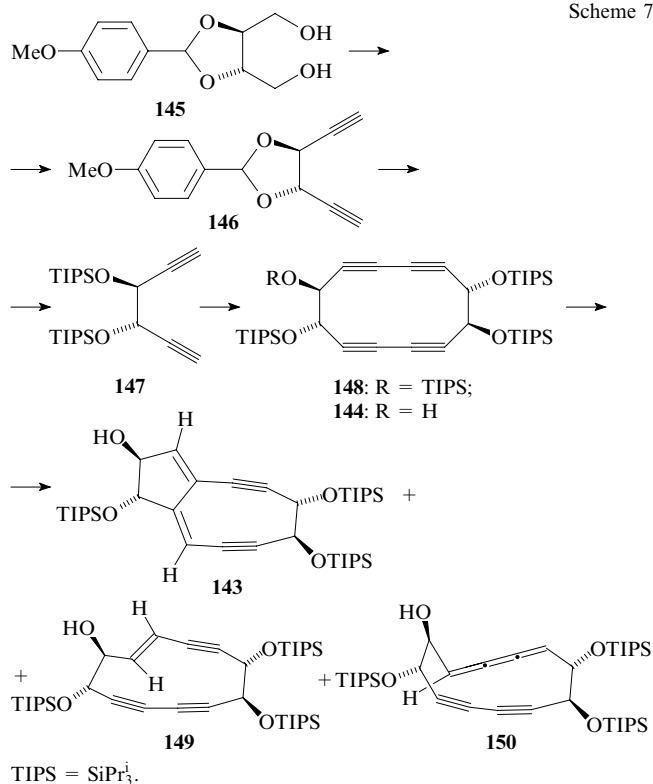
The synthesis of the bicyclic core of enediyne **143** by reductive cyclisation of the 12-membered tetrayne precursor **144** has been described¹⁹³ (Scheme 7).

Diol **145** synthesised from L-tartrate is converted into bis(di-bromoalkene) by oxidation followed by methylenation. Treatment of this product with *n*-butyllithium (4 equiv.) affords diyne **146**. Deacetalation followed by *O*-triisopropylsilylation (**146** → **147**) and oxidative dimerisation in the presence of copper derivatives converts this diyne into symmetrical cyclic tetrayne **148**.¹⁹³

The key step of the synthesis is the reductive cyclisation of non-symmetric tetrayne **144** on treatment with NaAlH(OCH₂CH₂NMe₂)₃ and KHMDS, which yields bicyclic compound **143** and two isomeric products: *trans*-alkene **149** and cumulene **150**.¹⁹³

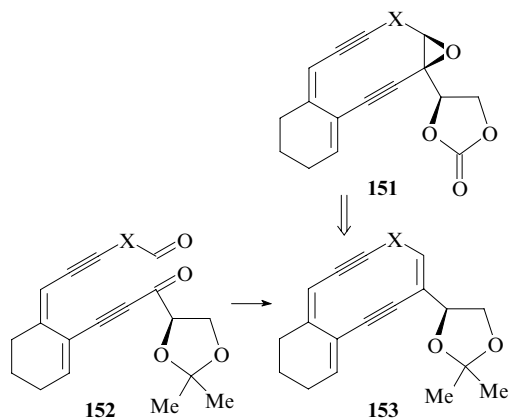
The interest in the neocarzinostatin chromophore stimulated the search for its stable analogues and development of numerous new synthetic procedures. In a number of papers, the McMurry reaction [coupling of carbonyl compounds under the action of

Scheme 7



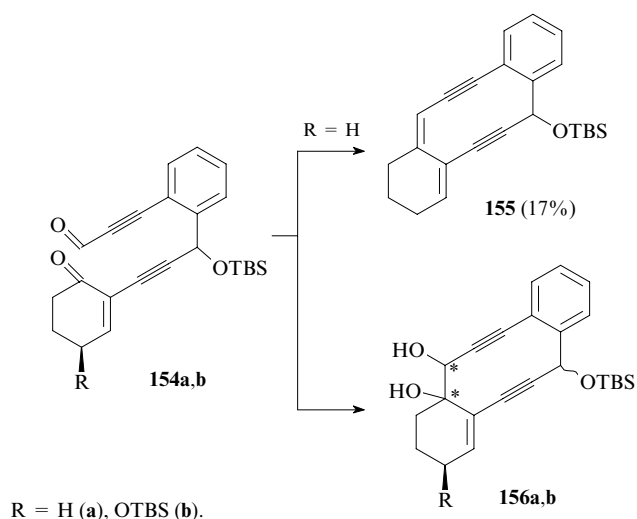
titanium(0) complexes] was shown to be promising for dienediyne ring closure.^{194–200}

On the way to NCS models containing an epoxy group and a carbonate ring (compound **151**), researchers^{195–198} prepared dienediynic oxo aldehydes **152** and successfully carried out the McMurry ring closure to obtain trienediyne products **153**.



X = CH_2CH_2 , CMe_2 .

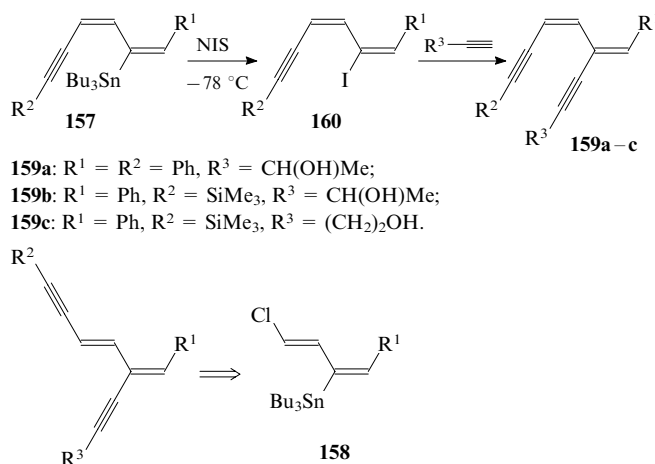
An alternative retro synthesis of this type of bicyclic systems implies scission of the diyne ring at its second double bond. This approach was implemented using cyclisation induced by titanium complexes.¹⁹⁹ In this case, oxo aldehydes **154a,b** were involved in the reaction. Olefination was possible only for unsubstituted compound **154a**.



In the case of bis-silylated oxo aldehyde **154b**, pinacol coupling (carried out with the same titanium reagent but at -20°C) proved to be efficient. Note that both pinacol couplings, **154a** $\rightarrow$ **156a** and **154b** $\rightarrow$ **156b**, are diastereoselective. The yields of diols **156a,b** (60% and 40%) are much higher than that of alkene **155**.¹⁹⁹

Analogues of natural antibiotics having a dienediyne fragment^{200–202} are also synthesised from α -bromocyclopentenone,^{203–205} bis(enol triflates)^{206–208} and xylitol.²⁰⁹

A stereocontrolled and flexible strategy for the synthesis of acyclic (*Z,E*)- and (*E,E*)-dienenediynes from readily available organotin compounds **157** and **158** has been proposed.²¹⁰



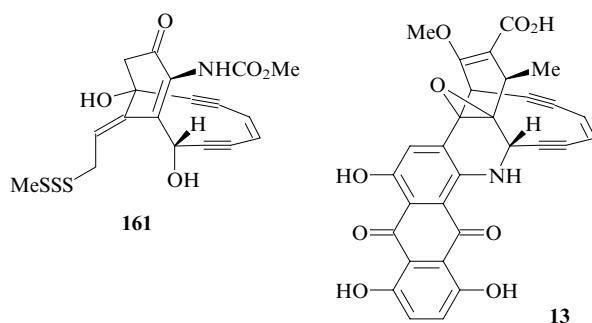
For example, the synthesis of (*Z,E*)-dienenediynes **159a–c** starts from dienyne **157**.²¹⁰ The use of *N*-iodosuccinimide allows stereoselective preparation of derivatives **160**, which yield dienediynes **159a–c** upon cross-coupling with terminal alkynes in the presence of a Pd/Cu-catalyst. The workup and concentration of the reaction mixtures on deactivated silica gel yields pure (*Z,E*)-dienenediynes **159a–c** (yields 49%–51%).²¹⁰

2. Calicheamicin and related molecules

Following the first publications dealing with the structure of calicheamicin, publications concerning the construction of its enediyne core appeared.^{21, 23, 30, 211–216} The total synthesis of calicheamicin-aglycone (calicheamicinone) and its analogues was carried out by Danishefsky and co-workers.²¹⁷ They also compared the behaviour of calicheamicin γ_1^1 and calicheamicinone in DNA cleavage and demonstrated the importance of the presence

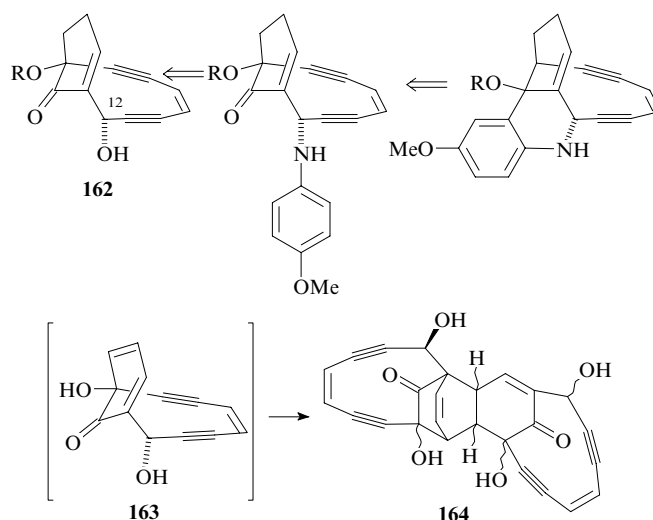
of carbohydrate fragments in the natural product.²³ The total synthesis of calicheamicin γ_1^1 carried out by Nicolaou and co-workers²¹⁸ includes 28 stages (1.4% overall yield).

A number of synthetic routes to calicheamicinone (**161**) (see Refs 211–216 and 219) and dynemicin (**13**) having a similar bicyclic core have been reported.^{214–216}



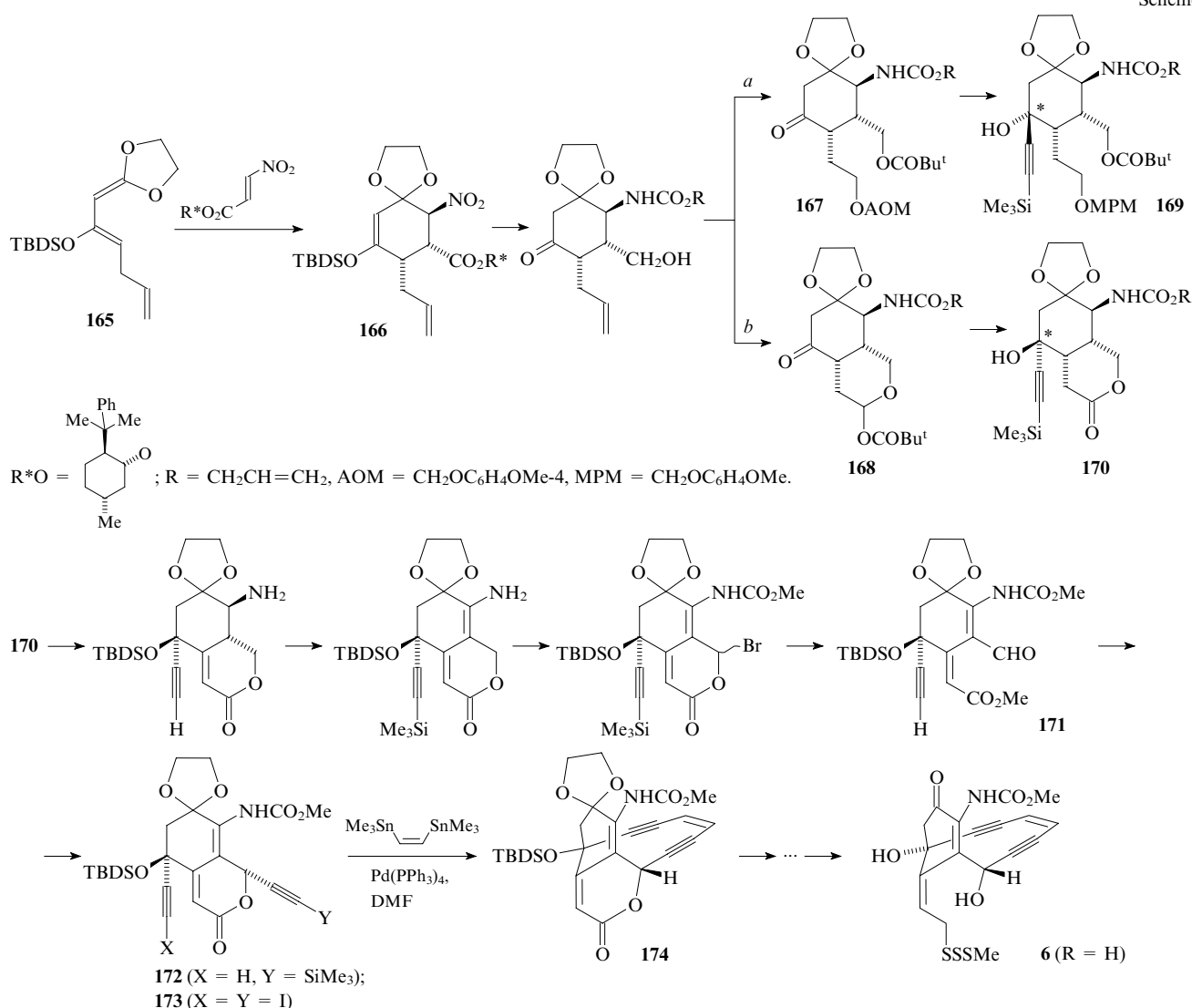
An attempt²¹³ to carry out interconversion of calicheamicinone and dynemicin analogues prompted by the obvious structural similarity of these two molecules deserves mention. A possible way of this transformation is the replacement of the 12-hydroxy group in compound **162** by an aniline fragment with retention of the configuration followed by intramolecular arylation.

However, the intermediate bicyclic ketones **163** formed underwent dimerisation through [2 + 4]-cycloaddition. Deprotection of the oxo group gave dimers **164** with different stereochemistry of ring fusion.²¹³



Detailed synthesis of optically pure calicheamicinone has been reported.^{220–222} The synthesis starts with stereoselective Diels–Alder reaction of ketene acetal **165** with chiral R^* -3-nitroprope-

Scheme 8



noate containing a (–)-8-phenylmenthol residue (Scheme 8).²²² Thus, the desired stereochemistry of the skeleton is founded in the initial stage. Then adduct **166** is converted, along two pathways, into ketones **167** (pathway *a*) and **168** (pathway *b*). These ketones add lithium trimethylsilylacetylide to give *syn*- and *anti*-addition products, *viz.*, alcohols **169** and **170**, respectively.

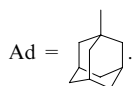
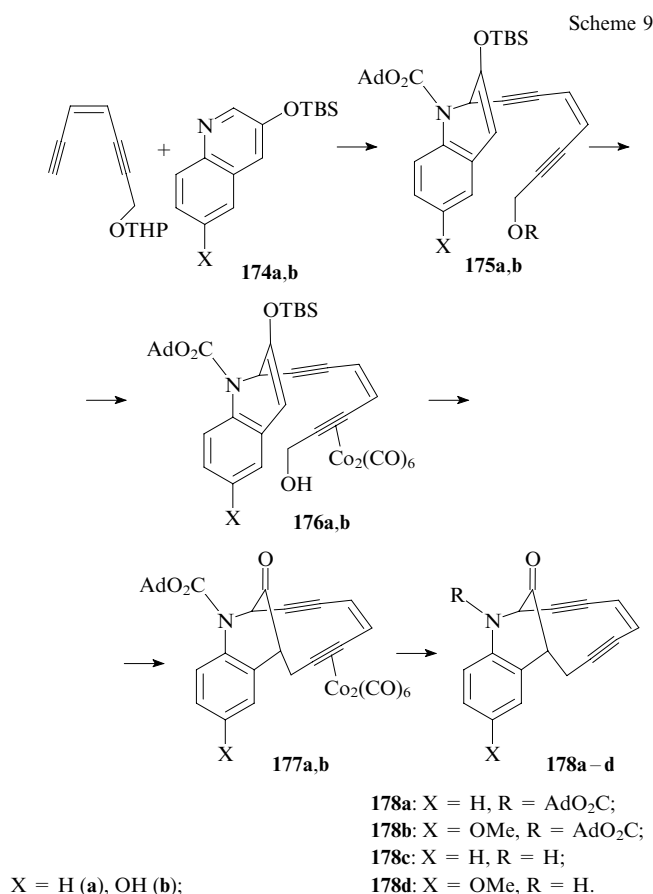
During the transformation of alcohols **169** and **170** into (–)-calicheamicinone, the stereogenic centres, except for C*, are racemised, both diastereomers giving the same final product.²²²

The subsequent series of oxidation stages (for introduction of double bonds), protecting group manipulations, halogenation and hydrolysis give aldehyde ester **171**, which stereoselectively adds lithium trimethylsilylacetylide to give diyne **172**. Calicheamicinone ring closure was accomplished by the reaction of diiodide **173** with *cis*-bis(trimethylstannyl)ethene to give precursor **174**. Nine more stages it took to introduce the trisulfide substituent and attain (after removal of the protecting group) the required functionalisation.^{223, 224}

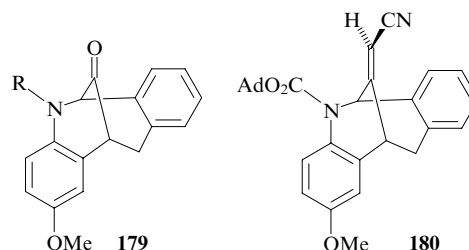
3. Dynemicin and its analogues

Structural features, the activation mechanism and total synthesis of the dynemicin chromophore are considered in the papers by Nicolaou and Smith,² Danishefsky *et al.*,²¹⁷ Myers *et al.*^{225, 226} and other researchers.^{35, 227, 228}

The synthesis of the enediyne fragment of dynemicin is shown in Scheme 9.⁴² *O*-Tetrahydropyranyl ether of hept-4-ene-2,6-diyne-1-ol reacted with protected 3-hydroxyquinolines **174a,b** to give adducts **175a,b**. The removal of the tetrahydropyranyl protection and the reaction with $\text{Co}_2(\text{CO})_8$ yield complexes **176a,b**, which cyclise to give bicyclic structures **177a,b**. Decomplexation of the latter affords products **178**. The structure of enediyne **178b** was proved by X-ray diffraction.²²⁹



The aromatisation rates of the synthesised enediynes were considerably different, although the distances between the acetylenic bonds in them are approximately the same. The determination of the cycloaromatisation rate of enediyne **178b** to give compound **179** in the temperature range from 65 to 114 °C allowed calculation of thermodynamic parameters of the reaction.⁴² The experimental data extrapolated to 37 °C show that **178b** is stable under physiological conditions.

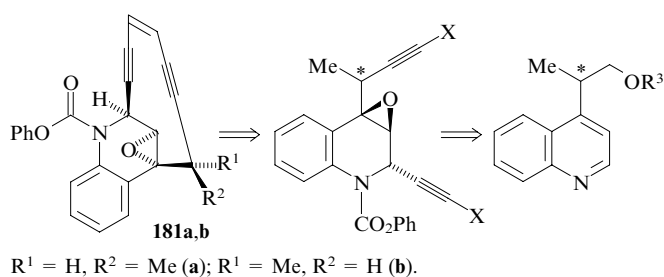


Amine **178d** undergoes cycloaromatisation in THF on heating to 51–67 °C. The cycloaromatisation rate of amine **178d** increases with temperature faster than that of carbamate **178b**. At 37 °C, amine **178d** cyclises 1.6 times faster than carbamate **178b**, while at 65 °C these rates differ by a factor of 20. The cycloaromatisation of nitrile obtained from ketone **178b** results in compound **180**. At 37 °C, this reaction proceeds 500 times faster than cycloaromatisation of ketone **178b**, although the distances between the acetylenic bonds in these compounds are almost the same.⁴²

The synthesis of the naphtho[2,3-*b*]quinoline part of the dynemicin molecule has been reported.^{42, 230, 231}

The subsequent development of the dynemicin chemistry^{232–236} confirmed that its specific antitumour properties are related to the presence of the 10-membered enediyne ring.^{237–242} Therefore, investigation into the synthesis of second-generation dynemicin analogues becomes topical.

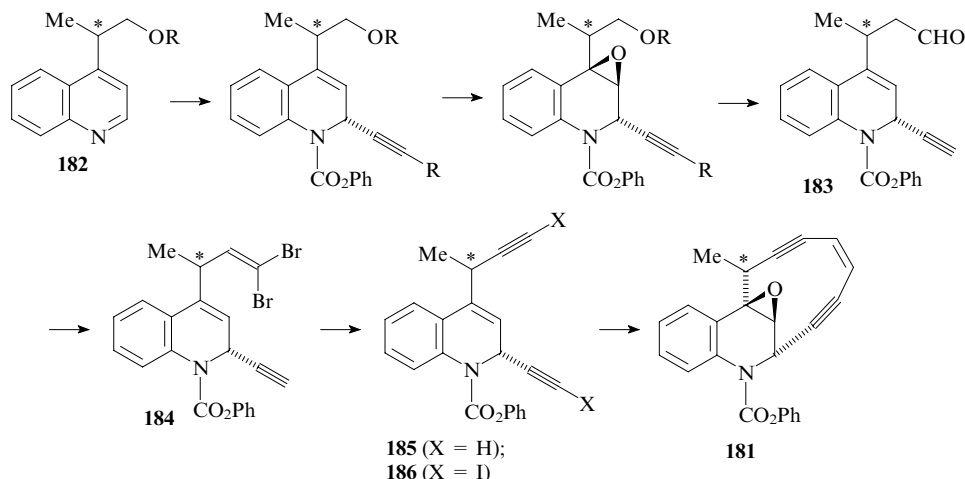
The total synthesis of two diastereomeric dynemicin analogues (**181a,b**) was carried out and their activities with respect to DNA cleavage was studied.^{243–246} The retro-synthetic analysis is presented below.



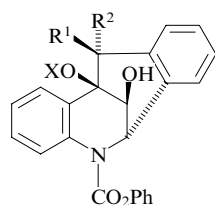
Chiral quinoline derivatives prepared^{247, 248} in an optically pure state by enantiomer resolution or by a microbiological procedure were used as the starting compounds. The stereoselective addition of protected acetylide to quinolines **182** and the subsequent modification of the alcohol function leads to aldehydes **183** (Scheme 10). To introduce the second triple bond, aldehydes **183** were converted into dibromoalkenes **184** and then into alkynes **185**.²⁴³ The macrocycle was closed by treatment with *cis*-bis(trimethylstannyl)ethene. For cross-coupling, diyne **185** was converted into diiodide **186**.

Epoxide ring opening (on treatment with *p*-toluenesulfonic acid) in the target enediynes **181a,b** was accompanied by their fast Bergman cyclisation.^{249, 250} After neutralisation of the acid with triethylamine and stirring for 24 h in the presence of CHD (as a

Scheme 10



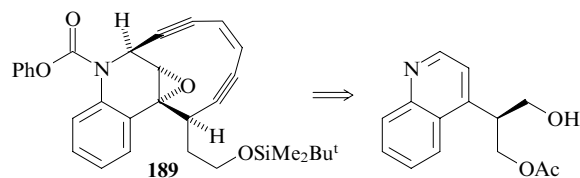
hydrogen atom donor), diol **187** and mono-*p*-toluenesulfonate **188** were isolated.



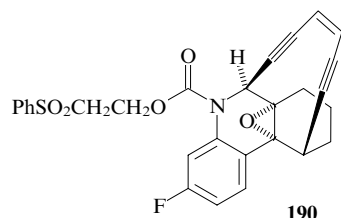
187 ($R^1 = \text{Me}$, $R^2 = \text{X} = \text{H}$);
188 ($R^1 = \text{H}$, $R^2 = \text{Me}$, $\text{X} = \text{Ts}$)

Biological tests revealed high activity of enediynes **181a,b** with respect to the plasmid DNA.²⁵¹

The stereoselective synthesis of the simplest dynemicin analogue **189**, which is active against plasmid DNA, has been described.²⁵²



The susceptibility to cycloaromatisation and the biological activity of tricyclic enediyne **190** have been studied.²⁵³



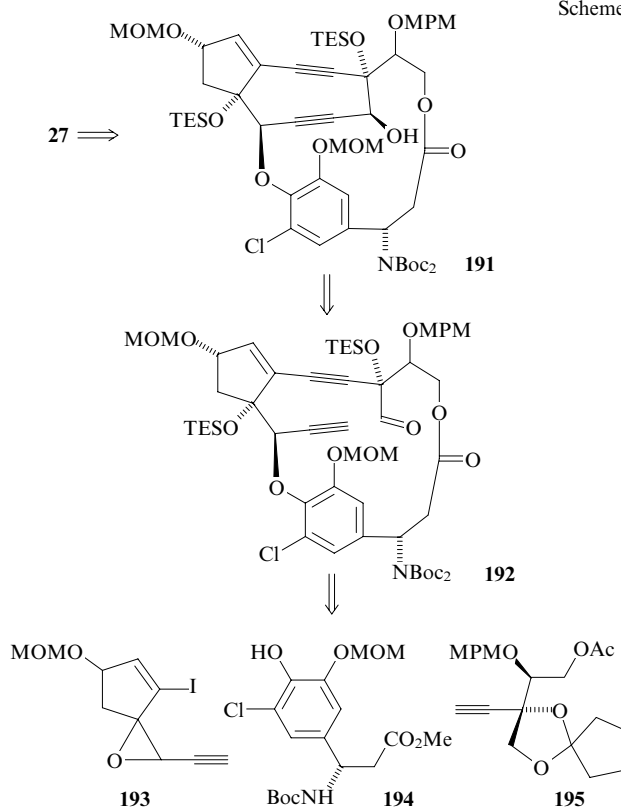
4. Antibiotic C-1027

The high biological activity of the enediyne antibiotic C-1027 stimulated the studies aimed at the construction of its nine-membered ring^{254,255} and its total synthesis.^{60,256–265}

The retro-synthetic analysis⁶⁰ of the chromophore macrolide **27** is shown in Scheme 11.

The total synthesis of molecule **27** is completed by introducing of an amino sugar and benzoxazine into the core **191** with simultaneous formation of two double bonds. Since diyne **191** is unstable (this is confirmed by experiments on model compounds),

Scheme 11



MOM = MeOCH₂, TES = Et₃Si.

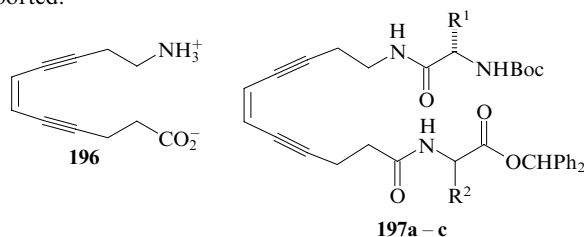
it is necessary to construct the macrolactone system prior to construction of the nine-membered ring. Diyne **191** is formed upon cyclisation of aldehyde **192** under the action of the LiN(SiMe₃)₂–CeCl₃ system. In turn, aldehyde **192** is prepared by the convergent coupling of three fragments, **193**, **194** and **195**.⁶⁰

V. Introduction of the enediyne fragment into other classes of organic compounds

Studies of enediynes have long been concentrated on their synthesis and reactivity. However, when it became clear that the biological activity of this class of compounds is correlated with the presence of (*Z*)-1,5-diyne-3-ene fragment,^{266–271} attempts were undertaken to introduce this structural unit into other classes of biologically active and natural compounds. A number of typical examples are given below.

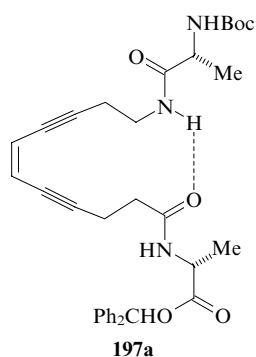
1. Enediyne tripeptides

The synthesis of amino acid **196** and peptides **197a–c**, promising compounds *en route* to new enediyne antibiotics, has been reported.²⁷²



$R^1 = R^2 = \text{Me}$ (**a**), Bn (**b**); $R^1 = \text{Me}$, $R^2 = \text{CH}_2\text{OH}$ (**c**).

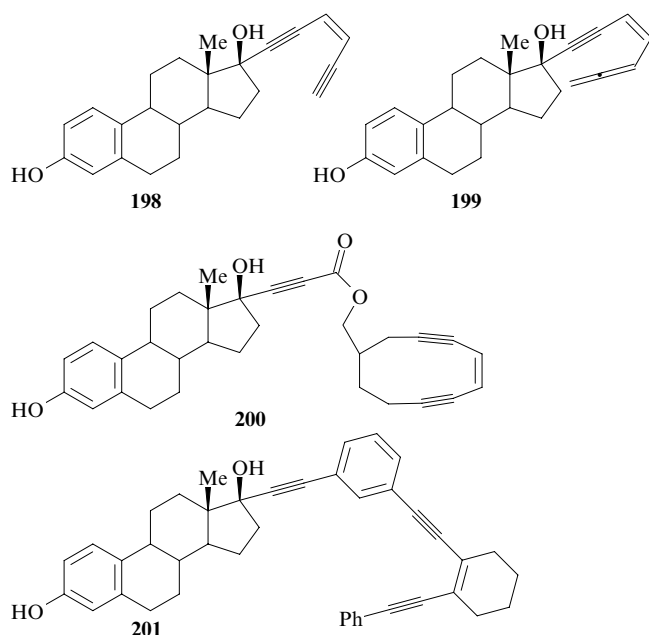
Cycloaromatisation of protected enediyne peptides **197a–c** yields polymers. A DSC study has shown²⁷² that the reaction has an isothermal peak typical of the Bergman cyclisation. Peptide **197b** cyclises more easily (135 °C) than peptide **197a** (180 °C), which is related to the presence of the hydrogen bond in the latter.



Analysis of changes in the NMR spectra of peptide **197a** depending on temperature suggests stabilisation of its conformations owing to hydrogen bonds (a similar situation is observed for free amino acid **196**).²⁷³

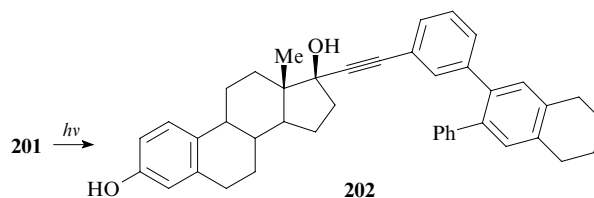
2. Enediyne estrogens

By introduction of substituents containing an enediyne system into the estradiol molecule, a family of steroid hormones **198–201** has been obtained.^{274, 275}

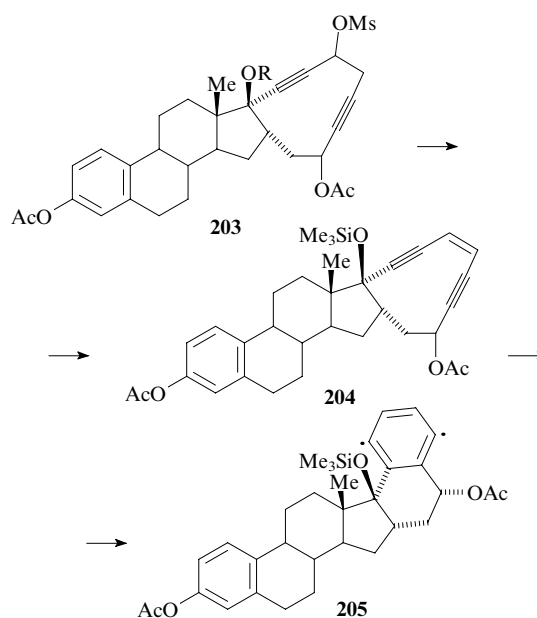


Enedinyln- and enyneallenylestrogens **198** and **199** were actually found to produce diradicals in the Bergman or Myers cycloaromatisation processes.^{276–281} The diradicals abstract hydrogen from DNA and proteins, which results in their degradation and agglomeration.

Compound **201** undergoes the Bergman photocycloaromatisation to give product **202**.^{274, 282–284} A series of estrogen–enediyne conjugates have been prepared and their affinity with respect to the hER α receptor has been determined.



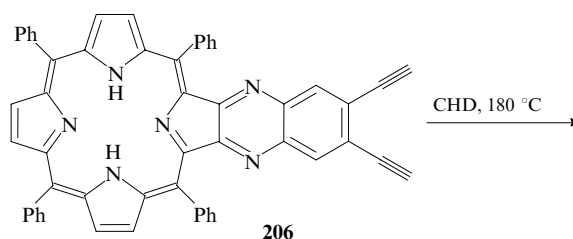
Estradiol derivatives of the type **203**[§] eliminate methanesulfonic acid to be converted into enediyne steroids **204**, which cyclise to give benzenoid diradical **205** at 25 °C (half-conversion time is 108 min).²⁸⁷



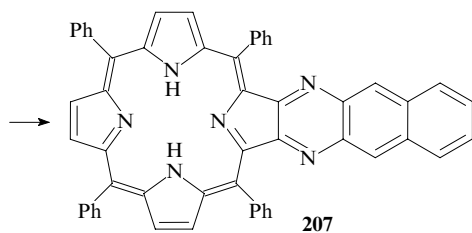
$R = \text{H}, \text{SiMe}_3$; $\text{Ms} = \text{MeSO}_2$.

3. Porphyrin enediynes

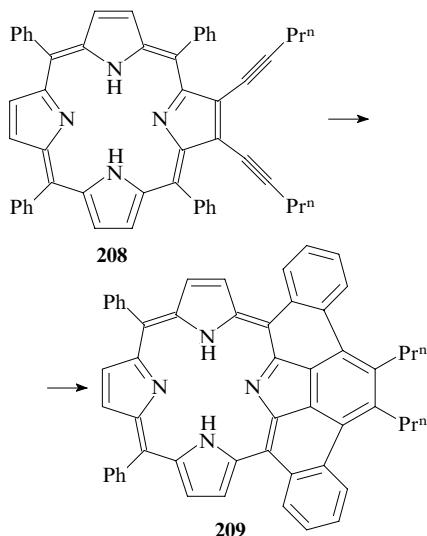
The synthesis of porphyrin **206** containing an enediyne fragment has been reported.²⁸⁸ Heating (180 °C) of derivative **206** in the presence of CHD results in cycloaromatisation to give porphyrin **207**.



[§] The synthesis of derivatives **203** has been described.^{285–287}



Porphyrin enediyne **208** with disubstituted triple bonds cyclises in a peculiar way, namely, with participation of neighboring phenyl groups to give a polyaromatic fragment in the porphyrin system **209**.²⁸⁹



Photoreactive porphyrin enediynes, which undergo cycloaromatisation on exposure to radiation, have been described.^{290, 291}

VI. Conclusion

During the last decade, a substantial progress in the enediyne chemistry has been achieved and information flow concerning these peculiar acetylenic derivatives has grown. The structures of the natural and synthetic compounds described above, which actively destroy cancer cells and suppress bacteria and microbes, are characterised by great diversity, but the presence of the (*Z*)-3-ene-1,5-diyne fragment is a common feature of all these derivatives. Its key chemical property and the cause for the unique biological action is the ability to undergo cycloaromatisation involving two acetylenic bonds, resulting in 1,4-benzenoid diradicals. Currently, this reaction is the subject of active theoretical and experimental research not merely due to the fact that this contributes to the understanding of the chemistry of enediyne antibiotics, but also because this is a new, exceptionally powerful synthetic method of organic chemistry as a whole¹²¹ and, in particular, acetylene chemistry.

The search for new types of enediyne structures active with respect to DNA cleavage remains topical; nitrogen-containing enediynes (dialkynyldiazenes) appear to be especially promising.¹³⁶

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New materials for SRS lasers

T T Basiev, V V Osiko

Contents

I. Introduction. Modern solid-state lasers	847
II. The laser wavelength conversion using stimulated Raman light scattering	849
III. The preparation and characterisation of single crystals of calcium, strontium, barium and lead molybdates and tungstates for SRS lasers	852
IV. Raman scattering spectra of calcium, strontium, barium and lead molybdates and tungstates	854
V. SRS converters and lasers based on novel crystals	860

Abstract. The problem of search for new materials for spectrally positioned laser sources, which is central for modern photonics, is discussed. The use of the stimulated Raman scattering effect in crystals offers a highly efficient way to the design of such sources. The recent results of investigations into this effect for a large number of various types of crystalline materials are presented. The most promising compounds, as regards the realisation of different laser operation modes, are considered, including calcium, strontium, barium and lead molybdates and tungstates. Several examples of functioning efficient lasers based on novel materials exhibiting the stimulated Raman light scattering effect are given. The bibliography includes 50 references.

I. Introduction.

Modern solid-state lasers

Photonics is one of the most rapidly emerging fields within modern high technologies. Generally, the term photonics refers to techniques for the generation and conversion of light or other types of electromagnetic radiation. Over the recent years, photonics has experienced an explosive growth. Partly, this is due to the fact that it determines to a large extent the progress in such fields as medical, environmental and scientific instrument production, advanced technologies of materials processing and armament industry. But the most important reason is that photonics ever deeper penetrates into the information technologies, *i.e.*, the techniques used for the information acquisition, storage, processing, transmission and retrieval. Furthermore, many experts believe that it is photonics that will determine the cutting edge of informatics in the future. This forecast is based on the unprecedented high performance, information capacity and noise immunity provided by photonic devices. The greatest contribution to the emergence of photonics was made in the middle of the 20th century by academicians A M Prokhorov and N G Basov and by an American scientist, professor Ch Townes, who laid the

foundations of quantum electronics and laser physics (these achievements were recognised with the Nobel prize in physics for 1964). These pioneering results gave rise to the development of various types of lasers exploiting substances in all possible aggregate states, *i.e.*, plasma, gas, vapour, crystal, glass and liquid, as working media. More recently, academician Zh I Alferov invented semiconducting heterostructures (the Nobel prize in physics for 2000 shared with H Kroemer and J S Kilby), which enabled the miniaturisation and functional integration of photonic devices.

It is dielectric and semiconducting crystals and structures derived from them that are the most typical materials used in photonics.¹ Crystals are superior to other types of materials due to the following factors:

- a high density of active particles (*e.g.*, atoms, ions, molecules, atomic clusters), which can be as high as 10^{23} cm^{-3} ; this provides the small size of photonic devices and a possibility of their further miniaturisation and functional integration;
- a regular periodic packing of atoms (ions, molecules), which gives rise to symmetric structures and degenerate energy levels and, consequently, to narrow resonances and large photon absorption and emission cross-sections and also to large nonlinear optical coefficients;
- a variety of possible compositions (in particular, a huge number of combinations of crystalline matrices and active dopants) and crystal structures.

Contemporary photonics is an extended research field with numerous subfields. It is next to impossible to comprehensively address the multitude of directions of photonics development in one paper. Therefore, in the present review, we limit ourselves to only one of the current directions, *viz.*, the design of spectrally positioned light sources and give emphasis to materials science-oriented aspects of this problem. A few examples given below will help to outline the current challenges associated with this direction.

Figure 1 depicts a typical IR transmission spectrum of the Earth's atmosphere together with absorption spectra of some molecular gases. It is apparent that the atmosphere has several so-called transmission windows, *i.e.*, spectral ranges of the optical transparency to the electromagnetic radiation. One of such windows is located in the visible region of the spectrum, which is actually a prerequisite to the existence of life on the Earth. A few of such windows also occur in the IR region of the spectrum, *e.g.*, at $2\text{--}2.5 \mu\text{m}$ ($5000\text{--}4000 \text{ cm}^{-1}$) and $4\text{--}5 \mu\text{m}$ ($2500\text{--}2000 \text{ cm}^{-1}$). The latter region is of particular interest since it encompasses vibrational features of many molecules, including

T T Basiev, V V Osiko Laser Materials and Technologies Research Centre, A M Prokhorov General Physics Institute, Russian Academy of Sciences, ul. Vavilova 38, 119991 Moscow, Russian Federation.
Fax/tel. (7-495) 135 02 67, e-mail: basiev@lst.gpi.ru (T T Basiev),
tel. (7-495) 135 77 44, e-mail: osiko@lst.gpi.ru (V V Osiko)

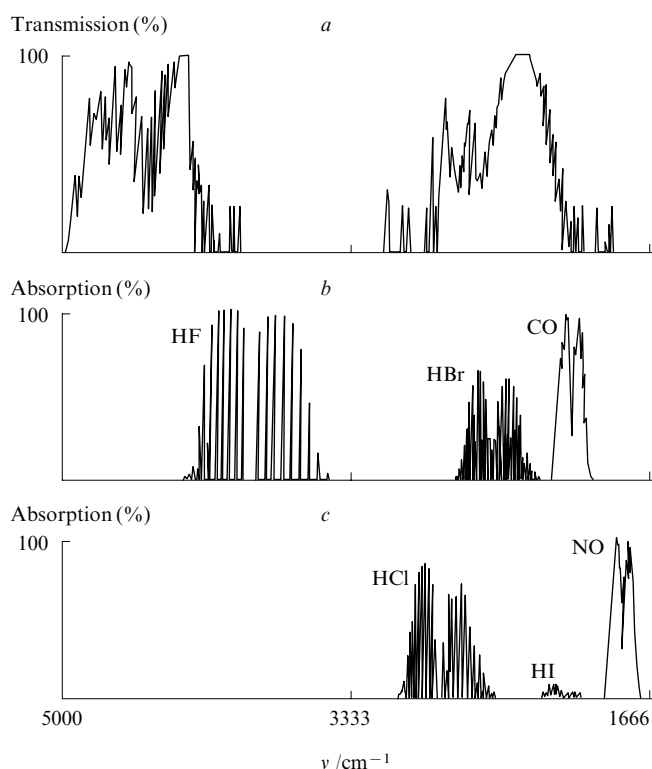


Figure 1. A transmission spectrum of the Earth atmosphere in the IR range (a) and IR absorption spectra of some molecular gases (b, c).¹

common atmospheric pollutants that are to be controlled, such as hydrogen halides or oxides of carbon, nitrogen and other elements. Remote measurements of the concentration of these molecules in the atmosphere can be accomplished by their excitation with a laser. This requires lasers radiating at strictly defined wavelengths corresponding to the absorption bands of the respective molecules, *i.e.*, spectrally positioned laser sources.

Table 1. Chemical elements possessing useful 'analytical' lines of electronic transitions in the wavelength range of 200–400 nm.¹

Element	λ_{ex} /nm	λ_{fluor} /nm	Element	λ_{ex} /nm	λ_{fluor} /nm
Ag	328.1	338.3	Ni	301.9	310.1
Al	308.2	308.2	Pb	283.3	405.8
Au	242.8	312.3	Pt	293.0	299.8
B	249.6	249.7	Re	289.6	439.1
Be	234.8	234.8	Sb	231.1	231.1
Cd	326.1	326.1	Se	297.4	534.9
Co	304.4	340.5	Si	251.4	298.8
Cr	335.2	464.6	Sn	286.3	300.9
Cu	324.7	510.5	Sr	293.1	716.7
Fe	296.7	373.5	Ta	287.3	304.9
Ga	287.4	294.4	Te	225.9	253.0
Ge	265.2	275.4	Th	306.0	347.1
Hg	253.6	253.6	Ti	293.3	296.7
In	303.9	329.5	Tl	276.8	352.9
Ir	295.1	322.1	U	311.5	311.5
Li	323.3	323.3	V	283.8	286.4
Lu	298.9	298.9	W	291.1	402.8
Mg	285.2	285.2	Y	297.4	302.2
Mn	279.5	279.5	Zn	307.6	307.6
Mo	294.4	444.3	Zr	296.1	301.1
Nb	374.2	376.4			

Here is another example. The wavelengths of the most intense atomic absorption (λ_{ex}) and fluorescence (λ_{fluor}) lines for a series of common metals are summarised in Table 1. These are the so-called 'analytical' spectral lines suitable for the determination of trace concentrations of these metals using atomic absorption or atomic emission spectroscopy. The remote determination of trace concentrations of metals in the atmosphere, subterranean waters or soils, for instance, for environmental control, also requires spectrally positioned sources but rather in the near UV spectral range.

The list of tasks requiring spectrally positioned sources is rather long. In addition to the aforementioned environmental science, it includes ground-based equipment for the communication with aircrafts and spaceships, fibre-optical communication systems, medicine, *etc.*

Conceptually, the problem of the design of such sources is similar to the problem of the generation and reception of radio waves with a radio receiver strictly tuned to the wavelength emitted by a transmitter. However in the present case, it is the operational frequency of the receiver that is strictly defined and thus the transmitter frequency has to be adjusted accordingly. Besides, modern radio devices allow easy frequency adjustments of the radio signal over a broad range to achieve the resonance. On the other hand, the majority of lasers emit nearly monochromatic radiation at a fixed frequency. Data on the most efficient modern laser crystals are compiled in Table 2. Unfortunately, the 'as is' spectral properties of radiation generated by laser crystals is unsuitable for the design of spectrally positioned radiation sources (since the emission frequencies of these crystals are not resonant with the absorption frequencies of the most convenient receivers). It has to be stressed that spectral lines in the absorption spectra of atoms, ions and molecules are very narrow with typical widths of only 10^{-1} – 10^{-2} cm^{-1} . The emission spectra of the majority of lasers are similarly narrow (0.1 – 1 cm^{-1}). Therefore, a random exact coincidence of a laser emission frequency and an absorption line of an atom or molecule is of vanishingly low probability.

Table 2. Most popular crystals used in monochromatic lasers.

Crystal	Activator : sensitiser	Oscillation wavelength /μm
Y ₃ Al ₅ O ₁₂	Nd ³⁺	1.064 (0.94; 1.32; 1.444)
	Yb ³⁺	1.030
	Er ³⁺	2.940
	Ho ³⁺ : Tm ³⁺	2.098
Gd ₃ Ga ₅ O ₁₂	Nd ³⁺ : Cr ³⁺	1.062
	Er ³⁺ : Cr ³⁺	2.790
Y ₃ Sc ₂ Ga ₃ O ₁₂	Nd ³⁺ : Cr ³⁺	1.058
	Er ³⁺ : Cr ³⁺	2.791
Gd ₃ Sc ₂ Ga ₃ O ₁₂	Nd ³⁺ : Cr ³⁺	1.061
YAlO ₃	Nd ³⁺	1.079
KGd(WO ₄) ₂	Nd ³⁺	1.067
YVO ₄	Nd ³⁺	1.064
LiYF ₄	Nd ³⁺	1.047 (1.053)

Two major ways to solve the problem of the design of laser sources with strictly spectrally positioned radiation for remote resonant excitation of atomic or molecular systems that are characterised by narrow spectral resonances can be envisaged:

(1) the application of tunable lasers generating light at a variable frequency according to the principle of a transmitter adjustment to resonant absorption frequencies of atoms or molecules;

(2) the conversion of radiation generated by existing lasers by a shift to shorter or longer wavelength ranges to make the spectrum of the transformed radiation match the required wavelength. The radiation of both monochromatic and tunable lasers can be a subject of conversion. A shift in the radiation wavelength

can be achieved with crystals manifesting prominent nonlinear optical properties based on such physical phenomena as harmonic conversion, parametric light generation or stimulated light scattering.

The most promising crystals applicable in tunable lasers and their respective tunability ranges are given in Table 3. It is evident that the frequency tuning can indeed fill up some gaps in the accessible range of laser frequencies, but only to a limited extent.

Table 3. Most popular crystals used in tunable lasers.

Crystal	Activator	Oscillation wavelength range / μm
Al_2O_3	Ti^{3+}	0.650–1.110
$\text{Y}_3\text{Al}_5\text{O}_{12}$	Cr^{4+}	1.340–1.570
Mg_2SiO_4	Cr^{4+}	1.130–1.367
LiSrAlF_6	Cr^{3+}	0.780–0.990
	Ce^{3+}	0.285–0.315
MgF_2	Co^{2+}	1.550–2.300
ZnSe	Cr^{2+}	2.200–2.812
LiF	F_2^- (see ^a)	1.060–1.300
	F_2^+ (see ^a)	0.800–1.100

^a F colour centre.

A significant extension of the accessible range of frequencies has recently been achieved owing to the discovery of materials capable of changing the laser frequency through the stimulated Raman scattering.

II. The laser wavelength conversion using stimulated Raman light scattering

1. Theoretical fundamentals of the purposeful search for efficient materials

The phenomenon known nowadays as Raman light scattering was discovered in 1928. It was independently observed by Raman and Krishnan in liquids² and by Landsberg and Mandelshtam in crystals.³ Essentially, this phenomenon consists of the generation of a secondary radiation shifted to longer wavelengths by a value corresponding to the energy required to excite vibrations of atoms or molecules upon the propagation of an intense monochromatic light beam in a transparent medium. The Raman scattering event can be conveniently considered as a two-photon resonance achieved when the difference between the frequencies of incident (ν_I) and scattered (ν_S) light becomes equal to the frequency of an atomic or molecular vibration in the medium (ν_R)

$$\nu_I - \nu_S = \nu_R.$$

Due to the two-photon nature of the process, its cross-section (σ) is extremely small, *i.e.*, of the order of 10^{-30} cm^2 . That is the reason, why light sources with ultimately high radiation spectral densities are necessary for the observation of Raman scattering.

In 1962, Woodbury and Ng⁴ observed an intense IR component shifted by 1345 cm^{-1} with respect to the incident light in experiments on the ruby laser light modulation with a nitrobenzene-filled Kerr cell. Later on, this effect was interpreted as the stimulated Raman scattering (SRS).⁵

According to the quantum theory,^{5,6} the SRS intensity (associated with the Stokes scattering, *i.e.*, scattering accompanied by a shift to the IR spectral range) is proportional to the density of occupied states corresponding to three interacting fields, *viz.*, laser pumping photons (N_I), photons of the generated scattered wave (N_S) and ground-state phonons (or, equivalently, molecular vibrations) of the crystal (N)

$$\frac{dN_S}{dz} \sim N_I N_S N$$

(z is a coordinate).

In a steady-state mode where the duration of the incident laser pulse is longer than the vibrational phase relaxation time of the medium ($\tau_p \gg T_R$), the SRS intensity (I_S) generated in a layer of a scattering medium with a thickness l is given by

$$I_S(l) = I_S(0) \exp(g_{\text{st}} I_I l), \quad (1)$$

where I_I is the incident light intensity, g_{st} is the steady-state-mode gain coefficient

$$g_{\text{st}} = \frac{(d\sigma/d\Omega) \lambda_I \lambda_S^2 N}{\pi c \hbar n_S^2 \Delta\nu_R}.$$

Here, $d\sigma/d\Omega$ is the integral scattering cross-section, c is the speed of light, n_S is the refraction index of the medium at the scattered light wavelength, $\Delta\nu_R$ is the width of the respective line in the Raman spectrum.

Therefore, in a steady-state mode, the gain coefficient g_{st} is directly proportional to the integral Raman scattering cross-section and inversely proportional to the width of the respective Raman transition. The line width is, in turn, governed by the mechanism of the vibrational phase relaxation in the medium.⁷ The product $\Delta\nu_R^{-1} d\sigma/d\Omega$ quantifies the scattering amplitude in the spectral maximum. Hereinafter, this parameter is referred to as the peak Raman scattering cross-section and denoted as Σ_{peak} .

Wang considered⁸ the so-called transient Raman light scattering occurring when $\tau_p \leq T_R$ and the pumping spectral width is larger than $\Delta\nu_R$. Under these conditions in the case of a rectangular-shaped pumping pulse, the transient SRS gain coefficient g_{tr} relates to the above parameters through the following expression

$$g_{\text{tr}} l \approx 2(g_{\text{st}} l c \Delta\nu_R \tau_p)^{1/2}.$$

It is apparent from this expression that g_{tr} depends on the pumping pulse duration τ_p and $g_{\text{st}} \Delta\nu_R$ product, which represents the integral Raman scattering cross-section. Furthermore, Wang suggested⁸ a more straightforward relation of the gain coefficient to fundamental properties of the material. The SRS intensity in the analytical form is given by the following expression

$$I_S(l) \sim I_S(0) \exp \left[2 \left(\frac{I_I \tau_p l 8\pi^2 c^2 N}{\hbar \omega_S^3 n_S^2} \frac{d\sigma}{d\Omega} \right)^{1/2} \right].$$

As follows from this equation, the SRS gain coefficient is proportional to square root of the integral Raman scattering cross-section $d\sigma/d\Omega$. In this case, the SRS amplification can be estimated from the integral intensity of the respective line in the spectrum of spontaneous Raman scattering

$$\Sigma_{\text{int}} \sim \frac{d\sigma}{d\Omega}.$$

This implies that the performance of a material as regards the efficiency of the SRS conversion of the laser radiation can be evaluated based on an analysis of the respective spontaneous Raman scattering spectra. Importantly, such measurements can be performed not only for bulk optically homogeneous species but also for fine polycrystalline powders, which greatly simplifies their experimental realisation.

2. Performance of various inorganic crystals in SRS lasers as estimated by spontaneous Raman light scattering

According to theoretical calculations, the SRS threshold corresponding to $I_S \approx I_I$ is achieved at an exponent argument in the formula (1) of ~ 30 . Typical values of g_{st} for gaseous and liquid

media lie in the range of $1\text{--}3\text{ cm GW}^{-1}$ (e.g., $g_{\text{st}} = 1.5\text{ cm GW}^{-1}$ and 3 cm GW^{-1} for hydrogen and nitrobenzene, respectively). This implies that the realisation of the SRS mode in these systems requires either a thick scattering medium layer ($30\text{--}100\text{ cm}$) or a highly intense ($\sim 1\text{ GW cm}^{-2}$) pumping radiation.

Among potential media for the SRS conversion of the laser radiation, solid systems and crystals in particular exhibit the following clear advantages:

- a high concentration of Raman-active sites, $N = 10^{22}\text{--}10^{23}\text{ cm}^{-3}$;
- a high gain coefficient, $g = 1\text{--}50\text{ cm GW}^{-1}$;
- a small scattering length (thin layers of a scattering medium), $1\text{--}10\text{ cm}$;
- a variety of possible Raman shifts, from 10 cm^{-1} to 2000 cm^{-1} ;
- a broad optical transparency range, from $0.2\text{ }\mu\text{m}$ to $100\text{ }\mu\text{m}$;
- a high heat conductivity, $1\text{--}20\text{ W (cm K)}^{-1}$;
- a weak temperature dependence of the refraction index n , $dn/dT = 10^{-6}\text{--}10^{-5}\text{ deg}^{-1}$;
- a resistivity towards adverse ambient conditions;
- a high thermal stability.

The first observation of the SRS in solids dates back to 1963. Eckhardt *et al.*⁹ investigated this effect in crystals of diamond, calcite and α -sulfur. Naturally occurring calcite CaCO_3 is a very common SRS material, since it typically forms large single crystals characterised by a relatively high optical homogeneity. Calcite reveals an intense quasi-molecular SRS-active vibrational mode at 1086 cm^{-1} with a width of $\sim 1.2\text{ cm}^{-1}$. The SRS gain coefficient is 5.5 cm GW^{-1} at an incident wavelength of 532 nm . Diamond crystals are characterised by a record high gain coefficient and a large Raman shift (1332 cm^{-1}) but are of low practical importance due to their small sizes and high costs. In 1980, crystals of metal nitrates, i.e., NaNO_3 , $\text{Ba(NO}_3)_2$ and $\text{Pb(NO}_3)_2$, were proposed as promising candidates for observation of the SRS effect.¹⁰ These materials reveal intense vibrational modes at $\sim 1050\text{ cm}^{-1}$ due to the internal totally symmetric vibrations of the quasi-molecular NO_3 groups. The gain coefficient of $\text{Ba(NO}_3)_2$ is 47 cm GW^{-1} at an excitation wavelength of 532 nm .¹¹ With these crystals, the conversion efficiency of the incident laser radiation as high as 80% was achieved at a duration of the laser pulse of a few nanoseconds.^{7, 12, 13} Owing to this high efficiency, a number of commercial solid-state SRS lasers were designed based on the $\text{Ba(NO}_3)_2$ crystals, in particular, those operating in a spectral range of $\sim 1.5\text{ }\mu\text{m}$, which is safe for human eyes. However barium nitrate performs well only for the conversion of nanosecond laser pulses. Upon a transition to shorter, picosecond, pulses, the performance of $\text{Ba(NO}_3)_2$ is drastically decreased: the SRS threshold is increased by one order of magnitude due to slow relaxation of the vibrational excitations therein ($\sim 30\text{ ns}$).¹⁴ In addition, $\text{Ba(NO}_3)_2$ is characterised by a low moisture resistance, poor heat conductivity and moderate mechanical properties.

Andryunas *et al.*¹⁵ and Basiev *et al.*¹⁶ observed the SRS activity in $\text{KGd(WO}_4)_2$ (potassium gadolinium tungstate, hereinafter, referred to as KGW) crystals. The SRS gain coefficient of this tungstate at an incident wavelength of 1064 nm is twice lower than that of $\text{Ba(NO}_3)_2$ (6 cm GW^{-1}). Nevertheless, owing to a higher integral gain coefficient, KGW crystals are highly efficient in ps-pulsed SRS lasers.¹⁷ Furthermore, in contrast to nitrates, KGW is characterised by a substantially higher hardness and chemical stability and is relatively inexpensive and available as large single crystals.

Over the last decade, hundreds of crystalline compounds belonging to different classes have been evaluated and compared in the Laser Materials and Technologies Research Centre at the A M Prokhorov General Physics Institute of the Russian Academy of Sciences. The classes of compounds studied include metal and ammonium carbonates, nitrates, phosphates, borates, sili-

cates, niobates, chlorates, bromates, iodates, sulfates, molybdates and tungstates. As a basic method for the preliminary evaluation of crystals under study, spontaneous Raman light scattering was utilised.^{16, 17}

An Ar ion laser operated at a wavelength of 488 nm was used as a radiation source in Raman scattering experiments. The power of the laser beam at a sample surface was 1 W . The Raman scattering spectra were acquired with a Spex Ramalog-1403 double spectrometer in the backscattering geometry. The spectral resolution of the setup was $0.2\text{--}1.0\text{ cm}^{-1}$. Both single crystals and polycrystalline powders were investigated. For a correct comparison of the integral and peak scattering cross-sections among different samples, the measurements were performed on rectangular plates with thicknesses of 0.7 mm or 2 mm cut from the respective single crystals. A plate with a thickness of 0.7 mm cut from a diamond crystal was used as an intensity reference. The intensity of the laser radiation and slit settings of the spectrometer were kept constant throughout the measurements. In order to study the orientational effects, the measurements were performed at different crystallographic orientations of the samples relative to the polarisation plane ($\mathbf{E}$) of the incident laser radiation. The as-measured Raman spectra were processed with a specialised software code to retrieve line widths as well as peak and integral scattering cross-sections. The accuracy of the line width determination, which is determined by the spectral resolution of the setup, was $\sim 10\%$ for moderately broad ($\Delta\nu_R > 1\text{ cm}^{-1}$) lines. The peak scattering cross-sections Σ_{peak} were determined to within $\sim 10\%$ and $\sim 20\%$ for broad and narrow lines, respectively. The accuracy of the Σ_{int} determination is estimated as 10% and $20\%\text{--}40\%$ for narrow and broad lines, respectively.

Results of the measurements are compiled in Table 4. The values of Σ_{int} and Σ_{peak} for all materials are scaled to those of diamond, since diamond is characterised by one of the most intense Raman lines. As has been discussed above, the integral Raman scattering cross-section determines the SRS gain coefficient in a transient mode. According to the tabulated data, large Σ_{int} are observed, apart from diamond, for lithium niobate (166%) for a vibrational mode at 632 cm^{-1} , various molybdates and tungstates (from 46% to 65%) and lithium iodate (54%). Smaller integral Raman scattering cross-sections are typical of sodium and barium nitrates (23% and 21% , respectively), calcite (6%), calcium and strontium fluorapatites (3.4%) and quartz (2.2%). All molybdates and tungstates studied can be subdivided into two groups based on their crystal structures: compounds with the scheelite (CaWO_4) structure corresponding to the tetragonal space group C_{4h}^6 and monoclinic structures characterised by the space group C_{2h}^0 . For the first group of crystals, intense Raman scattering lines are attributed to totally symmetric vibrations of the WO_4 tetrahedra. For the second group of compounds, the two intense lines observed in the Raman spectra are attributed to vibrations of the W--O bonds in the WO_6 octahedra.¹⁸

Meanwhile, the SRS amplification in a steady-state mode is determined by the peak scattering cross-section Σ_{peak} . According to the experimental data in Table 4, a large gain is expected for diamond and sodium and barium nitrates. Because of very narrow Raman lines, crystals of $\text{Ba(NO}_3)_2$ and NaNO_3 manifest large values of Σ_{peak} , despite the fact that the integral cross-sections corresponding to their SRS-active vibrational modes are $2\text{--}3$ times smaller than those of tungstates. Accurate measurements^{19, 20} afforded the record small line width of $\sim 0.4\text{ cm}^{-1}$ for $\text{Ba(NO}_3)_2$, which is severalfold smaller than that for diamond. The peak cross-section Σ_{peak} of this Raman mode in $\text{Ba(NO}_3)_2$ amounts to 63% of the respective diamond value and is more than twice larger than that in KGW crystals. In the case of NaNO_3 , Σ_{peak} is only 44% due to the larger line width ($\sim 1\text{ cm}^{-1}$). Lithium iodate and monoclinic tungstates are characterised by moderately broad Raman lines ($5\text{--}8\text{ cm}^{-1}$) and relatively large peak cross-sections ranged from 10% to 35% . A Raman mode of lithium niobate at 632 cm^{-1} is significantly broader (27 cm^{-1}) but is characterised by a relatively large peak cross-section Σ_{peak} (18%)

Table 4. Basic Raman parameters of crystals of inorganic compounds.

Crystal	Space group	Molecular group	Raman frequency /cm ⁻¹	Raman line width /cm ⁻¹	Σ_{int} (%)	Σ_{peak} (%)
Diamond	O_h^7	—	1332.9	2.7	100	100
Simple oxides						
SiO ₂	D_3^6	SiO ₄	464	7	2.2	1.2
TeO ₂			648	9	150	32
Nitrates and carbonates						
Ba(NO ₃) ₂	T_h^6	NO ₃	1048.6	0.4	21	63
NaNO ₃	D_{3d}^6	NO ₃	1069.2	1.0	23	44
CaCO ₃	D_{3d}^6	CO ₃	1086.4	1.2	6.0	10.6
Tungstates						
CaWO ₄	C_{4h}^6	WO ₄	910.7	6.95	50	18.6
SrWO ₄	C_{4h}^6	WO ₄	921.5	3	50	41
BaWO ₄	C_{4h}^6	WO ₄	926.5	1.63	52	64
NaGd(WO ₄) ₂	C_{4h}^6	WO ₄	919	14	—	—
NaY(WO ₄) ₂	C_{4h}^6	WO ₄	918	15	—	—
Sc ₂ (WO ₄) ₃	—	WO ₄	1024	15	—	—
In ₂ (WO ₄) ₃	—	WO ₄	1023	13	—	—
LiIn(WO ₄) ₂	—	WO ₄	920	8	—	—
Na ₂ WO ₄	O_h^7	—	929.2	1.8	—	—
KGd(WO ₄) ₂	C_{2h}^6	WO ₆	901	5.4	50	35
KY(WO ₄) ₂	C_{2h}^6	WO ₆	905.6	7	46	35
KYb(WO ₄) ₂	C_{2h}^6	WO ₆	908	7.4	48	34
Molybdates						
CaMoO ₄	C_{4h}^6	MoO ₄	879.3	5.0	65	34
SrMoO ₄	C_{4h}^6	MoO ₄	887.7	2.8	63	51
BaMoO ₄	C_{4h}^6	MoO ₄	892.4	2.1	55	64
Iodates and niobates						
LiIO ₃	C_6^6	IO ₃	821.6	5.0	54	25
LiNbO ₃	C_{3v}^6	NbO ₆	872	21.4	44	5
	C_{3v}^6	NbO ₆	632	27	166	18
LaNbO ₄	C_{2h}^3	NbO ₄	805	9	22	7.1
Phosphates						
Ca ₅ (PO ₄) ₃ F	C_{6h}^2	PO ₄	964.7	2.8	3.4	3.8
Sr ₅ (PO ₄) ₃ F	C_{6h}^2	PO ₄	950.3	2.8	3.4	3.8
Li ₃ PO ₄	—	PO ₄	951	7.7	—	—
Miscellaneous salts						
NaClO ₃	—	ClO ₃	937	4.9	—	—
NaBrO ₃	—	BrO ₃	799.5	2.5	—	—
NH ₄ Cl	O_h^1	NH ₄	1712	6	—	—

owing to a very large integral cross-section of 166%. A comparable value of Σ_{peak} is observed for crystals of natural calcite (10.6%). CaWO₄ crystals demonstrate a large integral cross-section of 50% but relatively low peak cross-section of 18.6% due to a significant line broadening of 6.95 cm⁻¹. As for SrWO₄ and BaWO₄, owing to small line widths of 3 cm⁻¹ and 1.63 cm⁻¹, their peak cross-sections Σ_{peak} amount to 41% and 64%, respectively, which is larger than that in other tungstates and comparable to values typical of nitrates. The highest-frequency Raman lines of lanthanum and lithium niobates (at 805 cm⁻¹ and 872 cm⁻¹, respectively) are characterised by relatively low Σ_{peak} values of 7.1% and 5%, respectively. Calcium and strontium fluorapatites reveal even higher-frequency lines but smaller Σ_{peak} values of 3.8%. All these values are small but nevertheless close to the respective Σ_{peak} value of calcite, which is used for the SRS generation on a commercial basis both with ns- and ps-pulsed lasers.

Due to the large Raman shifts (800–960 cm⁻¹) and broad lines ($\Delta\nu_R = 3–20$ cm⁻¹), the crystals of aforementioned niobates and apatites can prove useful for SRS in the picosecond range.

Other materials listed in Table 4 exhibit small peak Raman scattering cross-sections. Notwithstanding, they still can be useful, since they provide different Raman shifts.

Therefore, the above comparative analysis of the SRS-active modes for various crystalline materials based on their spontaneous Raman scattering spectra indicates that calcite and sodium and barium nitrates should provide large SRS gain coefficient in a steady-state mode for nanosecond pulses. A shortening of pumping pulses to 20–30 ps switches the SRS mode to a transient one, which gives rise to a substantial increase in the SRS threshold for these crystals. A more efficient SRS generation at shorter pumping pulses can be achieved with tungstate crystals, which are characterised by relatively broad Raman lines. Due to the large integral cross-sections, these crystals are expected to perform well

in a transient SRS mode. Due to their outstanding spectroscopic properties, SrWO_4 and BaWO_4 crystals are capable of providing high SRS gain coefficients both for ns- and ps-pulsed lasers, which substantiates their great potential as versatile nonlinear optical media for the highly efficient SRS-based frequency converters. It is also of note that, in addition to tungstates, molybdates demonstrate very attractive SRS properties.

III. The preparation and characterisation of single crystals of calcium, strontium, barium and lead molybdates and tungstates for SRS lasers

Calcium, strontium, barium and lead molybdates and tungstates represent congruently melting compounds having no (except for BaMoO_4) phase transitions over the entire temperature range from room temperature to the melting point. Single crystals of these compounds can be grown by melt crystallisation. Their melting points lie below 1535°C and thus platinum crucibles can be used for crystal growth. Platinum is characterised by a melting point of 1770°C , and platinum crucibles can be used in air. Most typically, crystals of molybdates and tungstates are grown by the so-called Czochralski method based on a slow pulling of a crystal growing on a seed from the respective melt.²¹ Ivleva *et al.*²² reported on the growth of single crystals of some tungstates by the modified Stepanov method based on the use of a bulk shaper.

Below we consider in more details the growth of barium tungstate crystals by the Czochralski and Stepanov methods. Barium tungstate crystallises in the tetragonal scheelite structure and has a melting point of 1475°C . Single crystals of this compound were grown on a Kristall-3M crystal-growth furnace equipped with an inductively heated platinum crucible with a melt. Starting BaWO_4 was prepared by sintering of BaCO_3 and WO_3 of the purity grade 5N taken in a stoichiometric ratio. The seed was oriented along the $[100]$ direction. The crystalliser is schematically depicted in Fig. 2. A cylindrical platinum screen was placed above the crucible to prevent overheating of the crucible walls and reduce temperature gradients along the growing crystal. The axial temperature gradient was kept in a range from

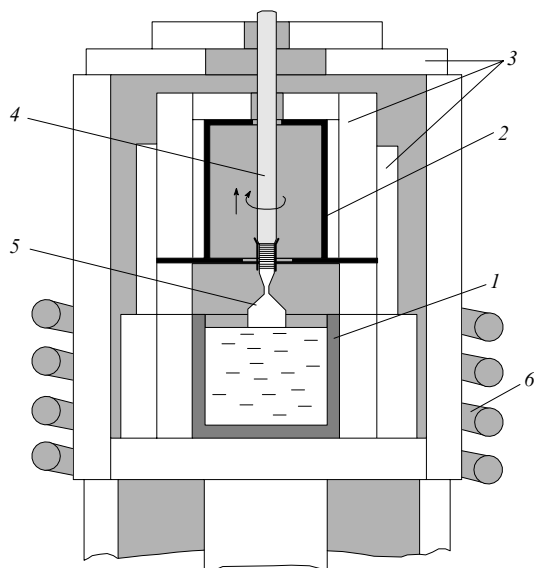


Figure 2. A scheme of the crystalliser furnace used for crystal growth of calcium, strontium, barium and lead molybdates and tungstates using the Czochralski method.

(1) Platinum crucible, (2) platinum thermal shield, (3) heat-insulating elements made from corundum ceramics, (4) seed holder, (5) growing crystal, (6) RF heater.

50 to 100°C per cm, while the radial temperature gradient was fixed at $\sim 5^\circ\text{C}$ per cm. High optical-quality crystals were grown at a pulling rate of $2\text{--}6\text{ mm h}^{-1}$ upon a constant rotation at 30 rpm . An excess of WO_3 of $0.5\text{ mass \%}$ – $1.2\text{ mass \%}$ was added to the melt to suppress emergence of light-scattering inclusions in the crystals.

The crystalliser used for crystal growth by the modified Stepanov method is schematically depicted in Fig. 3. According to this method, a special platinum shaper is plunged into the melt. The melt from the crucible is supplied through the feeding capillaries of the shaper to a thin layer of the melt in the contact with the crystal growth front. The thickness of the contact melt layer is controlled by the temperature of the crucible and the position of the shaper relative to the crucible. Meanwhile, the shape of the crystallisation field and the cross-section of the growing crystal are determined by the shaper profile. A crystal is grown on a seed, typically, without rotation. The growth process can be optimised by varying the shaper design and temperature gradients. The growth of specifically shaped crystals has some distinctive features related to their structures. In particular, the anisotropy of growth rates of different crystallographic faces has to be taken into account. According to the Curie principle, in the case of BaWO_4 that crystallises in the tetragonal space group $C_{4h}^{6_2}$, the crystallographic a axis is the preferable growth direction and a rectangle is the preferable contact surface of the shaper.

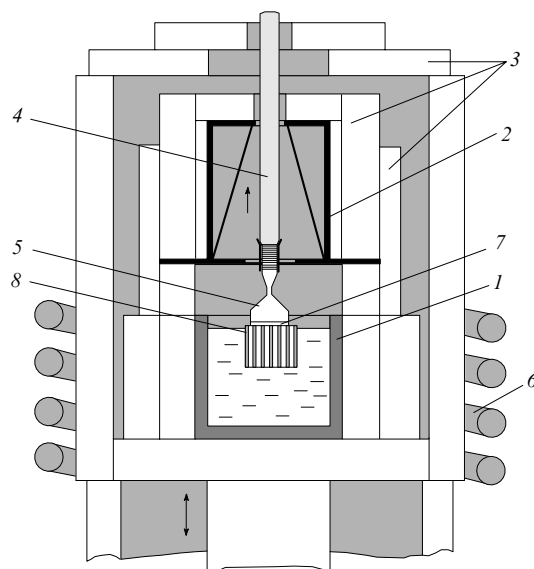


Figure 3. A scheme of the crystalliser furnace used for crystal growth of calcium, strontium, barium and lead molybdates and tungstates using the modified Stepanov method.

(1) Platinum crucible, (2) platinum thermal shield, (3) ceramic heat-insulating elements, (4) rod made from leucosapphire, (5) growing crystal, (6) RF heater, (7) meniscus of the melt, (8) shaper.

Photographic images of the tungstate crystals grown by both methods are shown in Fig. 4.

Laser devices place extremely strong requirements on the quality (optical perfection) of materials to be used as working media.²³ Such crystals and glasses should contain no solid or gaseous inclusions, domain boundaries and cracks. Refraction index gradients of a medium should not exceed $10^{-4}\text{--}10^{-6}\text{ cm}^{-1}$. The presence of any of these defects in an optical medium gives rise to efficiency losses (due to light scattering on optical inhomogeneities) and radiation damage of the material. Consequently, such materials are unsuitable for the practical use. The above requirements are even stricter for

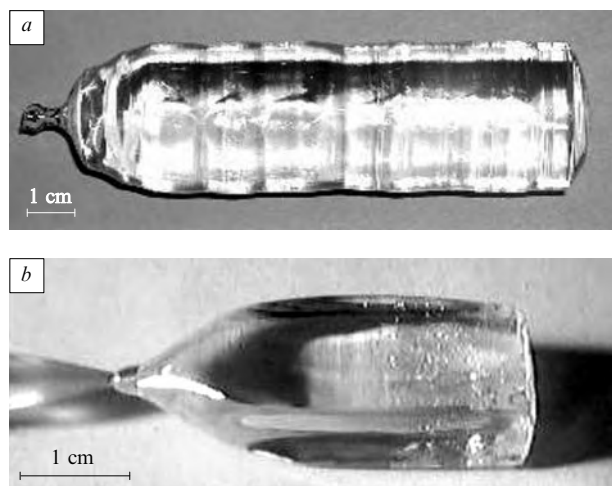


Figure 4. Photographic images of BaWO₄ crystals grown from melts using the Czochralski method at a pulling rate of 2–6 mm h⁻¹, a rotation rate of 30 rpm and a volume growth rate of < 1 cm³ h⁻¹ upon an excess of WO₃ in the melt of 1 mass %–1.5 mass % (a) and using the modified Stepanov method at a pulling rate of 5 mm h⁻¹ (no rotation) and a volume growth rate of 0.5 cm³ h⁻¹ upon an excess of WO₃ in the melt of 1 mass % (b).^{22, 23}

potential SRS crystals, which often operate at ultimately high laser radiation intensities of the order of 10⁸–10⁹ W cm⁻².

The crystal growth by the Czochralski method can produce the following specific defects intrinsic to the method:

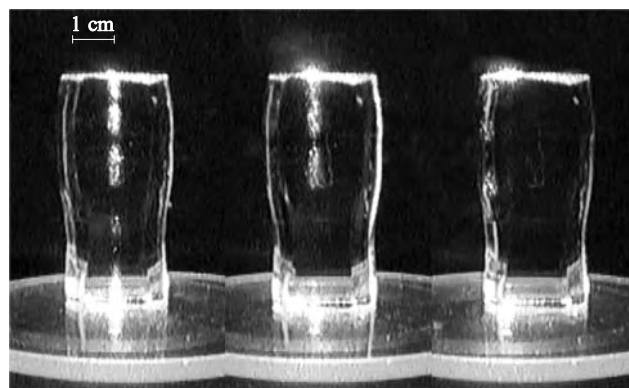


Figure 6. Microscopic inclusions of a foreign phase in a BaWO₄ single crystal grown by the Czochralski method (observation in a laser beam).^{22, 23}

— ‘a core’, *i.e.*, a central part of the crystal in the form of a core defect going along the entire crystal from bottom to top; the emergence of this defect relates to the face growth from the cone vertex at the interface between solid and liquid phases (Fig. 5);

— growth striations;

— microscopic inclusions of foreign phases (Fig. 6);

— cracks along the cleavage planes of a crystal.

In order to prevent or suppress the formation of a ‘core’, the growth front has to be the least convex or ideally flat. This can be achieved by a decrease in both the vertical temperature gradient along the crystal and the radial temperature gradient across the crystallisation front.

Growth striations occur as a result of a periodically inhomogeneous distribution of the main crystal components or admixtures due to variations in the growth rate. Typically, elimination of possible factors responsible for these variations, such as instabilities of pulling of the crystal and rotation mechanisms or fluctuations in the temperature of the melt, minimises this defect.

Tungstate crystals grown from exactly stoichiometric melts often contain microinclusions of foreign solid phases, which cause opalescence of crystals. These defects are attributed to a violation of the melt stoichiometry in the course of crystal growth due to progressive evaporation of tungsten trioxide. The use of a small excess of WO₃ (up to 1.5 mass %) in the furnace charge makes it possible to avoid the emergence of such light-scattering inclusions. Alternatively, optically homogeneous tungstates can be grown by the addition of ~0.5 mass % rare-earth metal oxides (La₂O₃, Nd₂O₃, *etc.*) to the melt for the crystal growth.

The specific defects in BaWO₄ crystals grown by bulk shaping methods include cracks along certain crystallographic directions, in particular, parallel to [001] and light-scattering micro- and macroinclusions. The use of exactly stoichiometric melts and too high pulling rates increases the probability of the appearance of inclusions. In this method of crystal growth, the shape of the crystallisation front is strongly dependent on the design of the shaper. The flatness of the crystallisation front is violated in the case of shapers with excessively wide slits (Fig. 7). This gives rise to crystals with a prominent domain structure and, consequently, abundant cracks. Ivleva *et al.*²² utilised shapers with capillary slits of 1 mm and 0.1 mm. In the latter case, the crystallisation front was nearly flat, which afforded highly homogeneous crystals.

The use of smaller temperature gradients also improves the optical homogeneity of the resultant crystals. In the growth experiments, platinum crucibles with diameters from 40 mm to 80 mm were tested. It is known that an increase in the crucible size and, respectively, in the melt volume decreases the temperature gradients, which gives rise to larger and higher-quality crystals.

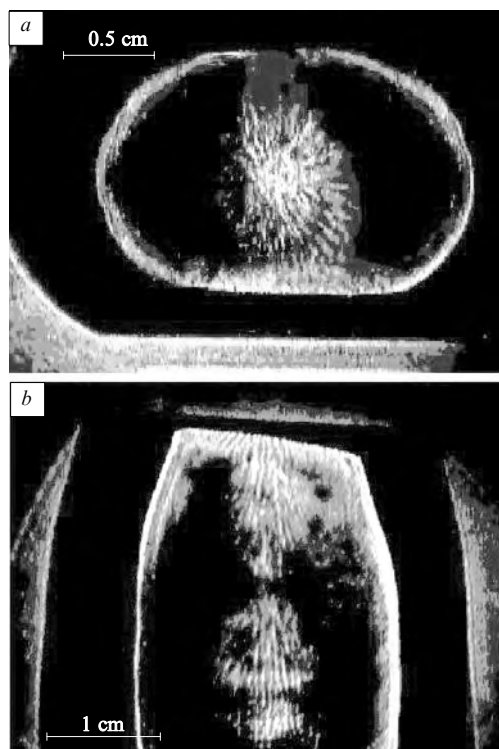


Figure 5. A typical central defect (a ‘core’) in a BaWO₄ single crystal grown by the Czochralski method.^{22, 23}
(a) A cross-section perpendicular to the growth axis, *a*; (b) a cross-section parallel to the growth axis, *a*.

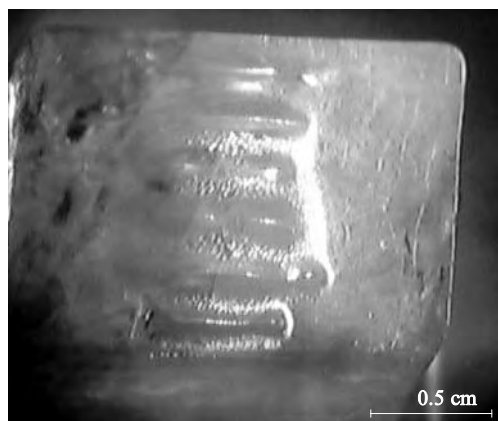


Figure 7. The crystallisation surface of a BaWO₄ single crystal grown by the modified Stepanov method with a shaper having slits with a thickness of 1 mm.^{22, 23} The intergrowth of the crystal into the capillary slits can easily be seen.

The optimum conditions for the growth of tungstate crystals were found to be: the pulling rate of 1–5 mm h⁻¹ at a volume growth rate no faster than 0.5 cm³ h⁻¹, the capillary slit width (if a shaper is used) of 0.1–0.2 mm, the excess of WO₃ in the melt of 1 mass %, the axial temperature gradient of 50 °C per cm. Under these or similar conditions, optically homogeneous crystals of calcium, strontium, barium^{22, 24–26} and lead²⁷ molybdates and tungstates with sizes of 30 × 100 mm were successfully grown.

IV. Raman scattering spectra of calcium, strontium, barium and lead molybdates and tungstates

As has been discussed above, crystals of molybdates and tungstates are characterised by similar integral scattering cross-sections, whereas the widths of the respective spectral lines are substantially different. It is the line width that determines the peak scattering cross-section provided that the integral cross-sections are almost identical. Furthermore, the value of the Raman shift strongly varies in a series of molybdates and tungstates. It is necessary to correlate these parameters with the chemical composition and crystal structure in order to enable the prediction of Raman scattering and SRS effects and purposeful search for novel efficient SRS-based laser converters. These issues are considered in detail elsewhere.²⁶ The spectra of spontaneous Raman light scattering were measured for an extended series of molybdates MMoO₄ and tungstates MWO₄ (M = Ca, Sr, Ba, Pb, Zn). The vast majority of samples for measurements were prepared as bulky single crystals. Only ZnMoO₄ and ZnWO₄ were obtained as polycrystalline ceramic specimens by sintering of thoroughly mixed zinc carbonate with either MoO₃ or WO₃ at 1100–1200 °C. The sample plates were cut from the single crystals either parallel or perpendicular to the crystallographic *c* axis upon the determination of the orientation by X-ray diffraction.

Raman spectra were excited with Ar laser radiation with $\lambda = 488$ nm and registered using a Spex Ramalog-1403 spectrometer at 77 K and 300 K. High-temperature Raman spectra (up to 1920 K) were measured using an original method described elsewhere.²⁸ Excitation was achieved with a pulsed Cu vapour laser operated at a wavelength of 501.5 nm and a pulse repetition rate of 10 kHz. The spontaneous Raman scattering spectra were recorded using the time-resolved technique, which provides a high signal-to-thermal background ratio. High-temperature Raman spectroscopy is indispensable in studies of solid-state phase transitions; additionally, it yields important information on

positions and widths of Raman lines as a function of the temperature up to and above the melting point.

First measurements of room-temperature spontaneous Raman scattering spectra of calcium, strontium and lead molybdates and tungstates date back to the mid-1960s.²⁹ Meanwhile, barium molybdate and tungstate spectra remained unstudied. All the above molybdates and tungstates except for zinc compounds crystallise with the scheelite structure corresponding to the tetragonal space group C_{4h}^6 . A primitive unit cell contains two formula units. The Mo–O and W–O bonds in the quasi-molecular tetrahedral [MoO₄]²⁻ and [WO₄]²⁻ anions are essentially covalent, and the anions are only weakly bound to the M²⁺ cations. With this regard, features in the Raman spectra of these crystals can be subdivided into two groups, *viz.*, internal and external vibrational modes. The internal vibrations include totally symmetric vibrations of the oxygen atoms relative to the central Mo or W atom, *i.e.*, the so-called breathing modes. The external (or lattice) phonons correspond to vibrations of the M²⁺ ions relative to rather rigid quasi-molecular [MoO₄] and [WO₄] groups. Free MoO₄ and WO₄ tetrahedra are characterised²⁹ by the point symmetry T_d . According to the group theory, 15 degrees of freedom are possible in this symmetry group, which can be classified into four internal vibrational [$\nu_1(A_1)$, $\nu_2(E)$, $\nu_3(F_2)$ and $\nu_4(F_2)$], one rotational [$\nu_{tr}(F_1)$] and one translational (F_2) modes. When [MoO₄] or [WO₄] groups are placed into the scheelite lattice, the crystal-field symmetry is lowered to S_4 . This gives rise to splitting of all degenerate vibrations due to the crystal field effects.²⁹ Furthermore, the presence of two formula units in a unit cell gives rise to an additional, the so-called Davydov, splitting (DS) of the vibrational modes. For instance, the $\nu_1(A_1)$ and $\nu_3(F_2)$ vibrational modes of a free tetrahedral group are split in the scheelite crystal field in the following way:

$$\nu_1(A_1) \longrightarrow \nu_1(A) \longrightarrow \nu_1(A_g) + \nu_1(B_u),$$

$$\nu_3(F_2) \longrightarrow \nu_3(E) + \nu_3(B) \longrightarrow \nu_3(E_g) + \nu_3(E_u) + \nu_3(B_g) + \nu_3(A_u).$$

Calculations within the group theory gives 26 different vibrations

$$\Gamma = 3A_g + 5A_u + 5B_g + 3B_u + 5E_g + 5E_u \quad (2)$$

corresponding to the wavevector $\mathbf{K} = 0$. All gerade vibrations (*i.e.*, $3A_g$, $5B_g$ and $5E_g$) are Raman-active, whereas the ungerade modes (*i.e.*, $4A_u$ and $4E_u$) can only be observed in IR absorption spectra. Three B_u vibrations represent the so-called silent modes. Two acoustic vibrations, A_u and E_u , also occur in the expression (2).

The Raman spectra measured by Basiev *et al.*²⁶ agree well with the earlier reported data.^{29, 30} The spectra of BaMoO₄ and BaWO₄ crystals studied for the first time are shown in Fig. 8. The results of spectra processing are collected in Table 5. The BaWO₄ crystals retain the scheelite structure over the entire temperature range from room temperature to the melting point. Meanwhile, it was found that BaMoO₄ undergoes a phase transition at 1600 K from the tetragonal modification (β) into a cubic structure (α). The Raman spectra in Fig. 8a clearly demonstrate that two ν_3 vibrations coalesce and the ν_{ext} band strongly shifts above 1600 K. A comparison of the Raman spectra of BaMoO₄ measured at two ultimate temperatures indicates that the crystal-field symmetry experienced by a [MoO₄] group in a melt at 1800 K is nearly the same as that in the crystalline state at 1605 K.

Shifts in the Raman-active frequencies for calcium, strontium, barium and lead molybdates and tungstates as a function of the cation mass and the unit cell parameter *c* are depicted in Figs 9 and 10, respectively. It is evident that the trends are identical in both series. There are several factors affecting the observed Raman shifts. Kanamory *et al.*³¹ suggested that it is the cation mass that is mainly responsible for the frequency of the low-energy external vibration ($2B_g + 2E_g$). This suggestion is supported by a monotonic decrease in the external vibrational frequency ν_{ext} with an increase in the cation mass *M* (see Fig. 9). However experi-

Table 5. Raman frequencies of BaWO₄ and BaMoO₄ in the crystalline and molten states.²⁶

Irreducible representation of the Raman mode	BaWO ₄			BaMoO ₄					Assignment
	300 K (see ^a)	1800 K (see ^a)	1820 K (see ^b)	300 K (see ^a)	1600 K (see ^c)	1605 K (see ^d)	1770 K (see ^d)	1800 K (see ^b)	
A _g	925	910	909	892	878	877	873	822	$\nu_1(A_1)$
B _g	831	816	804	837	825	802	794	777	$\nu_3(F_3)$
E _g	795	775	—	791	771	—	—	—	
E _g	353	338	370	358	347	359	356	356	$\nu_4(F_2)$
B _g	345	—	0	345	—	—	—	—	
B _g	332	318	326	324	313	313	313	314	$\nu_2(E)$
A _g	332	—	—	324	—	—	—	—	
E _g	191	109	—	188	143	134	—	—	$\nu_{fr}(F_1)$ (rotational mode)
A _g	150	—	—	—	140	—	—	—	
B _g	132	—	—	137	—	—	—	—	ν_{ext} (external modes)
E _g	101	73	—	110	—	—	—	—	vibrations of [MoO ₄] ²⁻ , [WO ₄] ²⁻ and Ba ²⁺
E _g	75	—	—	74	57	45	—	—	—
B _g	63	58	—	76	73	—	—	—	—

^a Crystal with the C_{4h}^6 symmetry. ^b Melt. ^c β -Modification with the C_{4h}^6 symmetry. ^d α -Modification with the cubic symmetry.

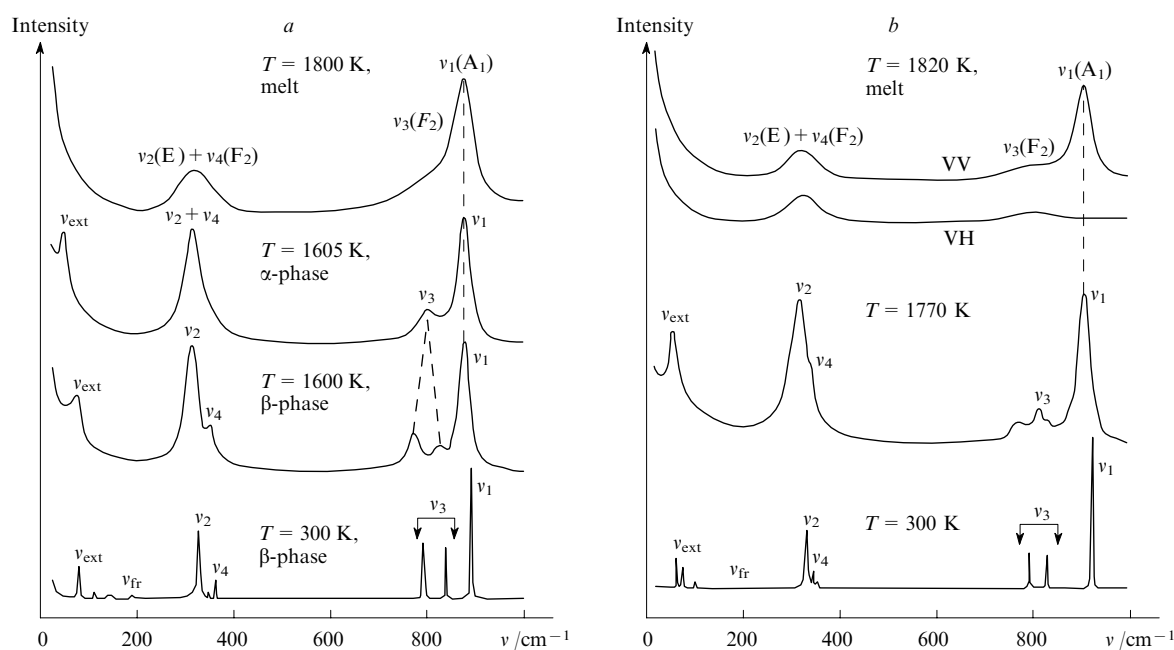


Figure 8. Temperature-dependent non-polarised Raman scattering spectra of BaMoO₄ (a) and BaWO₄ (b) in the crystalline and molten states.²⁶ Here and in other figures, the notation VV (VH) denotes the experimental geometry with the polarisation plane of the scattered beam parallel (perpendicular) to the polarisation plane of the incident beam.

ments showed²⁶ that the frequencies of the internal vibrational modes of the [MoO₄] and [WO₄] groups [except for the $\nu_2(E)$ doublet] also depend on the cation nature.

One of possible reasons for this effect lies in the fact that an increase in the ionic radii in the Ca–Sr–Ba series gives rise to some dilatation of the unit cell and, subsequently, to a small change in the Mo–O and W–O bond lengths within the tetrahedra. This should also be accompanied by a change in the force constants corresponding to certain internal vibrational modes. Apparently, the unit cell parameters exert the strongest influence on the force constants corresponding to the $\nu_4(F_2)$ and $\nu_{fr}(F_1)$ modes (see Fig. 10). On the other hand, the unit cell parameters of PbMoO₄ and PbWO₄ are close to those of SrMoO₄ and SrWO₄ (Table 6) and it seems logical to expect

similar internal vibrational frequencies for them. In contrast to these expectations, frequencies of all internal vibrations of PbMoO₄ and PbWO₄ deviate from the monotonic dependences plotted in Fig. 10. The largest shifts are observed for the high-energy modes, *i.e.*, $\nu_1(A_g)$, $\nu_3(B_g)$ and $\nu_3(E_g)$. This deviation cannot be explained by effects of the unit cell parameters alone. It was suggested that another crystal-chemical factor gets involved, *viz.*, a partially covalent character of the chemical bonds formed by the M²⁺ cations with the oxygen atoms constituting the MoO₄ and WO₄ groups. This factor also affects³² the force constants of the internal vibrations. A higher electronegativity of an M²⁺ cation gives rise to larger force constants corresponding to centrosymmetric vibrations and, respectively, to higher frequencies of the vibrational modes (see Table 6). Additionally, the formation of

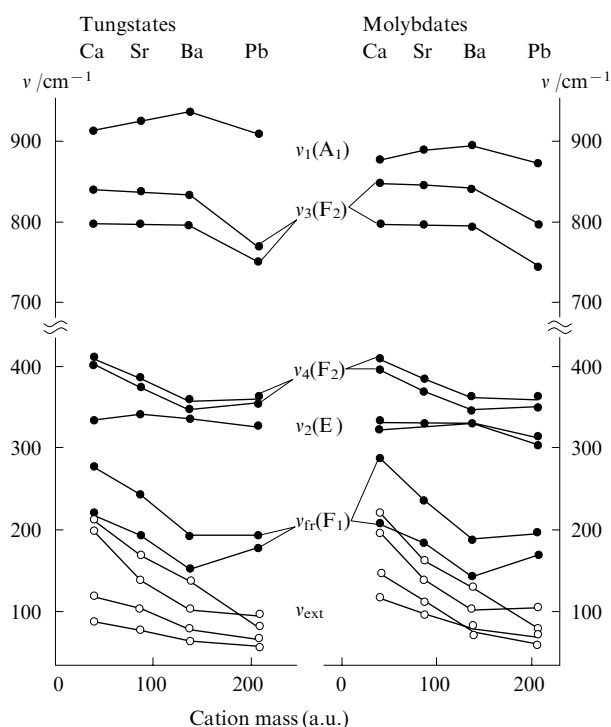


Figure 9. Changes in the Raman frequencies along the MMoO₄ and MWO₄ homologous series (M = Ca, Sr, Ba, Pb) as a function of the cation mass M²⁺ (see Ref. 26).

partly covalent M–O bonds changes the effective mass of vibrating atomic groups in a way that a reduced mass of the metal–oxygen pair should substitute the mass of a single oxygen atom in the frequency calculations. In this indirect way, the mass of an M²⁺ cation can affect the internal vibrational frequencies of the [MoO₄] and [WO₄] groups. The influence exerted by the nature of an M²⁺ cation on the internal vibrational frequencies is dominantly ascribed to the effects of force constants. However Lazarev *et al.*³² did not specifically address the case of a very heavy cation simultaneously characterised by a high electronegativity, such as Pb²⁺.

The ambiguity of the above interpretation concerning the dependence of the internal vibrational frequencies on the cation

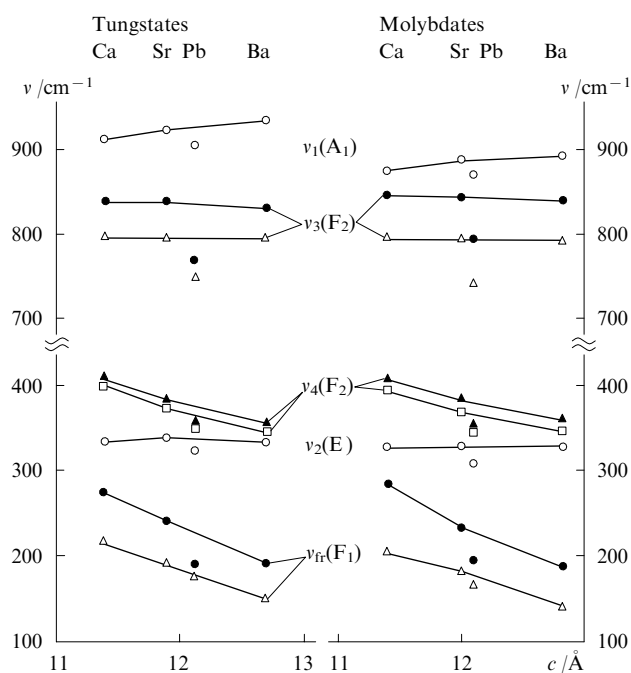


Figure 10. Changes in the Raman frequencies along the homologous series of calcium, strontium, lead and barium molybdates and tungstates as a function of the unit cell parameter.²⁶

nature relates to the fact that this dependence in real crystals is masked by static crystal-field effects and dynamical coupling of different vibrational modes. The crystal lattice effects can be excluded by measuring Raman spectra in melts of the respective compounds. High-temperature Raman spectra of the melts were measured using the experimental setup described above. The experimental spectra of melts derived from the scheelite-type crystals are fully consistent with the presence of tetrahedral groups with the *T_d* point symmetry (Fig. 11). They reveal four vibrational modes, *viz.*, ν₁(A₁), ν₂(E), ν₃(F₂) and ν₄(F₂). The ν₁(A₁) mode is attributed to totally symmetric vibrations of the oxygen atoms relative to the central atom (Mo or W). In order to monitor the effects of the cation mass on the internal vibrational frequencies, the Raman spectra of ZnMoO₄ and ZnWO₄ melts were also included into the comparative analysis. Zinc is characterised by

Table 6. Basic Raman parameters and selected crystallochemical characteristics of Ba(NO₃)₂, MMoO₄ and MWO₄ crystals (M = Ca, Sr, Ba, Pb, Zn).²⁶

Crystal	ν (at 300 K) /cm ⁻¹	Σ _{int} (%)	Σ _{peak} (%)	Δν _R /cm ⁻¹		Parameters of the M ²⁺ cation			Unit cell parameters /Å		ΔE /cm ⁻¹	Mo–Mo or W–W distance /Å
				300 K	77 K	m _{cat}	r _{cat} /Å	η _{cat}	c	a		
Ba(NO ₃) ₂	1048	21	63	0.4	0.3	137.34	1.42	0.78	8.11	8.11	<0.69	—
BaWO ₄	925	52	64	1.6	0.97	137.34	1.42	0.78	12.720	5.640	0–1	6.95
SrWO ₄	921	50	41	3.0	1.45	87.62	1.25	1.06	11.921	5.417	28	6.5
CaWO ₄	911	50	18.6	5.6	3.1	40.08	1.12	1.22	11.376	5.242	58	6.26
PbWO ₄	905	171	97	4.7	1.87	207.19	1.29	3.08	12.12	5.50	32	6.65
ZnWO ₄	908	—	—	8.0	5.0	65.38	0.9	2.98	—	—	—	—
BaMoO ₄	892	55	64	1.85	1.1	137.34	1.42	0.78	12.82	5.62	0–1	7.0
SrMoO ₄	887	63	51	2.5	1.2	87.62	1.25	1.06	12.02	5.394	22	6.58
CaMoO ₄	879	65	34	5.5	2.3	40.08	1.12	1.22	11.43	5.266	52	6.28
PbMoO ₄	871	397	146	8.0	3.2	207.19	1.29	3.08	12.108	5.436	36	6.63
ZnMoO ₄	971	—	—	—	—	65.38	0.9	2.98	—	—	—	—

Note. The following notations are adopted: *m*_{cat} is the atomic mass (a.u.); *r*_{cat} is the ionic radius; η_{cat} is the electronegativity; Δ*E* is the Davydov splitting. The electronegativities values used in this table and below were taken from the monograph by R T Sanderson *Chemical Bonds and Bond Energy* (New York: Academic Press, 1976).

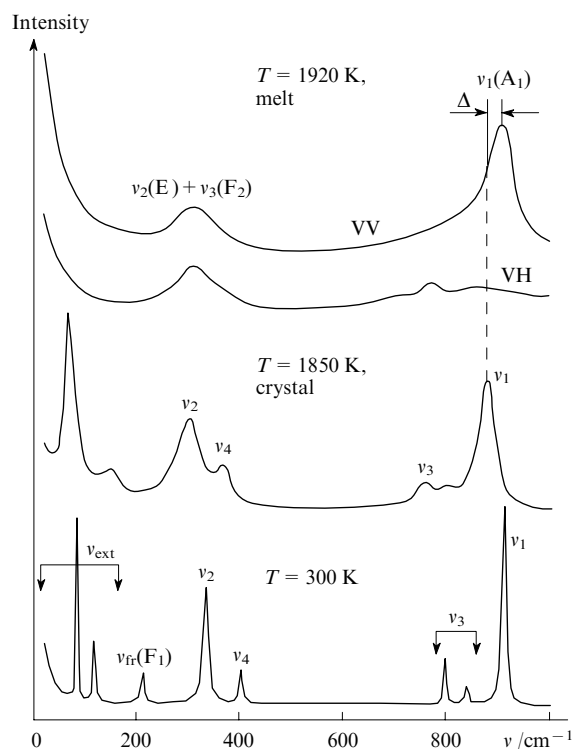


Figure 11. Temperature-dependent non-polarised Raman spectra of CaWO_4 crystals and polarised Raman spectra of CaWO_4 melt.²⁶

nearly the same electronegativity as lead, whereas the atomic mass of lead is far larger than that of zinc and other cations under consideration. It is of note that the crystal structures of zinc molybdate and tungstate differ from that of scheelite. The molybdenum and tungsten atoms therein are octahedrally coordinated by the oxygen atoms.³³ However it was established that their coordination changes to the tetrahedral one upon melting (Fig. 12).

Therefore Raman studies of melts make it possible to separate the effects of the cation mass and electronegativity on the Raman frequencies. Frequencies of the $\nu_1(\text{A}_1)$, $\nu_2(\text{E})$, $\nu_3(\text{F}_2)$ and $\nu_4(\text{F}_2)$ vibrational modes as a function of the cation electronegativity for melts of metal molybdates and tungstates are shown in Fig. 13. Frequencies of all these vibrational modes increase with an increase in the electronegativity in the Ba–Sr–Ca–Zn series thus indicating that it is the cation electronegativity that mainly determines the force constants corresponding to the internal vibrations within the $[\text{MoO}_4]$ and $[\text{WO}_4]$ groups. In contrast, the reduced mass of the M–O pair only weakly influences the vibrational frequencies within these groups for any M^{2+} except for Pb^{2+} . The vibrational frequencies of the $[\text{MoO}_4]$ and $[\text{WO}_4]$ groups in the melts of PbMoO_4 and PbWO_4 are drastically diminished with respect to compounds of other cations. Taking this into account, it might be suggested that the influence of a high electronegativity of Pb^{2+} on the Raman frequencies of the $[\text{MoO}_4]$ and $[\text{WO}_4]$ groups is effectively compensated by a large reduced mass of the Pb–O pair.

The above results imply that the cation radius, mass and electronegativity jointly influence the internal vibrational frequencies of the tetrahedral groups not only in the crystalline but also in the molten state, where these quasi-molecular groups experience a spherically symmetric crystal field. This effect has not been considered so far (see, for instance, Ref. 30). Only the spectra of PbMoO_4 and PbWO_4 deviate from the common trend for both crystals and melts (see Figs 9, 10 and 13). This can be explained by the prevailing influence of a large mass of the lead atom on the vibrational frequencies of the $[\text{MoO}_4]$ and $[\text{WO}_4]$

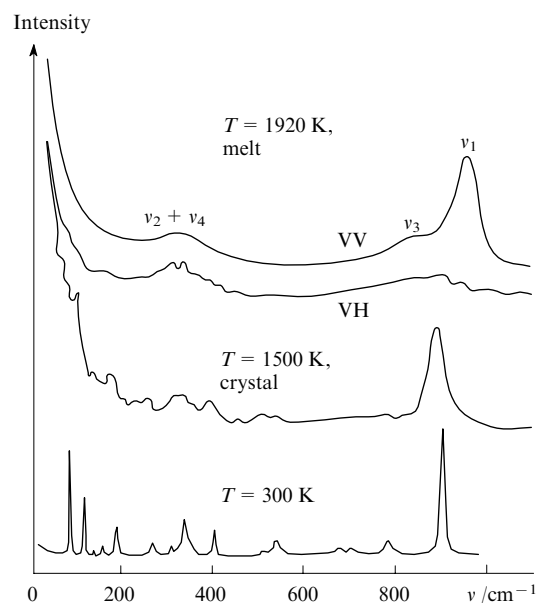


Figure 12. Temperature-dependent non-polarised Raman spectra of ZnWO_4 crystals and polarised Raman spectra of ZnWO_4 melt.²⁶

groups. Meanwhile, no strong mass dependence is observed in the Ba–Sr–Ca series. A monotonic increase in the internal vibrational frequencies for the melts of Ba-, Sr- and Ca-derived scheelites is totally consistent with an increase in the electronegativity of these cations (see Fig. 13). It is of note that the highest-frequency totally symmetric mode, $\nu_1(\text{A}_g)$, demonstrates the reverse trend in the crystalline state (see Figs 9 and 10). This effect was referred³⁴ to as the ‘negative mass dependence’. This dependence can be rationalised neither by an elongation of the Mo–O and W–O bonds due to a lattice dilatation nor by a decrease in the cation electronegativity. Both these factors would give rise to a decrease in the $\nu_1(\text{A}_g)$ frequency in the series of Ca–Sr–Ba scheelites, which is in direct contradiction to the experimental observations. Such a behaviour of the Raman frequencies can be explained assuming that it is the Davydov

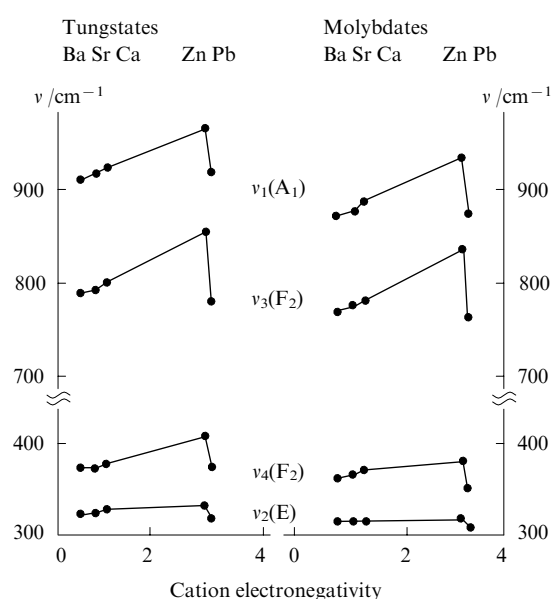


Figure 13. Changes in the Raman frequencies for melts of Ca, Sr, Ba, Zn and Pb molybdates and tungstates at 1920 K as a function of the cation electronegativity.²⁶

splitting that dominantly affects the $\nu_1(A_g)$ frequency. For the scheelite structures, the Davydov splitting gives rise to a splitting of the $\nu_1(A_g)$ mode into two components, A_g and B_u [see the expression (2)]. Provided that the ‘silent’ component $\nu_1(B_u)$ corresponds to a higher energy than $\nu_1(A_g)$, the frequency corresponding to the lower-lying $\nu_1(A_g)$ mode should increase with a decrease in the splitting gap $\Delta E = \nu_1(B_u) - \nu_1(A_g)$. According to the results by Scott,³⁴ the splitting gap ΔE depends on the Mo–Mo and W–W interatomic distances in the crystal structures. An increase in these distances coupled with a lattice dilatation gives rise to a decrease in ΔE and, respectively, to an increase in the $\nu_1(A_g)$ frequency. The problem is that ΔE cannot be directly determined from experimental data, since the $\nu_1(B_u)$ is inactive in both Raman and IR absorption spectra. Basiev *et al.*²⁶ utilised high-temperature Raman spectroscopy to estimate ΔE . Indeed, in the case of melts, the spontaneous Raman scattering spectra are not affected by the Davydov splitting and the vibrational modes of the MoO_4 and WO_4 groups appear unsplit. A frequency shift of the $\nu_1(A_g)$ mode upon melting can directly be determined from the temperature dependence of Raman spectra

$$\Delta = \nu_1(A_g)_{\text{cryst}} - \nu_1(A_g)_{\text{melt}}.$$

Assuming that the Davydov splitting of ν_1 is symmetric, the splitting gap ΔE can be estimated as 2Δ . The experimental temperature dependences of the $\nu_1(A_g)$ frequencies over a wide temperature range from 77 K to above the melting points for a series of molybdates and tungstates are plotted in Fig. 14. It is apparent that the $\nu_1(A_g)$ frequency demonstrates a jump-like increase upon melting for the majority of scheelites, whereas it changes rather smoothly for $BaMoO_4$ and $BaWO_4$. This strongly suggests that the $\nu_1(A_g)$ frequency in the scheelite crystals is smaller than the $\nu_1(B_u)$ frequency. The magnitudes of the Davydov splitting estimated under the assumption that $\Delta E = 2\Delta$ are listed in Table 6 (calculated based on the experimental data from

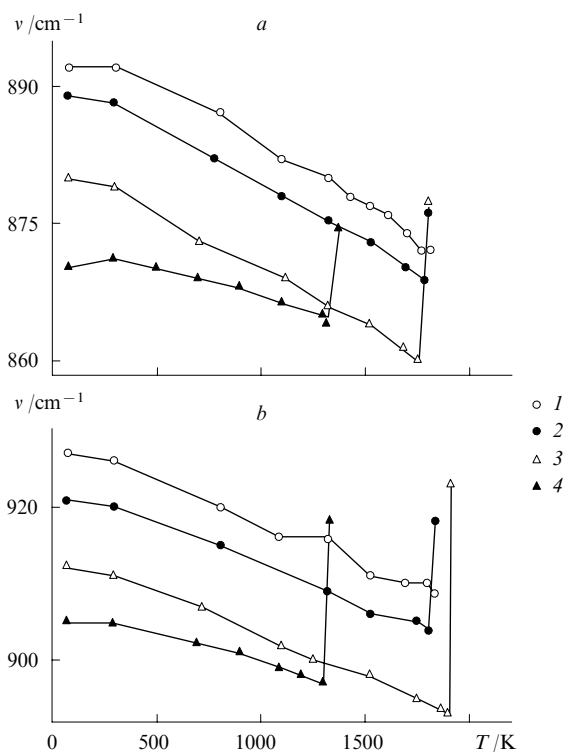


Figure 14. Changes in the Raman frequency of the $\nu_1(A_g)$ mode for homologous series of barium (1), strontium (2), calcium (3) and lead (4) molybdates (a) and tungstates (b) in the crystalline and molten states as a function of temperature.²⁶

Fig. 14). The data allow one to trace the character of changes in ΔE along the series of scheelites (both molybdates and tungstates). The splitting increases with a decrease in the Mo–Mo and W–W interatomic distances in the unit cell. It turns to zero in the case of large unit cells of $BaMoO_4$ and $BaWO_4$ and reaches the maximum of 52–58 cm^{-1} for the smallest unit cells of $CaMoO_4$ and $CaWO_4$ (see Table 6). Therefore it is the Davydov splitting that is responsible for a decrease in the $\nu_1(A_g)$ frequency in the series of Ba–Sr–Ca scheelites. The influence of this splitting on the $\nu_1(A_g)$ frequency prevails over all other factors involved.

The influence of various crystal-chemical factors on the spectral widths ($\Delta\nu_R$) of Raman lines has also been analysed in detail.²⁶ The values of $\Delta\nu_R$ corresponding to the $\nu_1(A_g)$ vibrational modes as a function of temperature for a series of molybdates and tungstates in both the crystalline and molten states are plotted in Fig. 15. In the scheelite crystals, $\Delta\nu_R$ is virtually linearly dependent on the temperature. Meanwhile, the spectral line widths of all scheelites increase drastically upon melting. This trend in $\Delta\nu_R$ was attributed²⁶ to a homogeneous broadening of Raman lines due to the dephasing and depopulation of the $\nu_1(A_g)$ vibrational modes. A substantial difference in the line widths between molybdates and tungstates, on the one hand, and nitrates, on the other hand, can be rationalised based on the different energy diagrams of the internal vibrons for the MoO_4 or WO_4 tetrahedra and the NO_3 triangles, which gives rise to different degeneracies of the phonon relaxation processes. In particular, the energy gap between the $\nu_1(A_g)$ mode and adjacent modes in $Ba(NO_3)_2$ is $\sim 300\text{ cm}^{-1}$. In such a case, a three-phonon relaxation is impossible and thus four-phonon relaxation processes characterised by low probabilities prevail. As a consequence, the experimental Raman spectra reveal

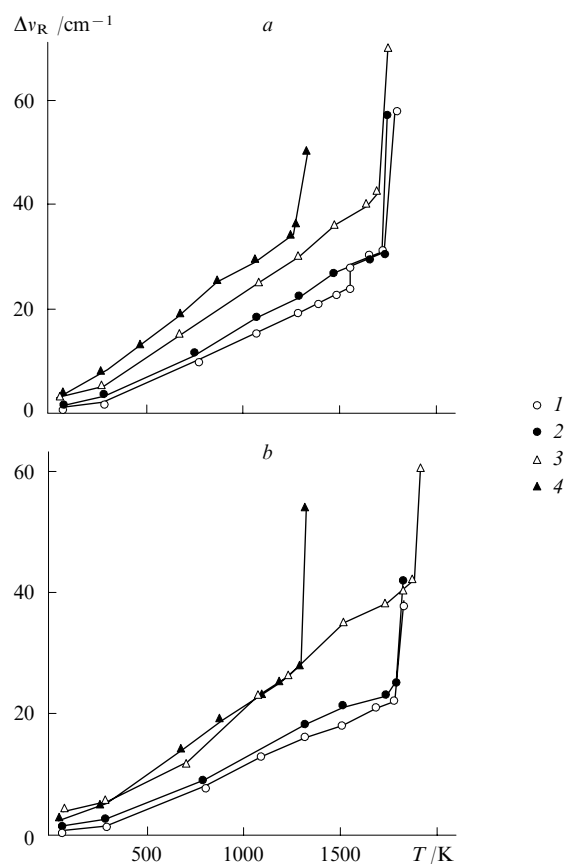


Figure 15. Changes in the widths of the Raman lines corresponding to the $\nu_1(A_g)$ mode for homologous series of barium (1), strontium (2), calcium (3) and lead (4) molybdates (a) and tungstates (b) as a function of temperature.²⁶

a small homogeneous broadening and an extremely narrow line corresponding to a large Σ_{peak} value. In the case of scheelites, the energy gap is $30\text{--}130\text{ cm}^{-1}$ and $70\text{--}150\text{ cm}^{-1}$ for molybdates and tungstates, respectively. At these energy gap values, the phonon relaxation is already dominated by three-phonon processes that are characterised by higher probabilities, which gives rise to a substantial homogeneous broadening of spectral lines corresponding to the internal vibrations.

A careful profile analysis of the $\nu_1(A_g)$ vibrational lines in the Raman spectra of a series of molybdates and tungstates measured under identical conditions revealed a continuous line narrowing in the Ca–Sr–Ba series (Fig. 16), which correlates with a decrease in the Davydov splitting and an increase in the cation mass. Lead molybdate and tungstate strongly deviate from the common trend showing an abnormal increase in $\Delta\nu_1(A_g)$, which can be explained by an increase in the Davydov splitting for the heavy but small lead cation as opposed to the heavy but large barium cation. Another prominent anomaly observed in the spectra of lead molybdate and tungstate by Basiev *et al.*³⁵ is related to their integral Raman scattering intensity. The experimental intensity of the $\nu_1(A_g)$ line was severalfold higher than that for other scheelites and the most intense scattering was observed in the orthogonal geometry, *i.e.*, with $E \perp C4$ (Table 7).

Based on the results of temperature-dependent spontaneous Raman scattering measurements performed over a wide temperature range, the following conclusions can be derived:

- parameters of vibrational spectra of crystals with the scheelite structure are dependent on the mass, size and electronegativity of the cation M;
- the cation mass factor prevails in the case of low-energy external vibrational modes;
- the internal vibrational frequencies of the MoO_4 and WO_4 groups are primarily dependent on the unit cell parameters and the degree of covalency of the M–O bonds;
- the Davydov splitting of totally symmetric $\nu_1(A_g)$ vibrational modes in the tetrahedral MoO_4 and WO_4 groups continuously increases in the Ba–Sr–Pb–Ca series.

Table 7. Abnormally high Raman scattering cross-sections Σ_{peak} and Σ_{int} for PbWO_4 and PbMoO_4 crystals.

Crystal	Polarisation of the pumping radiation	Σ_{peak} (%)	Σ_{int} (%)
BaWO_4	$E \parallel C4$	64	47
	$E \perp C4$	52	38
PbWO_4	$E \parallel C4$	65	120
	$E \perp C4$	97	171
PbMoO_4	$E \parallel C4$	64	203
	$E \perp C4$	146	397

The widths of Raman lines depend on specific features of the crystal lattice and the nature of an M^{2+} cation. A combination of ‘lightweight’ cations with short interionic distances gives rise to a substantial line broadening. The narrowest lines corresponding to the $\nu_1(A_g)$ modes are observed for the case of heavy cations with large ionic radii, *i.e.*, in BaMoO_4 and BaWO_4 (2.1 cm^{-1} and 1.6 cm^{-1} , respectively), which results in the record high SRS gain coefficients. The abnormal trends in the changes of vibrational modes for PbWO_4 and PbMoO_4 cannot be explained taking into account only atomic masses, ionic radii and structure type. A more careful in-depth analysis of effects related to the character of

Table 8. Integral Raman scattering cross-sections (relative to diamond) in crystals of different compounds and effective radii of the oxygen-containing anions.

Group of compounds	Σ_{int} (%)	Anion	Effective radius / Å
Silicates (SiO_2)	2.2	$\begin{array}{c} \text{O} \\ \\ -\text{O}-\text{Si}-\text{O}- \\ \\ \text{O} \end{array}$	2.3
Carbonates (CaCO_3)	6	$\begin{array}{c} \text{O} \\ \diagup \quad \diagdown \\ \text{O}-\text{C}=\text{O} \\ \diagdown \quad \diagup \\ \text{O} \end{array}$	1.8
Niobates (LaNbO_4)	22	$\begin{array}{c} \text{O} \\ \\ -\text{O}-\text{Nb}=\text{O} \\ \\ \text{O} \end{array}$	2.5
Nitrates [$\text{Ba}(\text{NO}_3)_2$]	21	$\begin{array}{c} \text{O} \\ \diagup \quad \diagdown \\ -\text{O}-\text{N}=\text{O} \\ \diagdown \quad \diagup \\ \text{O} \end{array}$	1.9
Iodates (LiIO_3)	54	$\begin{array}{c} \text{O} \\ \diagup \quad \diagdown \\ -\text{O}-\text{I}=\text{O} \\ \diagdown \quad \diagup \\ \text{O} \end{array}$	2.5
Molybdates (MMoO_4)	52–64	$\begin{array}{c} \text{O} \\ \\ -\text{O}-\text{Mo}-\text{O}- \\ \\ \text{O} \end{array}$	2.5
Tungstates (MWO_4)	47–52	$\begin{array}{c} \text{O} \\ \\ -\text{O}-\text{W}-\text{O}- \\ \\ \text{O} \end{array}$	2.6

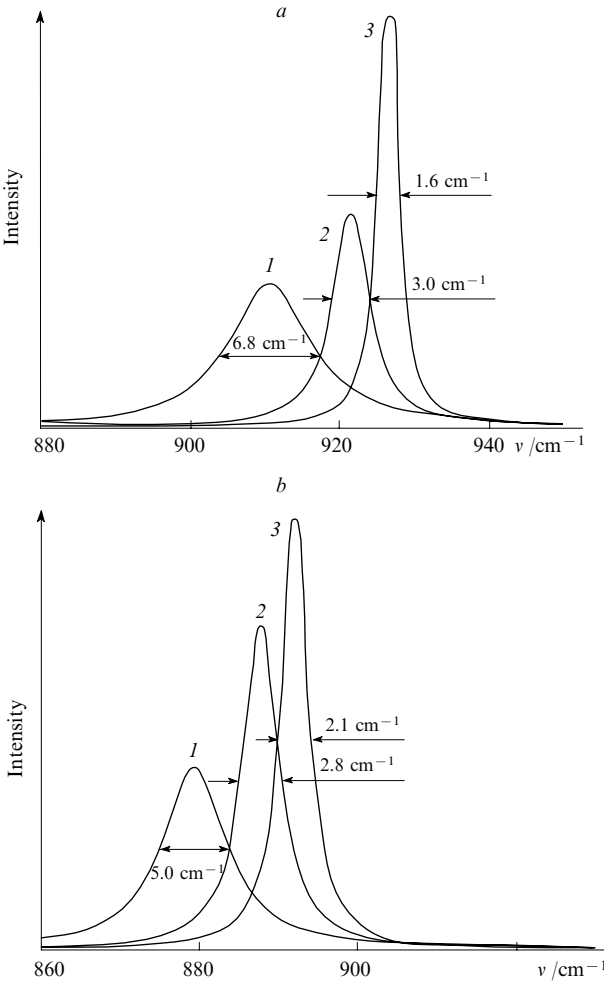


Figure 16. Room-temperature Raman line profiles [corresponding to the $\nu_1(A_g)$ mode] for calcium (1), strontium (2) and barium (3) tungstates (a) and molybdates (b).

the Pb—O chemical bonds is required. The integral line intensity represents the most difficult problem as regards the interpretation and prediction of Raman scattering and SRS parameters. This problem is additionally complicated by the fact that an incident radiation generates simultaneously several Raman components characterised by different intensities in the vast majority of crystalline media, which effectively gives rise to a distribution of the converted radiation energy over several vibrational modes (in contrast to, for instance, diamond, where all scattered energy is concentrated in a single line profile).

The integral intensities Σ_{int} corresponding to internal vibrational lines of quasi-molecular ions in different types of crystals are compiled in Table 8 together with their respective effective radii.³⁶ A correlation between Σ_{int} and the effective anion radius exists: Σ_{int} increases with an increase in the anion size. In particular, Σ_{int} in crystals of molybdates, tungstates, niobates and iodates significantly exceeds those in such compounds as borates, carbonates and nitrates.

V. SRS converters and lasers based on novel crystals

According to the data considered in previous sections, it can be concluded that an efficient SRS conversion of the laser radiation (that is the conversion with a high efficiency) can be realised in materials complying with the following requirements:

- large peak and integral Raman scattering cross-sections;
- low optical losses of both pumping radiation and SRS radiation; this implies that the crystals have to be optically homogeneous and defect-free and have a wide spectral window of transparency;
- crystals should be mechanically strong and chemically stable; in particular, they should provide a high radiation damage threshold and do not degrade in terms of optical homogeneity under atmospheric humidity, sun light, *etc.*

Below we give a few examples of successful application of novel crystals in SRS lasers.

1. Nanosecond SRS lasers with BaWO₄ and SrWO₄ crystals

Zverev *et al.*³⁷ reported on the results of comparative tests of novel BaWO₄ crystals and well-known Ba(NO₃)₂ and KGd(WO₄)₂ crystals. The crystal elements made from BaWO₄, Ba(NO₃)₂ and KGd(WO₄)₂ were placed into a Fabry–Perot resonator with a length of 9 cm. The input mirror had a reflection coefficient of 5% and 98% at the pumping radiation wavelength of 1.064 μm and in the range of the generated Stokes components, *i.e.*, $\lambda = 1.1$ –1.25 μm , respectively. The output mirror had a reflection coefficient $R_{1.0-1.2} = 55\%$. As a pumping source, a single-mode Nd-doped yttrium–aluminium garnet laser (YAG:Nd³⁺) with a passive LiF:F₂[−] Q-switch was used. The pulse duration of SRS radiation was 20 ns at a repetition rate of 10 s^{−1}. The efficiency of SRS radiation was 26% and 20.5% with Ba(NO₃)₂ and BaWO₄ crystals, respectively. In both cases, the slope efficiency exceeded 75% at nearly identical SRS thresholds. It is of note that the SRS properties of BaWO₄ are polarised; in particular, the efficiency was higher for $E \parallel C4$ and lower for $E \perp C4$. The KGd(WO₄)₂ crystals demonstrated a higher SRS threshold and a slope efficiency of only 45% under strictly identical experimental conditions.

The SRS-based frequency conversion of radiation produced by an Nd-doped gadolinium–gallium garnet laser was also elucidated.³⁸ A BaWO₄-based SRS converter shifted the incident laser wavelength from 1.0621 μm to 1.1779 μm . As a result of the conversion with a slope efficiency above 30%, pulses with an energy of 15 mJ at a power in the MW range and a repetition rate of 10 s^{−1} were produced.

The efficiency of an SrWO₄-based SRS laser was characterised under similar conditions.³⁹ Strontium tungstate crystals can be doped with a large amount of neodymium. In such a case, the same crystal can simultaneously serve for the generation of the laser radiation with $\lambda = 1.06 \mu\text{m}$ on Nd³⁺ sites and its SRS conversion to $\lambda = 1.18 \mu\text{m}$. This functional integration admits a significant decrease in the size of the laser device and strongly enhances the reliability of its operation.

2. Nanosecond SRS lasers in the mid-IR region with BaWO₄ crystals

BaWO₄ crystals are highly transparent in the intermediate IR spectral range, which can be exploited in the design of lasers generating radiation with a wavelength within 2–5 μm . As has been mentioned above, this spectral range is extremely important for practical applications but remains poorly developed. The major problem there is that the longest possible wavelengths of pumping radiation have to be used in a combination with the second (or even the third) Stokes components of the Raman spectrum, since a typical SRS frequency shift is on the order of $\sim 1000 \text{ cm}^{-1}$. Furthermore, the SRS gain coefficient rapidly decreases with an increase in the pumping wavelength. Basiev *et al.*⁴⁰ utilised crystal elements made from BaWO₄ with a length of 42 mm to convert the pumping radiation of 1.34 μm generated by a YAG:Nd³⁺ laser equipped with an acoustooptic Q-switch. The SRS-converted spectrum is shown in Fig. 17. The spectrum reveals the first (1.53 μm), second (1.78 μm) and third (2.13 μm) Stokes components. The slope efficiency for the conversion of the pumping energy (1.34 μm) into the first and the second Stokes components was higher than 22%.

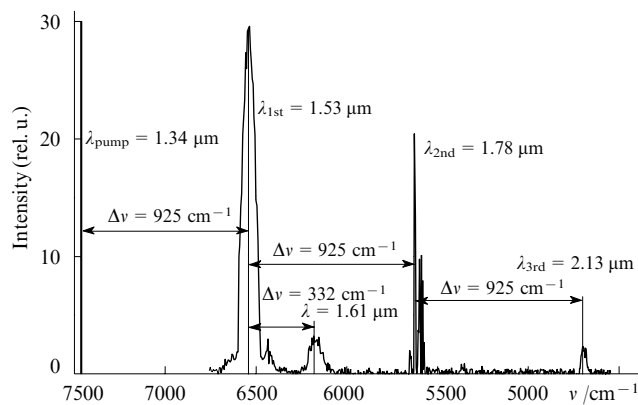


Figure 17. The SRS generation spectra of BaWO₄ crystals pumped by a neodymium-doped yttrium–aluminium garnet laser operated at a wavelength of 1.34 μm .⁴⁰

Recently, a significant advancement towards the mid-IR region has been achieved.⁴¹ It relates to the SRS spectral conversion of nanosecond laser pulses at wavelengths of 1.56 μm and 1.91 μm with BaWO₄ crystals. It has been shown that the pumping radiation with $\lambda = 1.56 \mu\text{m}$ undergoes a multi-stage conversion into the first, second, third and fourth Stokes SRS components corresponding to wavelengths of 1.82, 2.19, 2.75 and 3.69 μm , respectively. The generated SRS components are shown in Fig. 18 in a comparison with the transmission spectrum of BaWO₄ crystals.

In the case of nanosecond pumping pulses with $\lambda = 1.91 \mu\text{m}$, the first Stokes SRS component with 2.32 μm was successfully generated. It is important that the BaWO₄ crystal utilised in the converter was only 27 mm long.

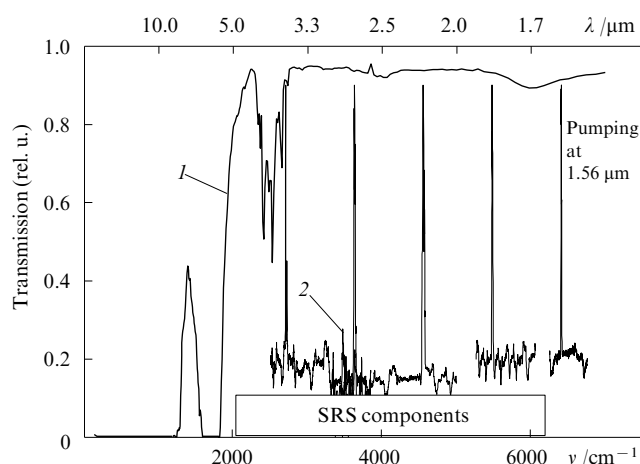


Figure 18. A transmission spectrum of BaWO₄ crystals (1) and the BaWO₄ Raman laser oscillation spectra in the mid-IR region (2).

3. The SRS conversion of picosecond laser pulses with BaWO₄ crystals

Černý *et al.*⁴² accomplished a comparative analysis of the performance of BaWO₄, KGd(WO₄)₂ and KY(WO₄)₂ crystals in the SRS conversion of picosecond pulses. The pumping radiation was characterised by wavelengths of 0.53 μm and 1.064 μm and pulse durations of 28 and 40 ns, respectively. In the case of the green pumping light (0.53 μm), the gain coefficients were 14.4 cm (GW)⁻¹, 11.5 cm (GW)⁻¹ and 18.7 cm (GW)⁻¹ with BaWO₄, KGd(WO₄)₂ and KY(WO₄)₂ crystals, respectively. While the gain coefficient provided by the BaWO₄ crystal was three times larger than that with KGd(WO₄)₂ in the steady-state SRS mode, its advantage was not as evident in the picosecond mode. This is explained by the narrower Raman line and shorter relaxation time in BaWO₄ as compared with the respective values in KGd(WO₄)₂. A different situation is observed when the BaWO₄ performance is compared with that of Ba(NO₃)₂. For nanosecond pumping pulses (in the steady-state mode), the gain coefficient provided by the BaWO₄ crystal was 20%–30% lower than that with Ba(NO₃)₂. Meanwhile, in the picosecond (transient) mode, BaWO₄ performs three times better than Ba(NO₃)₂. The gain coefficients for picosecond pumping pulses with λ = 1.064 μm were 3.8 cm (GW)⁻¹, 4.7 cm (GW)⁻¹ and 3 cm (GW)⁻¹ for BaWO₄, KY(WO₄)₂ and KGd(WO₄)₂, respectively. The maximum efficiency of a working element made from BaWO₄ with a length of 30 mm for picosecond pumping pulses with λ = 0.53 μm was 30% for the first Stokes component. The respective value for a KGd(WO₄)₂ crystal with a length of 40 mm was only 18%. According to the detailed measurements on the efficiency of the SRS generation,⁴³ the efficiency of the conversion of pulsed pumping radiation with a wavelength of 1.064 μm and a pulse duration of 50 ps into the first Stokes component of 1.180 μm increases from 25% to 35% on going from a one-pass to a two-pass optical scheme. When the BaWO₄ element was placed into a resonator with a length of 38 cm equipped with an output mirror with the optimised transmission spectrum, the absolute efficiency increased to 55%, whereas the slope efficiency (estimated by the slope) reached nearly 100%.⁴⁴

4. SRS frequency converters and lasers with PbWO₄, PbMoO₄ and PbMoO₄:Nd³⁺ crystals

Kaminskii *et al.*^{45,46} studied radiation of an SRS laser with PbWO₄ crystals pumped by a YAG:Nd³⁺ pulsed laser with λ = 1.064 μm and a pulse duration of 100 ps. The conversion efficiency of 20% was achieved at an energy of the pumping pulses of 5 mJ using a resonator with planar-convex mirrors having a length of 200 mm. The length of a working PbWO₄ element was 30 mm. The same authors reported on the SRS conversion of

pulsed green radiation with a wavelength of 0.53 μm and a pulse duration of 30 ps. The PbWO₄ crystal provided a gain coefficient of 8.4 cm (GW)⁻¹.

Another study⁴⁷ was devoted to the generation of SRS by one or two elements made from PbWO₄ with a length of 45 mm placed into a ring resonator. The pumping was achieved with the first harmonic of a pulsed YAG:Nd³⁺ laser with a pulse duration of 7 ns. With one element in the resonator, the energy of SRS radiation was 5.3 mJ at an energy of pumping pulses of 36 mJ (which is already close to the laser damage threshold of PbWO₄ crystals). The conversion efficiency of 20% was achieved with two elements in the resonator.

Atypically high values of Σ_{peak} and Σ_{int} observed for PbMoO₄ crystals make it a promising candidate for achieving unprecedentedly high efficiencies of the SRS conversion for both nanosecond and picosecond pulse duration regimes. Furthermore, the PbMoO₄ crystal lattice easily accommodates a large amount of doping rare-earth elements, which makes it possible to combine the laser light generation and its SRS conversion within one crystal. According to a series of recent publications,^{27,35,48} these predictions are well justified. The following experiments have been reported:

- the generation of SRS in PbMoO₄ crystals as a function of the sample orientation relative to the polarisation vector of the incident radiation;
- the laser light generation by the Nd³⁺ ions in PbMoO₄:Nd³⁺ in the free-running mode;
- the laser light generation by the Nd³⁺ ions in the Q-switched mode;
- the laser light generation by the Nd³⁺ ions with its simultaneous conversion to the first Stokes SRS component.

The pumping was achieved with a semiconductor laser diode emitting at a wavelength of 0.808 μm and a power of 1.5 W. The radiation of the laser diode was fully linearly polarised and pulsed with a pulse duration of 250 μs at a repetition rate of 5 s⁻¹. As laser elements, PbMoO₄:Nd³⁺ crystals with neodymium concentrations of 0.3 mass % and 2 mass % were employed. Rectangular plates with thicknesses of 1 mm were cut perpendicular to the crystallographic *a* axis. In the free-running oscillation mode, the radiation with a wavelength of 1.0556 μm was produced. The differential generation efficiency was 53% for the sample with 0.3 mass % of Nd. In the case of the sample with 2 mass % of Nd, an average oscillation power of 0.65 W was achieved.

Q-Switching was accomplished with a passive shutter based on lithium fluoride crystals with F₂⁻ colour centres. Under these conditions, a pulsed SRS oscillation mode was realised with a pulse repetition rate of (7.5–190) × 10³ s⁻¹ at a peak power of ~2 kW and an average power of ~0.36 W. The pulse duration was from 8.7 ns to 1.4 ns. These results prove that PbMoO₄:Nd³⁺ provides a high average power in the Q-switched operation mode (only 1.8 times lower than in the free-running oscillation mode).

In experiments on the self-conversion of the laser radiation generated by the neodymium ions in PbMoO₄:Nd³⁺ into the SRS, the thickness of working elements was 3 mm. With a LiF:F₂⁻ Q-switch, the first Stokes SRS component was observed at a wavelength of 1.163 μm. The output pulse energy was 6 μJ at a pulse duration of < 500 ps. This implies that the peak pulse power achieved was higher than 12 kW.

Potential application fields of the novel SRS crystals and lasers on their base are comprehensively considered elsewhere.^{49,50}

* * *

The recent experimental data on the SRS-based laser wavelength conversion considered above proves the significant predictive power of the approach to the search for novel SRS-active media described in the present review. The theoretical conclusions on the

frequencies and widths of SRS lines with their relation to the conversion efficiency of laser pulses with different durations are fully supported by experimental results.

The conclusions regarding the homologous series of alkali-earth metal molybdates and tungstates can be extended (with minor correction) to other homologous classes of inorganic compounds.

Therefore, the use of stimulated Raman scattering in crystals of inorganic compounds has a huge potential in solving the problem of the design of spectrally positioned laser sources.

The authors are grateful to L N Ershova and M N Basieva for help in the manuscript preparation.

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^a — *J. Exp. Theor. Phys. Lett. (Engl. Transl.)*

^b — *Crystallogr. Rep. (Engl. Transl.)*

^c — *J. Exp. Theor. Phys. (Engl. Transl.)*

^d — *Phys. Solid State (Engl. Transl.)*

From the Gomberg radical to organic magnets

N M Shishlov

Contents

I. Introduction	863
II. Exchange interactions in di- and polyradicals	863
III. Mesoscopic and monomolecular magnets. Spin clusters	864
IV. Triarylmethyl type di- and polyradicals	866
V. Conclusion	882

Abstract. The synthesis and properties of triarylmethyl di- and polyradicals including perchlorinated ones are considered. The achievements in the design of magnetic clusters and organic magnets based on the Gomberg radical are described. Data on mixed-valence compounds containing triarylmethyl type radicals and carbanions as electroactive groups are given. The bibliography includes 117 references.

I. Introduction

Magnetism as a universal natural phenomenon is intensively studied by fundamental science. Magnetic phenomena are widely used in engineering. The traditional magnetic materials (ferro-, ferri- and antiferromagnets) contain metal atoms or ions with partially occupied d and f shells and represent metals, metal alloys and ceramics. In both fundamental and applied aspects, the interest of researchers is aroused by creation of an organic magnet, *i.e.*, an ensemble of organic molecules or macromolecules containing only light (non-metal) elements (C, O, H, N, S, *etc.*) and possessing spin ordering, *i.e.*, ferro- or ferrimagnetism. Various approaches to the design of organic magnets and achievements along this line have been summarised in reviews.^{1–6}

This review considers the key methods for the synthesis and properties of di- and polyradicals and organic magnets based on the first experimentally detected (Gomberg, 1900) triphenylmethyl radical (TPMR). The chemical and spectroscopic properties of the Gomberg radical and other triarylmethyl type (TAMT) radicals have been described, for example, in a number of books.^{7,8} The research area related to the molecular magnetism has developed so vigorously in recent years that it is difficult to cover it within one review. Works devoted to particular types of radicals are therefore required. For example, of the 373 references present in the recent review by Blundell and Pratt⁶ dealing with organic and molecular magnets, only two references concern polymeric polyradicals. Somewhat more information on these species can be found in another publication.⁴ A number of reviews by Rajca,^{3,9–13} who is actively engaged in the synthesis of TAMT

polyradicals, have been published; the recent review¹³ deserves special mention.

The problem of the creation of organic magnets can be divided into the molecular and supramolecular aspects. In the molecular aspect, it is clear that organic paramagnetic compounds with unpaired electrons, stable radicals and carbenes should serve as the building blocks for organic magnets.

Currently, an enormous number of paramagnetic organic species are known, and ferromagnetic spin ordering in the crystal or in an amorphous solid, *i.e.*, the supramolecular aspect, remains the major problem. Indeed, according to Dougherty,² ‘...Nature favours antiferromagnetic coupling of two weakly interacting electrons’. However, several cases of ferro- and ferrimagnetism in the crystals of small radicals or organic charge transfer salts have recently been observed experimentally.^{1–6} Two McConnell mechanisms demonstrating the possibility of through-space intermolecular ferromagnetic ordering of organic paramagnetic molecules (radicals and carbenes) have been considered in detail in reviews^{1,4} which give references to original publications.

II. Exchange interactions in di- and polyradicals

Yet another approach to the design of organic magnets (alternative to the spatial ordering of small radicals) is the synthesis of polyradicals in which the intramolecular magnetic ordering of unpaired electrons occurs through chemical bonds. It is meant that pair exchange interactions between unpaired electrons are transferred through a system of conjugated π -bonds of a polymer. Since in some conjugated diradicals (including those stable under ambient conditions), very strong ferromagnetic coupling has been found,³ this approach offers hope for the preparation of organic magnets with the Curie temperature equal to, or higher than, room temperature.

The descriptions of di- and polyradicals widely use^{2,3} the notions ‘ferromagnetic coupling unit’ (FCU) and ‘antiferromagnetic coupling unit’ (ACU) (in some cases, they are referred to as the corresponding bridges). The simplest π -conjugated hydrocarbon diradical is trimethylenemethane (TMM) (CU-1 structure in Fig. 1). In this diradical, two methyl radicals are attached to one end of the ethylene molecule (1,1-coupling) and the p orbitals with unpaired electrons are conjugated with the π -system of ethylene. The electron coupling is ferromagnetic, and TMM exists in a triplet ground state (T) with the full spin $S = 1$. In this case, ethylene acts as an FCU. Conversely, for the CU-2 structure in Fig. 1 in which the radical centres are attached to different ends of the ethylene molecule (1,2-coupling), the ground state is singlet (S, $S = 0$) and in this case the double bond is an antiferromagnetic

N M Shishlov Institute of Organic Chemistry, Ufa Scientific Centre of the Russian Academy of Sciences, prosp. Oktyabrya 71, 450054 Ufa, Russian Federation. Fax (7-3472) 35 60 66, tel. (7-3472) 35 61 19, e-mail: shishlov@anrb.ru

Received 27 December 2005

Uspekhi Khimii 75 (10) 956–979 (2006); translated by Z P Bobkova

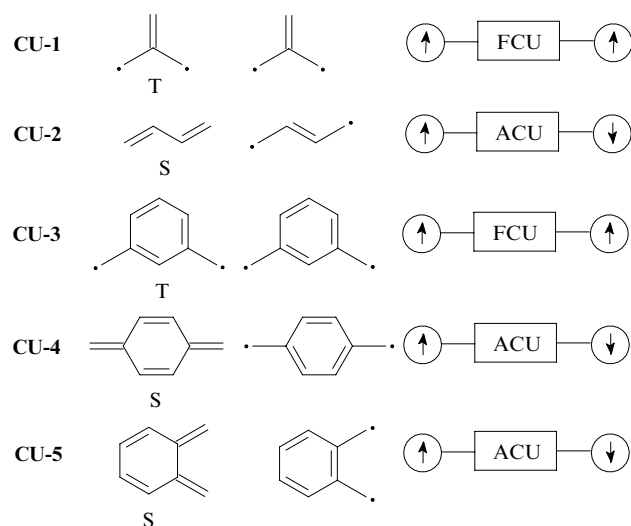


Figure 1. Structure (topology) of conjugated diradicals and spin coupling in them (see the text).

coupling unit. The exchange interaction of the unpaired electrons through a benzene ring also depends on the arrangement of the radical centres. The 1,3-coupling (*meta*-coupling) usually results in a triplet ground state of the molecule and a ferromagnetic coupling of electrons (CU-3 structure in Fig. 1), whereas 1,4(*para*)- and 1,2(*ortho*)-coupling of the radical centres gives rise to a singlet ground state and, correspondingly, antiferromagnetic coupling of the unpaired electrons (CU-4 and CU-5 structures in Fig. 1).

It should be emphasised that the type of binding through phenylene units as well as the conjugation effect depend appreciably on the mutual arrangement of the orbitals bearing unpaired electrons and the plane of the benzene ring. Conformational distortions of the structure may result in a decrease in the exchange coupling and in the reversal of its sign, *i.e.*, a *meta*-phenylene unit may become an ACU, and a *para*-phenylene unit may be transformed into an FCU. Zang *et al.*¹⁴ calculated the dependence of the singlet–triplet splitting energy and, hence, the exchange integral on the rotation angle of the p orbitals with unpaired electrons with respect to the plane of the benzene ring for the CU-3–CU-5 units and gave references to the experimentally proven cases of sign reversal in the exchange coupling caused by steric distortion of the structure of the unit. Some examples of this sort are considered below.

A ‘magnetic’ polymer should, in a general case, be a macromolecule with a large number (10^3 – 10^4 or more) radicals that interact through coupling units, *i.e.*, a polyradical. Two differing in principle approaches for radical coupling within a conjugated polymer have been developed: in class I polyradicals, the radicals alternate with the coupling units, while in class II polyradicals, the radicals are attached to the conjugated polymer backbone (Fig. 2). The idea of using the conjugated polymer backbone as the common ferromagnetic coupling unit was first proposed by Ovchinnikov and co-workers¹⁵ and subsequently developed by Nishide *et al.*¹⁶

The progress in the design of magnetic polymers may be evaluated using the average full spin S in the ground state of the macromolecule (for n ferromagnetically coupled spins equal to $1/2$, $S = n/2$).

III. Mesoscopic and monomolecular magnets. Spin clusters

On the one hand, researchers try to obtain magnetic molecules as large as possible (ideally, macroscopic, for example, as networks). On the other hand, it should be borne in mind that for the

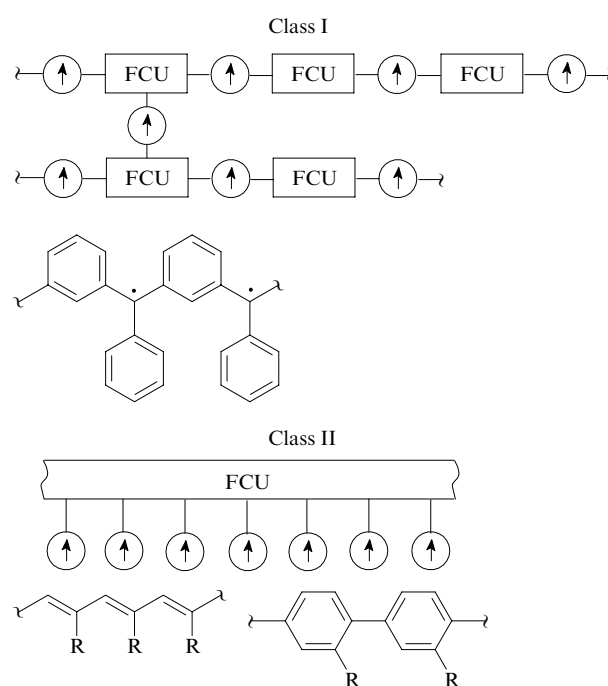


Figure 2. Two classes of polyradicals. R is a stable radical.

condensed phase, three main sorts of magnetic ordering (ferro-, antiferro- and ferrimagnetism) may be supplemented still by at least nine types (metamagnetism, ‘seed’ ferromagnetism, superparamagnetism, speromagnetism, asperomagnetism, helimagnetism, spin glass, mictomagnetism, sperimagnetism).¹⁷ These sorts of magnetic order can apparently be also manifested in organic magnets, and one should, first, be ready to encounter them, and, second, to deliberately prepare compounds with these sorts of ordering. In particular, a new line of research closely connected with the superparamagnetism, called magnetic mesoscopies, has been actively developed in recent years;^{18,19} this deals with small magnetic particles with a size of ~ 1 – 100 nm containing ~ 10 – $10\,000$ atoms. These mesoscopic magnets (or nanomagnets) are of obvious fundamental interest as regards transition from the magnetism of separate atoms to the collective magnetism (ferro, ferri, *etc.*) of amorphous and crystalline macrobodies. From the technology standpoint, the use of mesoscopic magnets is promising for increasing the density of magnetic data recording.

Now we consider briefly the magnetic properties of mesoscopic magnets, which are rather small single-domain particles and often behave as superparamagnets.^{3,18,19} In small single-domain particles, magnetisation along the easy magnetisation axis is blocked: an energy barrier (E_A) to the rotation of the magnetisation vector appears due to the anisotropy energy. There are many types of magnetic anisotropy;²⁰ the most frequently encountered types are the crystallographic anisotropy caused mainly by the spin–orbit coupling and the shape anisotropy the microscopic cause of which is the long-range dipole–dipole coupling between the elementary magnetic moment carriers.²⁰

Figure 3 shows the dependence of the energy (E) of a single-domain particle on the angle (θ) between the magnetisation vector (M) and the easy magnetisation axis in the absence of a magnetic field and on its switching on. The field is oriented oppositely to the z axis, which is directed upward. The transition of a magnetic particle from the metastable state (the left minimum in Fig. 1b, $\theta = 0$) to the equilibrium state ($\theta = \pi$) requires overcoming an energy barrier the height of which decreases with an increase in the field and becomes equal to zero at the critical value $H_c = 2E_A/M$. At this instant, the particle is remagnetised, namely, the magnetisation vector is oriented along the external field. This process is called switching and the H_c is the switching

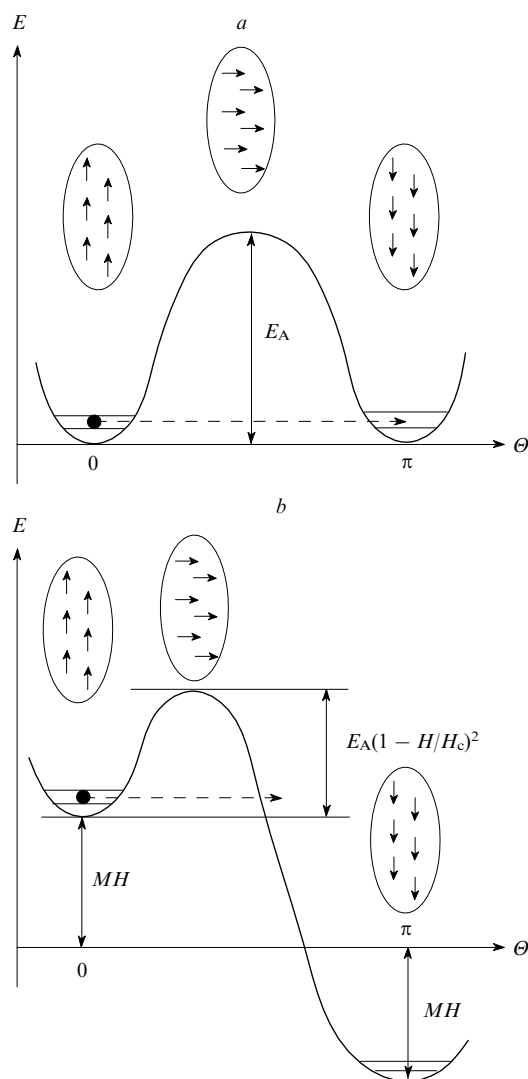


Figure 3. Energy barrier to remagnetisation of a single-domain particle of an oblong shape: (a) without an external magnetic field; (b) in an external magnetic field H .

field. This bistability of small magnetic particles can be used for data recording. The transition over the barrier is facilitated by thermal fluctuations of magnetisation, which are, in particular, interfering factors for data recording. Owing to the thermal fluctuations, magnetisation of a material consisting of small magnetic particles decreases with time, the relaxation rate decreasing with a decrease in temperature according to the Arrhenius law

$$\tau^{-1} = f_0 \exp\left(-\frac{E_A}{k_B T}\right),$$

where τ is the characteristic relaxation time, f_0 is the pre-exponential factor equal to $\sim 10^{-9} - 10^{-10} \text{ s}^{-1}$ for typical magnetic particles, k_B is the Boltzmann constant, T is temperature.

It is noteworthy that the magnetisation vector may tunnel from one minimum to another upon quantum fluctuation, as shown by a dashed arrow in Fig. 3. These tunnelling transitions were actually detected experimentally; they are most clear-cut for a number of high-spin magnetic clusters that are considered below. This quantum effect is called macroscopic quantum tunnelling or magnetisation quantum tunnelling (MQT), its discovery being ranked among most prominent achievements of physics in the late 20th century. The violation of the Arrhenius

law at low temperatures ($T \rightarrow 0$), in particular, reaching a constant relaxation rate, is a consequence of the MQT.

In 1993, Rajca realised the possibility and importance of investigation of the magnetism of high-spin organic molecules on a mesoscopic scale.⁹ He noted that the spin-orbit coupling in carbon-centred radicals and carbenes is negligibly low, as follows from the small deviation of g -factors of these species from the g -factor of a free electron. Therefore, shape anisotropy is expected to be important for these species, and organic synthesis opens up extended opportunities for controlling this factor. For a particle with volume V , magnetisation I_s and the shape factor N , which is related to the demagnetisation factor ($0 \leq N \leq 2\pi$, $N = 0$ for a sphere, $N = 2\pi$ for an infinite rod), the energy barrier (in Kelvins) in the case of coherent rotation of the magnetisation is described by the formula

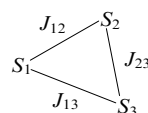
$$E_A = \frac{0.5 N I_s^2 V}{k_B}. \quad (1)$$

A calculation by this formula for triarylmethyl polyradicals with a moderately oblong shape (for example, an oblong ellipsoid of revolution with $a:b \approx 2$, $N \approx 3$) shows that about 200 ferromagnetically coupled spins (correspondingly, $S \approx 100$) are required to ensure a barrier of about 2 K.^{21, 22}

Nanomagnets can, in principle, be approached in two ways: 'top-down', *i.e.*, by grinding magnetic macrobodies, and 'bottom-up', *i.e.*, by synthesising large magnetic clusters. A magnetic, exchange or spin cluster is a set of several (two or more) spin centres connected by chemical or exchange interactions. Clusters in which magnetic transition metal ions (Fe, Mn, Cr, *etc.*) act as the spin centres are best known and best studied. The paramagnetic clusters are fairly convenient model systems in which all main physical interactions that form the properties of magnetic materials, including exchange interactions, are manifested for a limited number of atoms (ions) and, hence, they can be analysed more easily. Magnetic clusters, being adjacent to mesoscopic magnets, also represent a connecting unit between the microscopic and macroscopic magnetism. Extensive literature is devoted to various aspects of the physics and chemistry of inorganic exchange clusters; all relevant references can be found in books.^{23–25} The traditional theoretical base for the description of magnetic and spectroscopic properties of exchange clusters comes from the Heisenberg–Dirac–Van Vleck model, which is often called for short the Heisenberg model. In this model, exchange interactions for polynuclear clusters are described by the Hamiltonian

$$\hat{H} = - \sum_{ij} J_{ij} \hat{S}_i \hat{S}_j,$$

where J_{ij} is the exchange parameter, which is positive in the case of a ferromagnetic spin coupling and negative in the case of antiferromagnetic coupling; $\hat{S}_i$ and $\hat{S}_j$ are operators of the coupled spins.



For example, for a trinuclear cluster of the spins S_1 , S_2 and S_3 , the Heisenberg Hamiltonian in the general case has the form

$$\hat{H} = -2 J_{12} \hat{S}_1 \hat{S}_2 - 2 J_{23} \hat{S}_2 \hat{S}_3 - 2 J_{13} \hat{S}_1 \hat{S}_3.$$

With known structure or symmetry of the polynuclear cluster, the number of independent exchange parameters in the Hamiltonian can be reduced, which substantially facilitates its solution. The corresponding Hamiltonian can be composed based on simple considerations almost for any system of exchange-coupled spins (paramagnetic ions, radicals, *etc.*).²³ The next stage, namely, the calculation of the spin level energies and derivation of the

theoretical equation for the magnetic susceptibility for rather simple clusters, is not faced with serious difficulties either. The limitations inherent in the Heisenberg model have been considered in detail in books.^{23,24}

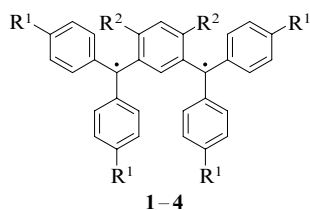
The research dealing with exchange clusters resulted in the development of single-molecular ensembles of paramagnetic ions, 'single-molecule magnets' (SMM). In 1980, Lis²⁶ reported the synthesis, structure and some magnetic properties of the nano-sized molecule $[\text{Mn}_{12}\text{O}_{12}(\text{OAc})_{16}(\text{H}_2\text{O})_4]$, which is usually designated as Mn_{12} . Each molecule contains a group of 12 manganese ions: four Mn^{4+} ions with the spins $S_1 = 3/2$ forming an internal tetrahedron and eight Mn^{3+} ions with the spins $S_2 = 2$ located outside the tetrahedron. The antiferromagnetic interactions of manganese ions with different oxidation states through oxygen ions give rise to a ferrimagnetic structure with the full spin of the molecule $S = 10$ ($8 \times 4/2 - 4 \times 3/2 = 10$). In 1993, it was found²⁷ that Mn_{12} has a substantial barrier of the magnetic anisotropy ($E_A = 60$ K) to the reversal of the magnetisation vector; this was manifested as a magnetic hysteresis loop at temperatures below 4 K. Since this type of hysteresis behaviour of these molecules is similar to the behaviour of small single-domain magnetic particles, the name 'single-molecule magnets' was proposed for them (as has been noted,²⁸ this name is not completely correct). This and similar molecular clusters demonstrate most clearly macroscopic quantum tunnelling mentioned above, as their chemical synthesis ensures the creation of ensembles comprising fully identical and equally oriented SMM.^{6,28}

The progress achieved in the preparation of mesoscopic magnets, magnetic clusters and SMM based on transition metal ions prompt the idea of preparing similar objects from organic radicals, the more so, that the synthesis of polyradicals having nanometre sizes is quite a realistic task.

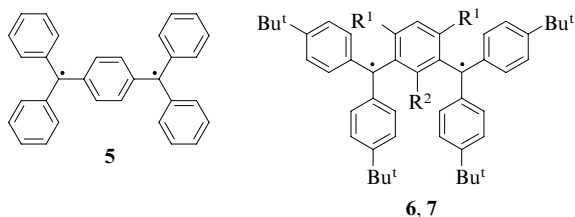
IV. Triarylmethyl type di- and polyradicals

1. Diradicals

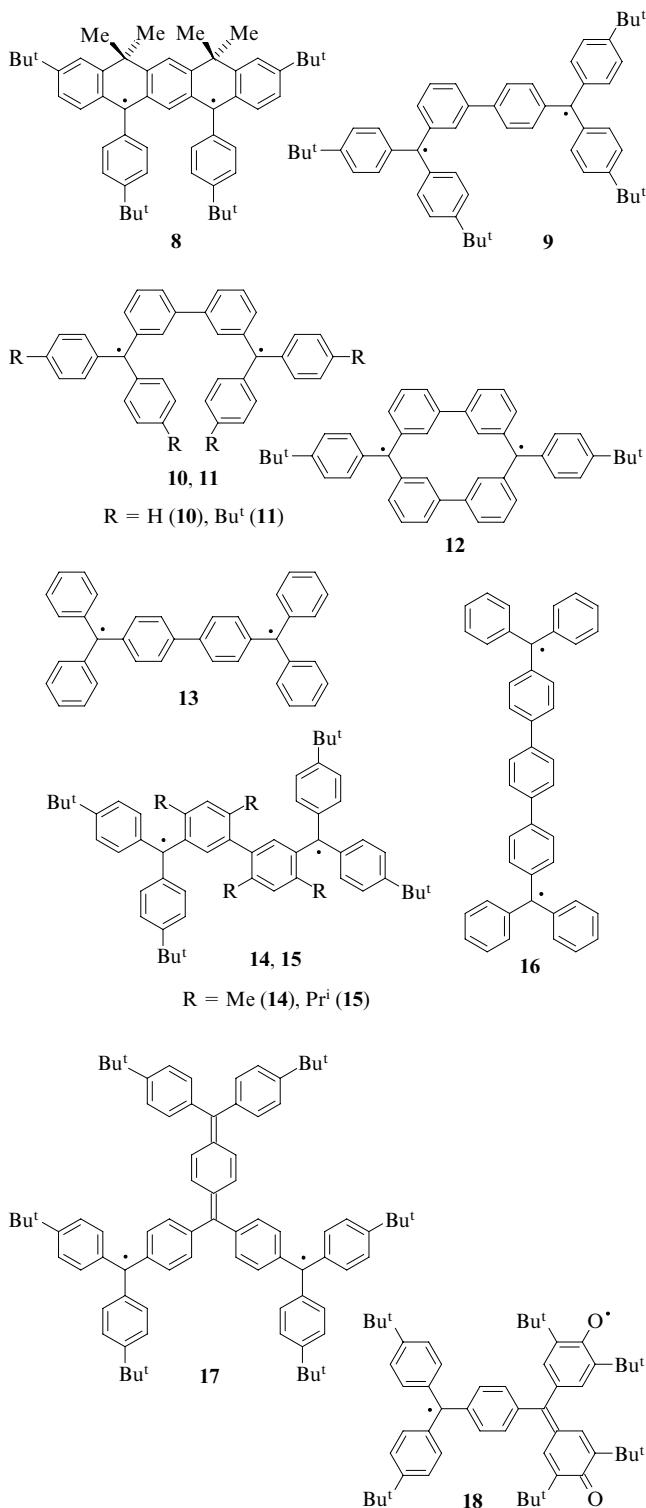
It is reasonable to consider first the diradicals obtained from the Gomberg radical in which the magnetic interactions of the unpaired electrons are manifested most clearly. The achievements in the synthesis of triarylmethyl diradicals and their properties have been discussed in a number of reviews and monographs (see, for example, the publications^{3,29,30}). Table 1 presents the properties of hydrocarbon diradicals of the triarylmethyl type **1–18** including both the diradicals synthesised recently and those known long ago with known magnetic properties. Let us briefly discuss some of the diradicals. It is believed that for structures **5** (Thiele's hydrocarbon), **13** (Chichibabin's hydrocarbon, ChH) and **16** (Muller's hydrocarbon, MH), the singlet states exist as



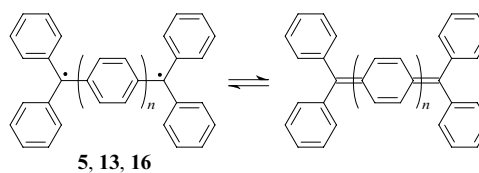
$\text{R}^1 = \text{R}^2 = \text{H}$ (**1**); $\text{R}^1 = \text{Bu}^t$; $\text{R}^2 = \text{H}$ (**2**), Me (**3**), Pr^i (**4**).



$\text{R}^1 = \text{R}^2 = \text{Me}$ (**6**),
 $\text{R}^1 = \text{CF}_3$, $\text{R}^2 = \text{H}$ (**7**).



the corresponding quinonoid structures, which are in equilibrium with the triplet (diradical) states; for Thiele's hydrocarbon, the equilibrium is entirely shifted to the right due to the great energy difference between the singlet and triplet states and only the singlet state has always been observed.



$n = 1$ (**5**), 2 (**13**), 3 (**16**).

Table 1. Some properties of hydrocarbon diradicals of the triarylmethyl type.

Diradical	$10^3 D/hc / \text{cm}^{-1}$; $10^3 E/hc / \text{cm}^{-1}$ (see ^a)	Ground state ^b	Ref.
1	7.9; 0.7	T	31
2	6.6; ~ 0.8	T	32–34
3	8.7; ~ 0	T	33, 34
4	9.9; ~ 0	T (0.2)	32–34
5	—	S	7, 35
6	10.7; ~ 0	S (0.2)	33, 34
7	—	T	3
8	—	T	3, 36
9	2.5; —	T	37
10	4.9; ≤ 0.3	T (0.3)	38
11	5.0; —	S (~ 0.1)	37
12	8.1; 0.8	S (~ 0.2)	39
13	16.6; 0.58	S (5.5)	40
14	~ 0	T (0.04)	41
15	~ 0	T (0.004)	41
16	3.5; ≤ 0.2	S (0.9)	38
17	4.0; 0	T (> 0.05)	42
18	7.0; ~ 0	T	43

^a D and E are zero-field splitting parameters; ^b in parentheses, the energy differences between the singlet and the triplet states $|\Delta E_{ST}|$ (kcal mol^{−1}) are given.

Analysis of the published data on the ChH casts some doubt in their interpretation. The solution of the famous diradical paradox formulated by McConnell⁴⁴ by no means completed the study of the ChH.^{35,45,46} Sugimoto *et al.*⁴⁵ concluded that the data obtained by Brauer *et al.*⁴⁰ refer, most likely, to radical pairs rather than to the triplet state of the ChH molecules. In their opinion, zero-field splitting (ZFS) parameters for the triplet state of the ChH should be much lower than those measured by Brauer *et al.*;⁴⁰ hence, its signal should be difficult to observe against the background of a monoradical impurity. According to Sugimoto *et al.*,⁴⁵ this is the reason why no triplet EPR signals were detected for the ChH single crystals studied earlier.³⁵ Indeed, it can be seen in Table 1 that the zero-field splitting parameters for Chichibabin's hydrocarbon are markedly distinguished from the general trend. It is beyond doubt that this fact requires additional reasoning and new experiments dealing with the triplet state of the ChH.

Muller's hydrocarbon also call for additional investigation, as a number of reasons have been proposed attesting to its triplet ground state.⁴⁷ Determination of the ground state of the Schlenk–Brauns diradical (10) is also doubtful.¹³

Using diradical 6 as an example, one can see that structural distortions may transform even an obvious FCU (with *meta*-phenylene connection) into an ACU, and this should be taken into account in the synthesis of magnetic polymers. An assumption³⁴ that diradical 6 has a conformer with $\Delta E_{ST} \approx -0.02$ kcal mol^{−1} also deserves attention. This brings about the question of how the singlet state is realised for this and other diradicals in which the formation of a quinonoid structure is impossible and what is the electronic spectrum of these diradicals in the singlet state.

An approximately twice higher singlet–triplet splitting of the cyclophane diradical 12 compared to diradical 11 is probably due to the presence of two parallel 3,3'-biphenyl exchange routes in the former case, while in diradical 11, only one route is present.³⁹

Diradical 17 is an analogue of the simplest and, hence, one of the best studied both theoretically and experimentally, π -conjugated organic diradical, trimethylenemethane (CU-1). This diradical is stable at room temperature and has a triplet ground state

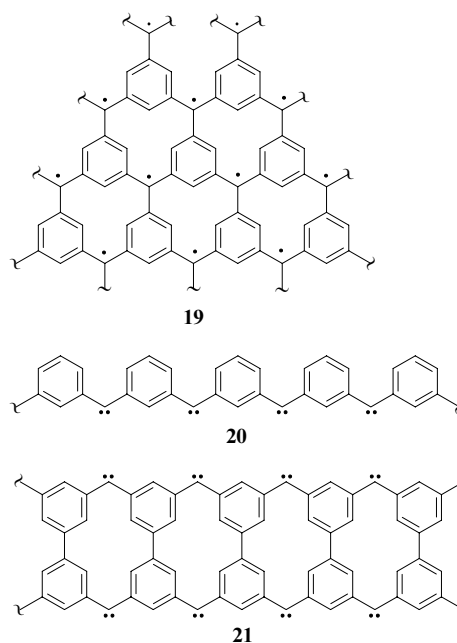
with a relatively strong ferromagnetic interaction, which makes it, in the opinion of Rajca *et al.*,⁴² a promising structural block for organic magnetic polymers stable at room temperature.

A successful attempt⁴³ of the synthesis of combined diradical 18 comprising a triarylmethyl and a galvinoxyl radicals opens up the prospects for using other combinations of stable radicals, which may substantially extend the area of search for organic magnets.

Modes of interactions of unpaired electrons in TAMT tri- and tetradicals have been considered in reviews^{3,13} and experimental data for these radicals are presented below.

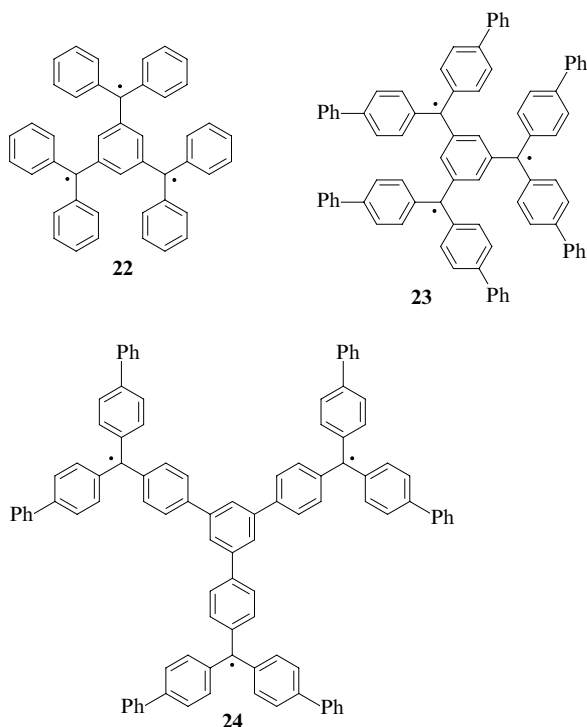
2. Theoretical background for the development of magnets based on triarylmethyl type radicals

Judging by the number of references, an important role in drawing the attention of researchers to the design of organic ferromagnets belongs to the theoretical publication by Mataga.⁴⁸ He was the first to propose planar high-spin two-dimensional hydrocarbon structures constructed from triphenylmethyl radicals (19) or from triplet diphenylcarbenes (20 and 21) as potential precursors of organic magnets. It can be seen that coupling of the unpaired electrons in structures 19, 20 and 21 occurs through the *meta*-position of the phenyl rings, as in the Schlenk diradical (1). The Leo triradical (22), which can be considered as a repeating unit for system 19, should have $S = 3/2$, according to the known Ovchinnikov rule.⁴⁹ For structure 19, the possibility of magnetic ordering at finite temperatures was demonstrated⁵⁰ in the framework of the Ising model; for an exchange integral of ~ 0.05 eV, the critical temperature should be ~ 1000 K. In an ensemble of one-dimensional chains of methyl radicals, the magnetic order can arise theoretically at a finite temperature only in the case where interchain exchange interactions are taken into account.⁵⁰ In a publication,⁵¹ a critical review of the theoretical studies on linear organic ferromagnets is given and the possibility of stabilisation of the ferromagnetic ordering in linear chains of methyl radicals bound through the *meta*-positions of the phenyl rings is demonstrated using the density of states method. In the polymers where the methyl radicals are bound by *para*-phenylene bridges, the density of states method predicts pairing of the neighbouring spins to give quinonoid structures. For the polymer with quinonoid and benzenoid types of conjugation resulting from the pairing of spins, a high electrical conductivity upon doping has been predicted.⁵¹



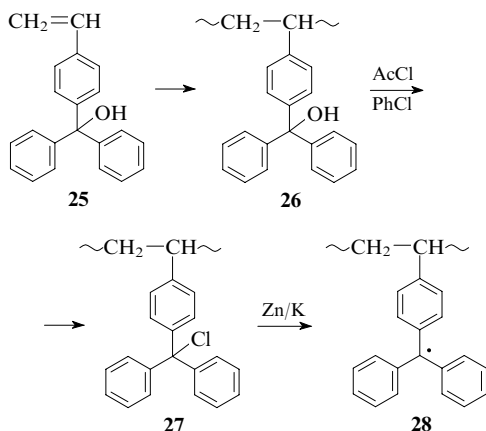
3. The Leo triradical and its analogues

The first attempt to synthesise triradical **22** (without the purpose to design organic magnets) dates back to 1937. Subsequently, it was found that the Leo radical (**22**) exists in solution mainly as diamagnetic tetramers, monomeric species in the quartet state ($S = 3/2$) being present only in minor amounts.⁵² Analogues of the Leo radical, compounds **23** and **24**, were prepared and shown, by EPR spectroscopy, to have the quartet ground state.^{53, 54}



4. Triarylmethyl type radicals in polymers

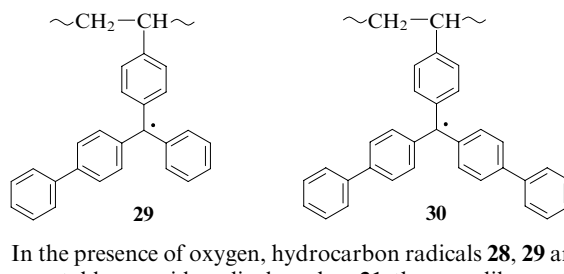
The first successful experiments on the synthesis of polyradicals based on TPMR in polymers were reported by Braun *et al.*^{55–58} and partially surveyed in a review⁵⁹ and a book.⁶⁰ Polymerisation of 4-vinyltriphenylmethanol (**25**) gave poly(*p*-vinyltriphenylmethanol) (**26**), which reacted with acetyl chloride in chlorobenzene to give poly(*p*-vinyltrityl chloride) (**27**). In order to obtain the expected poly(*p*-vinyltriphenylmethyl) radical (**28**), compound **27** was reduced with a zinc–potassium alloy.



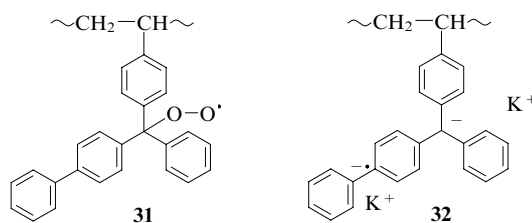
Polymer **26** and, correspondingly, polyradical **28** had a degree of polymerisation of 300–350. The highest yield (~ 10 radicals per molecule) was attained when the K/Na alloy was used. Polyradical **28** gave an EPR signal with poorly resolved hyperfine structure (HFS). Poor resolution of the spectrum was attributed to the interaction of radicals at their relatively high local concen-

tration in macromolecular coils in combination with low splitting values for triphenylmethyl type radicals.

The same method was used to prepare poly(4-vinyl-4'-phenyltriphenylmethyl) radical (**29**) and poly(4-vinyl-4',4''-diphenyltriphenylmethyl) radical (**30**). These polyradicals had degrees of polymerisation of 325 and 350 and were formed in yields of 40 and 100 radicals per molecule, respectively (in the reduction of polymers with the K/Na alloy at room temperature in benzene or THF).

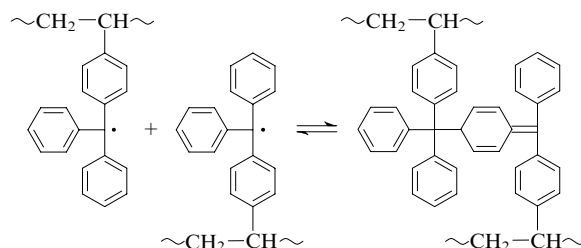


In the presence of oxygen, hydrocarbon radicals **28**, **29** and **30** form unstable peroxide radicals such as **31**; these readily react with the initial hydrocarbon radicals to give cross-linked polymeric radicals. For radicals **31**, a narrow smooth singlet was detected in the EPR spectrum (g -factor was not measured).



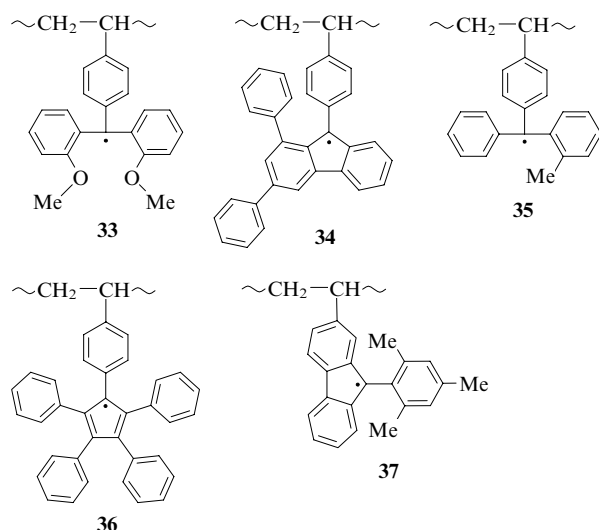
The use of the K/Na alloy results in high yields of radicals but leads to further reduction of the polymers to give carbanions; when the molecule contains biphenyl fragments, radical anions are formed, which can be detected by EPR and produce well-resolved spectra. The monomeric unit of polyradical **29** forms a doubly-charged radical anion, which can be represented as structure **32**. Unfortunately, Braun *et al.* did not report the electronic spectra of the polymeric radicals, carbanions or radicals but described only the changes in the solution colour during the reduction.

According to the views existing at that time, Braun believed in his early works that the radical centres of the polyradicals dimerise (both inside the coil and between the macromolecules) to give hexaphenylethane structures and that the dimers (non-radical species) and monomers (radicals) occur in equilibrium, which shifts, for example, toward the radicals as the temperature increases. This dimerisation equilibrium giving quinonoid structures can be depicted in the following way:⁶¹

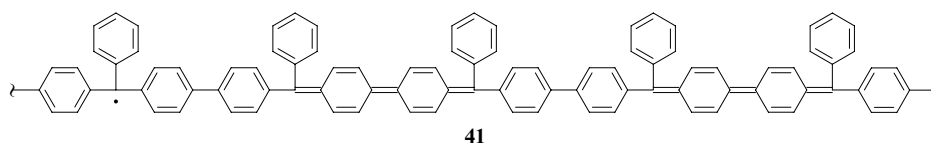
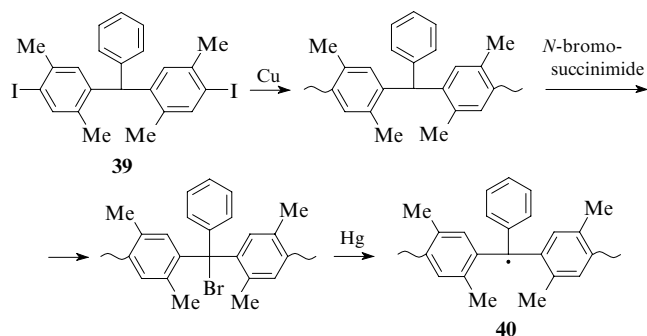


Dimerisation, resulting in a lower concentration of the radicals and giving rise to cross-linked polymers can be diminished by introducing bulky substituent into the *ortho*-position with respect to the unpaired electron. Polyradicals **33**–**37** were prepared⁶² by a route similar to that described above, but chloro derivatives were reduced using mercury in order to stop the reaction after the formation of radicals. The least concentration of spins was found for polyradical **33**, because steric shielding by the methoxy groups

slightly influences dimerisation of the radical centres. This polyradical showed a resolved HFS in the EPR spectrum; this was attributed⁶² to insignificant interaction of the radical centres due to their low concentration. The highest concentration of spins and the highest stability (the radical centres survived for at least several months) were found for polyradical **36**, which had a violet colour in benzene solution. The other hydrocarbon polyradicals obtained by Braun's research group were yellow or reddish. The high stability of polyradical **36** is due to pronounced delocalisation of the unpaired electron over the cyclopentadienyl ring and to steric shielding of the radical centre by five phenyl groups, which cannot fit in the plane of the pentadienyl ring due to the mutual repulsion of hydrogen atoms. The EPR signal for polyradical **36** is a smooth singlet only ~ 4 G wide, whereas for other polyradicals, the signal widths are ~ 10 G. Polyradical **37** was found to be 100% dissociated, fully non-cross linked and fairly stable.⁶²



The polyradicals described above have unpaired electrons in the side chains of polymers. More interesting consequences of the interaction of radical centres in polyradicals should be expected for the case where they are located in the polymer backbone. Braun and Lehmann synthesised^{63,64} a number of polyradicals with triphenylmethyl type radical centers in the backbone. Bis(4-iodophenyl)phenylmethane (**38**) and bis(4-iodo-2,5-dimethylphenyl)phenylmethane (**39**) were prepared⁶³ and used as the starting compounds for the synthesis of polyradicals in which TPMPR are linked by *p*-phenylene bridges. Compounds **38** and **39** were condensed according to Ullmann to give the corresponding polymeric hydrocarbons, which were then brominated with *N*-bromosuccinimide at the tertiary carbon atom. This was

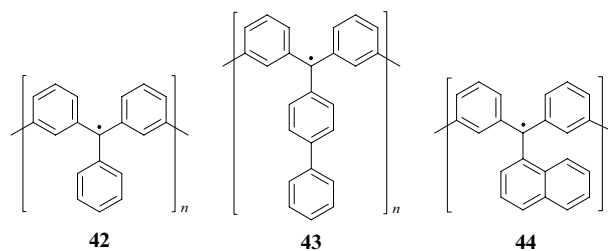


followed by generation of the triphenylmethyl type radicals. The bromo derivative obtained from compound **39** was reduced with mercury to the corresponding polyradical **40**.

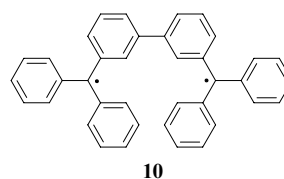
Analogous chemical transformations in the case of compound **38** resulted, as expected, in macromolecules **41** containing some triarylmethyl type radical centres apart from the quinonoid structures of the Chichibabin hydrocarbon type. A benzene solution of polymer **40** is yellow, the colour being due to the radicals, while a benzene solution of polymer **41** is deep-blue in thick layer and blue-green in thin layer. This colour was attributed⁶³ to quinonoid structures.

The EPR spectrum of a benzene solution of compound **40** is nearly a singlet (four HFS components can be distinguished) with a total width of 27.5 G; the EPR spectrum of a benzene solution of polymer **41** shows fairly well resolved 16 components with a splitting of ~ 1.5 G, the total width of the EPR signal being 29 G. For the polymers, precursors of polyradicals **40** and **41**, the number-average molecular masses (M) and the average degrees of polycondensation (P) were determined by osmometry: for compound **40**, $M = 2300$, $P = 7$; for compound **41**, $M = 3970$, $P = 15$. Polycondensation of compound **39** was accompanied by an undesirable side reaction, *viz*, cross-linking of fragments through the methyl groups.

In order to avoid side reactions and annihilation of neighbouring radicals in the polymer, Braun and Lehmann synthesised,⁶⁴ by a similar route, polyradicals **42–44** in which the radicals are bound through the *meta*-positions of the phenyl groups.



This gives a polymer with paramagnetic structures such as the Schlenk–Brauns hydrocarbon (**10**) in which, in the Braun's opinion, no formation of a quinonoid structure is possible.



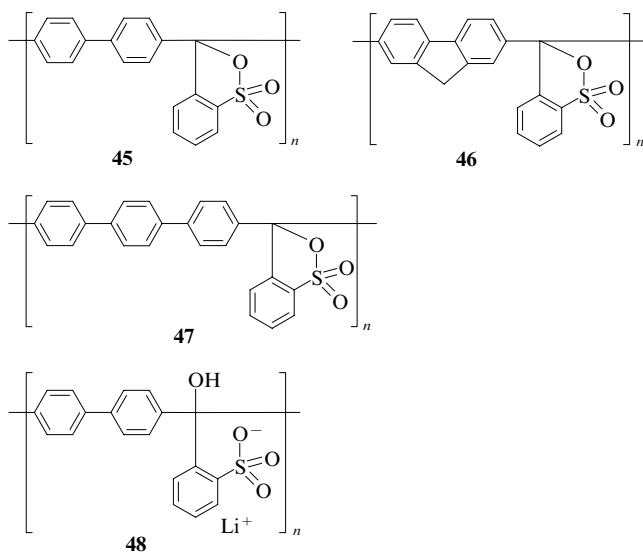
The polymeric precursors of polyradicals **42–44** had average degrees of polymerisation of 5–8 and average molecular masses of 1640–1940. The EPR signal of polyradical **42** in a benzene solution has an overall width of ~ 31 G and splits into (at least) 19 lines; the colour of the solution is dark yellow. The EPR signal of the solution of polyradical **43** in benzene has an overall width of ~ 30 G and a poorly resolved hyperfine structure; the solution is violet. The EPR spectrum of a benzene solution of polyradical **44** has a total width of ~ 31 G and a poorly resolved hyperfine structure, and the solution is red-brown. In the absence of air, benzene solutions of polyradicals are stable for more than a month even in the light. On contact with oxygen, the solutions are rapidly decolourised and no longer give EPR signals. Braun and

Lehmann⁶⁴ were unable to detect spin coupling in the polyradicals, which would produce broadening of the EPR spectra.⁶⁵

Thus, Braun's research group synthesised at least 13 polyradicals of the triarylmethyl type. Among compounds with radical centres in the side groups usually characterised by higher degrees of polymerisation (up to 350) than polyradicals with backbone radical centres, the highest concentration of radicals (nearly 100%) was found for compounds **36** and **37**. In the case of polyradicals with radical centres in the backbone, the degree of polymerisation was, most often, 5–8 and only in the case of compound **41**, it reached 15, *i.e.*, actually the obtained compounds were oligomers, and the yield of radicals in them was not estimated. Usually, the colour was indicated for polyradicals, but, unfortunately, in none of the cases, was the electronic spectrum reported. For all the obtained polyradicals, EPR spectra were recorded. No clear-cut manifestation of coupling (exchange, dipole–dipole, *etc.*) between neighbouring spins was noted for the polyradicals, except for some broadening of the spectral components, resulting in the loss of resolution. Usually, the EPR spectra of the polyradicals resembled the spectra of low-molecular-mass models, differing only in a poorer resolution. However, the loss of resolution in the EPR spectra may also be due to an increase in the viscosity of polymer solutions.

Film-forming cardo polymers, poly(arylenesulfophthalides) (PASP), are quite attractive for the generation of TAMT polyradicals and quinonoid structures; the synthesis and properties of these polymers have been reported.⁶⁶

Poly(biphenylenesulfophthalide) (**45**), poly(fluorenylenesulfophthalide) (**46**) and poly(terphenylenesulfophthalide) (**47**) have been studied; alkaline hydrolysis of compound **45** gives polymer **48**.⁶⁷



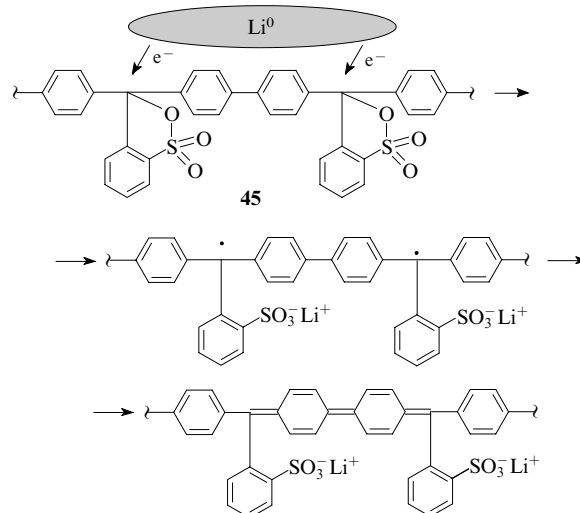
We have shown that the action of various physical and chemical factors on these polymers results in generation of the TAMT radicals and the quinonoid structures derived from them. First, the formation of TAMT radicals upon the thermolysis of polymers **45** and **48** was established.^{68, 69} The highest concentrations of the radicals ($\sim 10^{20}$ spin g^{-1}) were achieved for compound **48** at 280 °C and for compound **45** at 320 °C. At this concentration, one unpaired electron per ~ 20 polymer units is present. Upon thermolysis of polymer **48**, coupling of neighbouring TAMT radicals was observed as the formation of blue colour centres with an absorption band at 595 nm, which is attributable to the quinonoid structures like the Chichibabin hydrocarbon.

Quantum chemical PM3 calculations for the model diphenylsulfophthalide (DPSP) molecule show the presence of low-energy vacant orbitals and relatively large positive adiabatic electron affinity (1.76 eV), which should be favourable for the capture of electrons by the sulfophthalide ring. Indeed, DPSP is easily

reduced by hydroxide ions on alkaline hydrolysis in DMSO to give triphenylmethyl radicals, as was detected⁷⁰ by EPR and electronic spectroscopy. The TAMT radicals and the derived quinonoid structures are also formed on the alkaline hydrolysis of PASP,⁷¹ and in the complex system, PASP–aniline–cyclohexanone,⁷² in which the mechanism of their formation is still unknown.

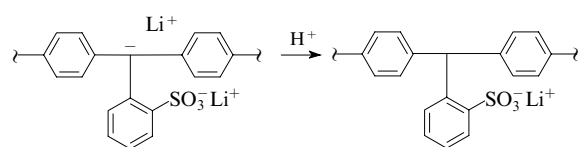
As expected, the reduction of these polymers with alkali metals proved to be an appropriate method for radical generation. The reduction of both dilute ($\sim 10^{-3}$ mol litre⁻¹) solutions of polymers **45**–**47**^{73, 74} and concentrated (~ 0.1 mol litre⁻¹) solutions of polymer **45**⁷⁵ in DMSO with metallic lithium at room temperature has been studied by spectroscopic methods. The results (for compound **45** as an example) can be summarised as follows.

1. The transfer of an electron from the lithium atom to the sulfophthalide ring having high electron affinity results in its dissociation to give a triarylmethyl radical and a salt group (distonic radical anion). The weak absorption band at 410 nm and a singlet in the EPR spectrum with $g = 2.0028$ and $\Delta H = 10$ G were assigned to the TAMT monoradicals. The neighbouring TAMT radicals give rise to the ChH type quinonoid structures responsible for the strong absorption bands at 568 and 350 nm.



2. The reduction of the quinonoid structures and triarylmethyl radicals gives rise to carbanions responsible for an absorption band at 640 nm.

3. This is followed by protonation of the carbanions to give the major final reduction product.



The reduction process of compound **45** comprises a sequence of electron and proton transfer reactions, resulting in a mixture of the intermediate and final products listed above. The ratio of the formation rates of these products ensures a high yield of the ChH type quinonoid structures. The predominant formation of one final reduction product (protonated salt form) attests to a single major reaction route.

The reduction of polymer **46** also gives TAMT radicals and ChH type quinonoid structures. The reduction of compound **47** with lithium does not give quinonoid structures but results in a high content of TAMT radicals ($\sim 100\%$) in the polymer backbone. This fact confirms good prospects of PASP for the synthesis and study of high-spin polyradicals. In the case of polymer **47**, the absorption bands at 430 nm (allowed transition) and 638 nm

(forbidden transition) in the electronic spectrum and a singlet with $g = 2.0028$ and $\Delta H \approx 10$ G in the EPR spectrum were assigned to the TAMT radicals.

The possibility of reduction of films of polymer **45** and three poly(arylene phthalides) in the liquid ammonia–sodium system has been demonstrated.⁷⁶ Polyarylene phthalides are PASP-related polymers in which the labile sulfophthalide rings were replaced by more stable phthalide rings. The sulfophthalide and phthalide rings in these polymers are cleaved by solvated electrons to give TAMT radicals and quinonoid structures of the ChH type, which is confirmed by EPR and electronic spectroscopy. Poly(arylenephthalides) react with the $\text{NH}_3 + \text{Na}$ system more slowly and the radical products of this reaction are less stable than in the case of compound **45**. Apart from TAMT radicals, the reduction of poly(diphenylenesulfophthalide) affords paramagnetic species that produce a singlet EPR signal with $g \approx 2.0028$ and $\Delta H \approx 4\text{--}5$ G , while the reduction of poly(diphenylenephthalide) yields paramagnetic species responsible for a singlet EPR signal with $g \approx 2.0047$ and $\Delta H \approx 4$ G .

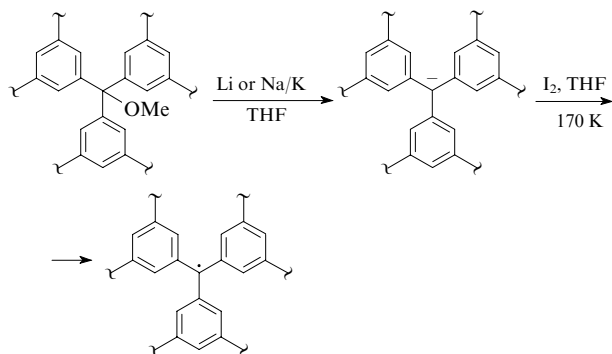
Low-temperature (77 K) γ -radiolysis of films of polymers **45–47** also gave rise to EPR singlets with $g = 2.0028$ and $\Delta H \approx 10$ G and electronic absorption bands at $\sim 410\text{--}430$ nm; it is beyond doubt that they refer to the TAMT radicals. In view of the radiolysis mechanism and the properties of PASP, it can be assumed with a high degree of probability that the TAMT radicals are formed upon dissociative capture of secondary electrons by the sulfophthalide ring. Whereas the reduction of compounds **45** and **46** yields mainly quinonoid structures derived from TAMT radicals, radiolysis of these polymers gives rise to single TAMT radicals, which is apparently due to the deficiency of secondary electrons under radiolysis conditions, *i.e.*, the probability that two secondary electrons occur in neighbouring sulfophthalide rings of the macromolecule is low.

It would hardly be possible to obtain practically valuable magnets from the linear polymers [poly(arylenesulfophthalides) and poly(arylenephthalides)] we consider. Nevertheless, the synthesis of relatively stable di- and polyradicals in these polymers is quite realistic. Good solubility in polar solvents and the possibility of their synthesis directly in the polymer films are promising properties of the polyradicals in PASP. Study of the properties of these radicals would evidently contribute to the views on the coupling of unpaired electrons in high-spin systems.

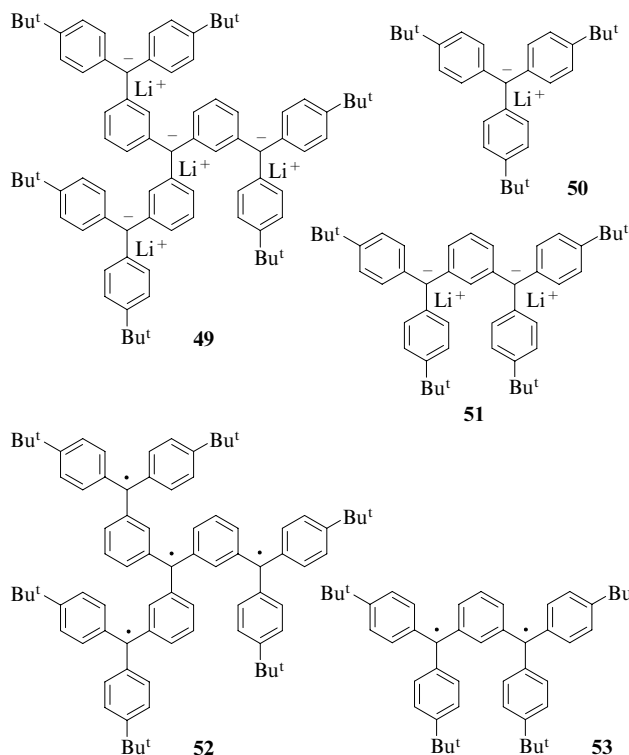
5. The latest achievements in the synthesis of triarylmethyl type polyradicals

a. Carbanionic method of synthesis

Apart from the diradicals mentioned above, Rajca's group (University of Nebraska, Lincoln) prepared a large number of polyradicals based on the Gomberg radical in which record values of the total spin were repeatedly attained. A 'carbanionic' method for the synthesis of triarylmethyl type polyradicals was developed.^{32, 77} According to this method, an appropriate polyether is prepared and reduced with an alkali metal in an ether type solvent (most often, THF) to the polyanion, which is then oxidised with iodine to the polyradical.



The synthesis and the properties of polyanions **49–51** were reported,⁷⁷ and the preparation and some properties of tetraradical **52** and diradical **53** were described.³² Subsequently, Rajca used this method relying on Mataga's ideas on polyradical polymers to synthesise the first plastic magnet in the world.



b. Star-shaped and dendritic polyradicals. The role of defects

Star-shaped homologues of tetraradical **52**, namely, heptaradical **54** and decaradical **55**, having the highest spin states ($7/2$ and 5 , respectively) among the radicals known at that time, have been synthesised.⁷⁸ EPR studies (at 100 K) and magnetic susceptibility measurements by NMR (at 150 K) showed that the heptaradical with $S = 7/2$ and the decaradical with $S = 5$ were the predominant species. The magnetic susceptibility measurements on a SQUID magnetometer gave lower values, $7/2 > S > 5/2$ [radical **54** in 2-methyltetrahydrofuran (MTHF) at $T \geq 5$ K] and $S = 4$ (radical **55** in THF at $T = 10$ K). Presumably, the lack of a noticeable amount of other paramagnetic species (thermal population of low-spin excited states) implies that both polyradicals have high-spin ground states with a strong intramolecular ferromagnetic coupling. Low-temperature magnetic susceptibility measurements for these polyradicals show weak intermolecular antiferromagnetic coupling at $T \leq 5$ K for heptaradical **54** and at $T \leq 20$ K for decaradical **55**. In the study cited, the decrease in the spin has not yet been attributed to the inevitable presence of defects in polyradicals.

Owing to lower sensitivity to defects, dendritic molecules should surpass the usual linear macromolecules as regards the spin order. Nevertheless, dendritic heptaradical **56**, pentadecaradical **57** and polyradical **58** with 31 radical centres synthesised by Rajca and co-workers had average total spins of only 3 , $7/2$ and $5/2$, respectively, instead of the expected $7/2$, $15/2$ and $31/2$.^{21, 22}

Among other reasons, the lower spins may be due to either chemical defects (an atom or a chemical group instead of the unpaired electron) or topological defects (interruption of the ferromagnetic coupling caused by unfavourable spatial arrangement of orbitals with neighbouring unpaired electrons). Generally, the common spin coupling is highly sensitive to both types of defects, as they break the exchange interaction paths. For example, an internal defect present in pentadecaradical **57** divides it into three non-interacting parts with lower total spins, which markedly

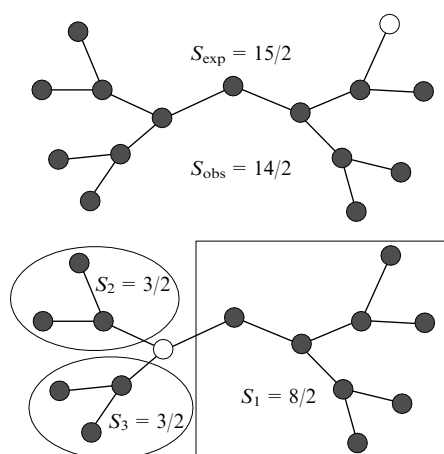
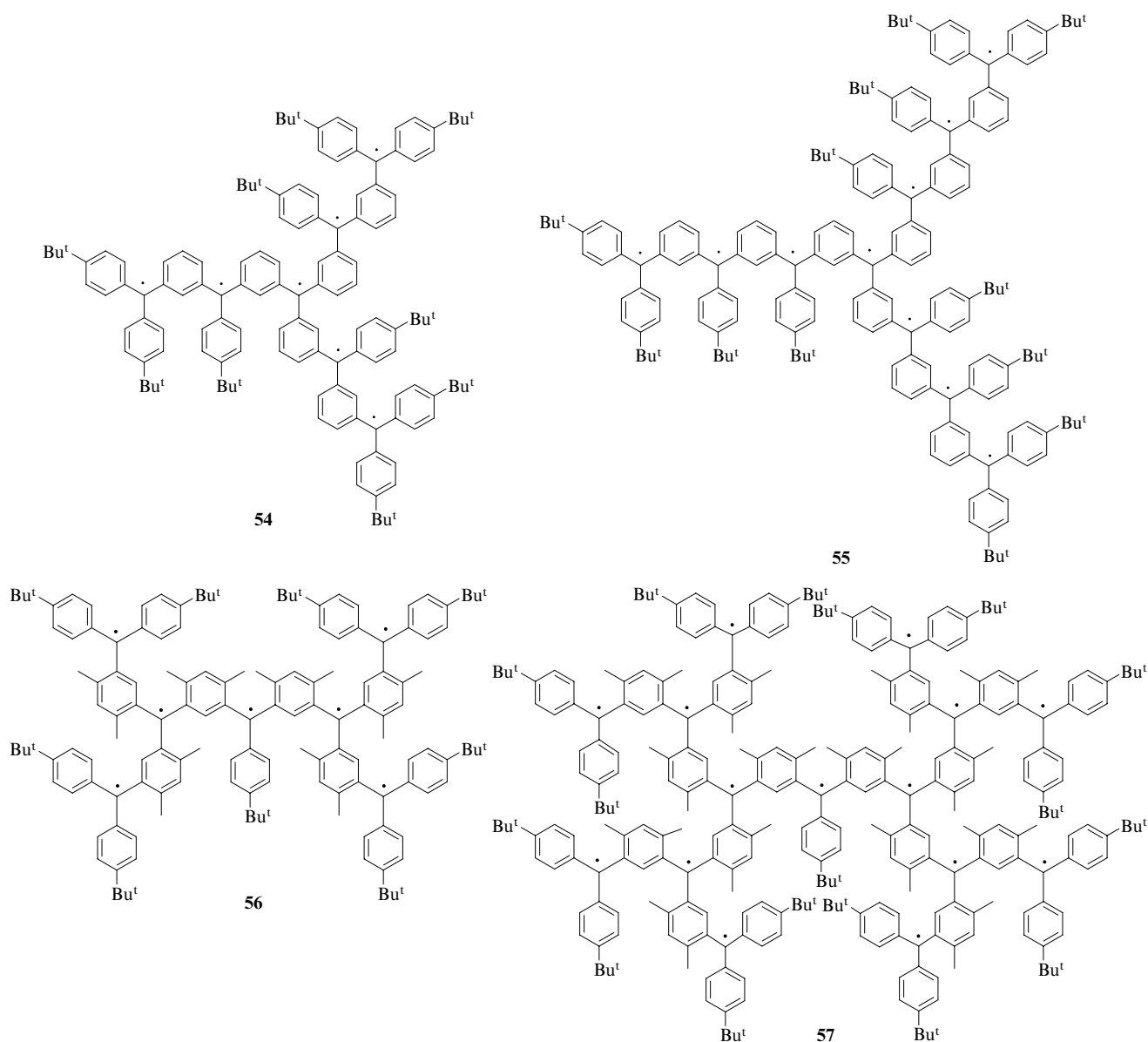


Figure 4. Effect of the defects on the total spin S of dendritic pentadecaradical **57**.

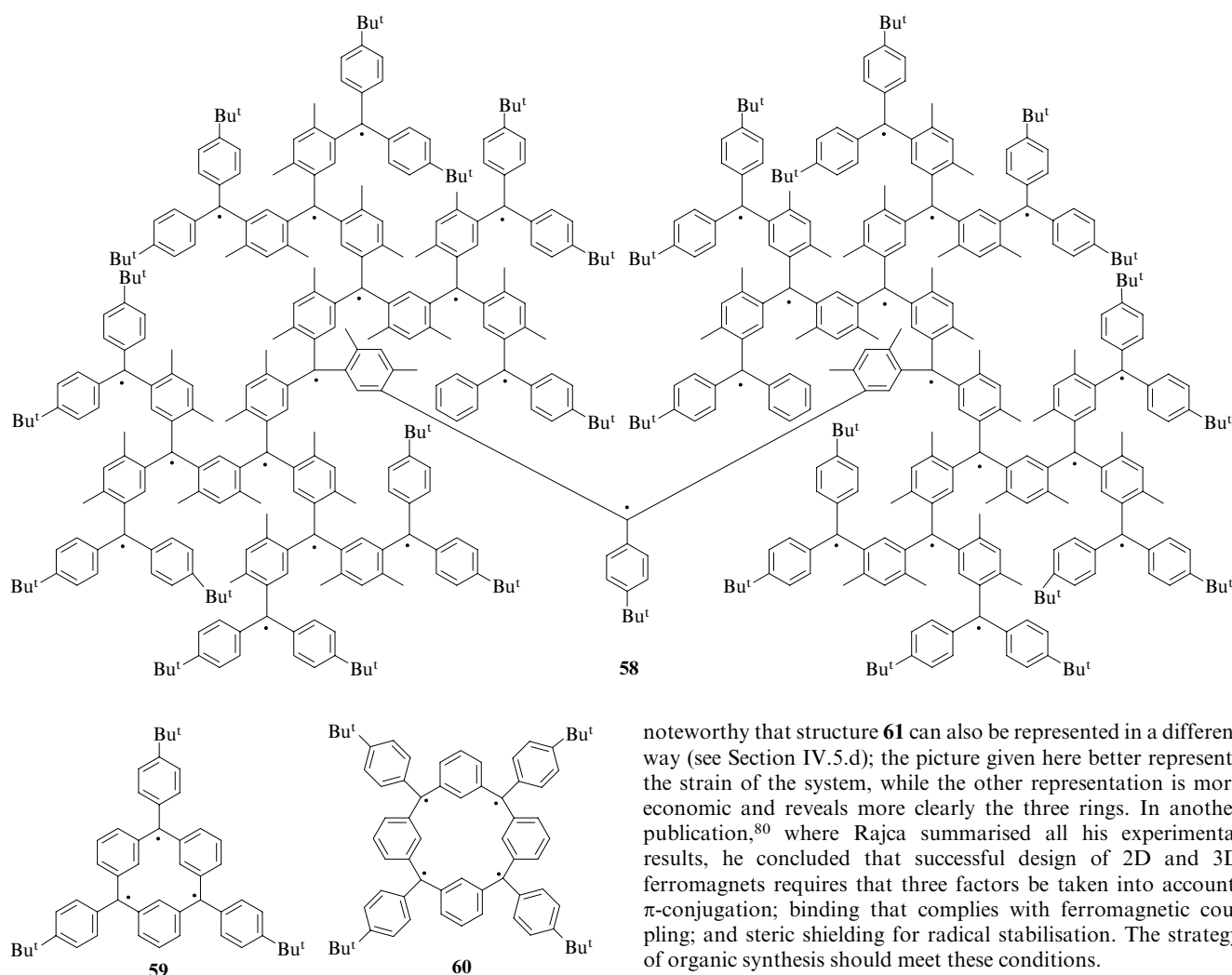
Light circles are defects; dark circles are unpaired electrons; lines are ferromagnetic coupling units.

decreases the effective total spin of the whole polyradical (Fig. 4). The peripheral defects have a less pronounced effect on the total spin.

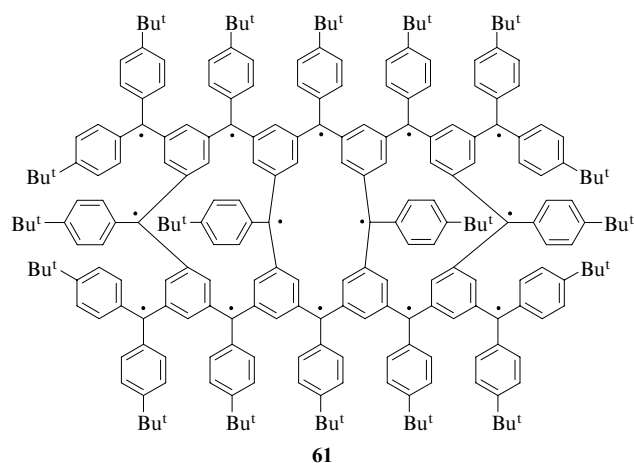
c. Macrocyclic polyradicals

Rajca decided to avoid the problem of defects by designing polyradicals of the macrocyclic calixarene type, which should have low sensitivity to spin defects owing to multiple paths of spin coupling. The calix[3]arene triradical **59** and calix[4]arene tetradical **60** were synthesised.⁷⁹ It is clear that in the presence of one defect in the ring, exchange interaction between the spins is retained. It was found that triradical **59** readily dimerises, probably, due to insufficient steric shielding. The steric shielding in calix[4]arene **60** was sufficient for its stabilisation, and out-of-plane distortions were slight, which allowed the ferromagnetic spin coupling to be retained. It was concluded⁷⁹ that these macrocycles may be suitable as building blocks for polyradicals with low sensitivity to defects.

Highly annulated polymacrocyclic systems are rather difficult to synthesise; however, Rajca's group have obtained, for example, trimacrocyclic tetradecaradical **61** and demonstrated that both π -conjugation and ferromagnetic spin coupling are retained in this



species even in the presence of defects.⁸⁰ A study of this polyradical in the THF- d_8 -MTHF system by SQUID magnetometry gave $S = 6.2$, which is lower than the theoretical value of 7 expected for a strong ferromagnetic coupling of 14 unpaired electrons.

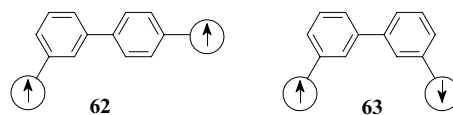


An analysis of the products obtained by quenching of the polycarbanion corresponding to polyradical 61 with methanol showed that the insertion of approximately one deuterium atom per polyradical from the solvent (THF- d_8) is one of the reasons for the appearance of defects and the decrease in the spin. A study of the temperature dependence of the magnetisation showed that the ferromagnetic coupling between the spins is relatively weak, probably, due to the out-of-plane distortion of the π -system. It is

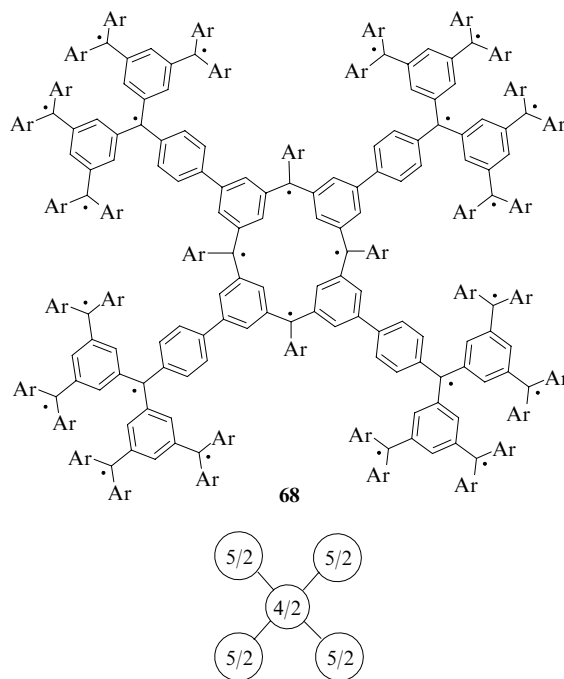
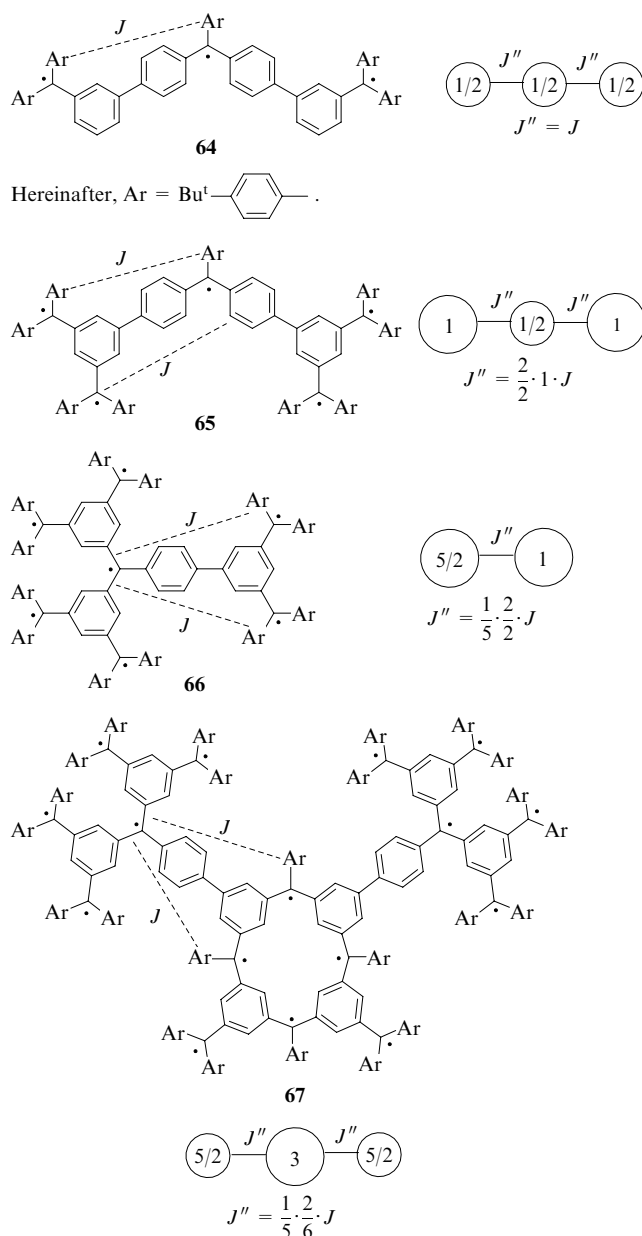
noteworthy that structure 61 can also be represented in a different way (see Section IV.5.d); the picture given here better represents the strain of the system, while the other representation is more economic and reveals more clearly the three rings. In another publication,⁸⁰ where Rajca summarised all his experimental results, he concluded that successful design of 2D and 3D ferromagnets requires that three factors be taken into account: π -conjugation; binding that complies with ferromagnetic coupling; and steric shielding for radical stabilisation. The strategy of organic synthesis should meet these conditions.

d. Spin clusters based on triarylmethyl type radicals

In principle, any polyradical can be considered as a spin cluster, as was actually done by Rajca in his early works where he analysed the spin states of the synthesised TAMT di- and polyradicals using the Heisenberg Hamiltonian. Subsequently, it has been proposed^{81,82} to design high-spin organic polyradicals as simple spin clusters consisting of high-spin modules with strong intra-module ferromagnetic coupling J' connected to each other by relatively weak inter-module ferromagnetic coupling J , the J value being comparable in magnitude with the thermal energy, *i.e.*, $J' \gg J \approx kT$. This splitting into modules and the introduction of a hierarchy of exchange interactions markedly simplified the problem of determination of the energy spectrum of the cluster (polyradical) and, hence, analysis of its magnetic characteristics (magnetisation, susceptibility, *etc.*). To construct high-spin clusters from the macrocyclic and dendritic blocks proposed previously in which 1,3-phenylene or benzene-1,3,5-triyl units were used as 'strong' FCU, Rajca chose biphenyl-3,4'-diyl bridges 62 as an alternative to *meta*-phenylene bridges. In a study of the properties of diradical 9, it was found that units 62 are ferromagnetic with weak coupling capable of additional stabilisation of radicals.³⁷ The properties of diradical 11 imply that the biphenyl-3,3'-diyl bridge 63 is an antiferromagnetic coupling unit, which, however, can also be used to construct ferrimagnetic high-spin clusters.



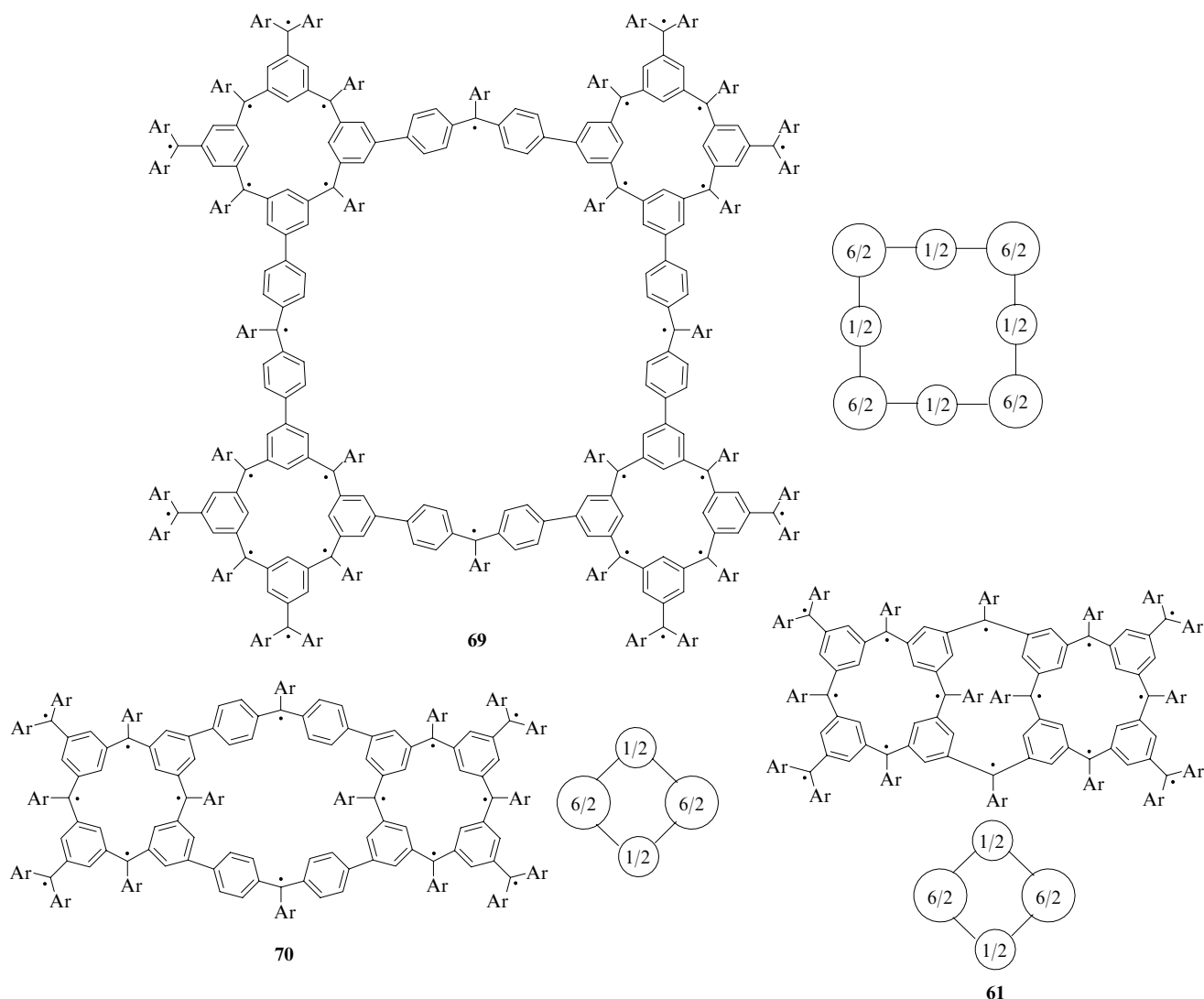
Using the Suzuki cross-coupling,⁸³ Rajca and co-workers synthesised⁸² spin clusters **64**–**67**, in which the intra-module ferromagnetic coupling through 1,3-phenylene units was much stronger than the inter-module coupling through biphenyl-3,4'-diyl (or biphenyl-3,5,4'-triyl) units. An estimate based on the hyperfine coupling in the triphenylmethyl and (biphenyl-4-yl)diphenylmethyl monoradical gives $J:J' \approx 1:6$. In addition, Rajca carried out energy scaling for the inter-module ferromagnetic coupling J'' in each cluster, according to the approach described earlier.⁸⁴ This scaling takes into account the number of coupling paths (1 path for biphenyl-3,4'-diyl and 2 paths for biphenyl-3,5,4'-triyl units) and the fraction of directly interacting spins from neighbouring modules. Polyradicals **64**–**66** have only one site where a single defect can interrupt the spin coupling, whereas polyradical **67** has two such sites. This can potentially be a hexadecaradical with $S = 8$; according to magnetic measurements, the spin value was high, $S = 7.2$, *i.e.*, the yield of generation of unpaired electrons for this polyradical reached 98%. Subsequently, using the Negishi cross-coupling reaction,⁸⁵ polyradical **68** with the total spin $S = 10$ was synthesised.⁸⁶



Four dendritic branches and the macrocyclic core of this polyradical form a ferromagnetically coupled pentamer, four terminal modules of which have $S = 5/2$, while the central fragment has $S = 2$. Theoretically, the total spin of polyradical **68** should be equal to 12. The dependence of magnetisation M on the H/T value (H is the magnetic field strength, T is temperature) gives $S \approx 10$ at 5 K. At that time (1998), this was the record-breaking value of the total spin.

More recently, spin clusters **61**, **69**–**74** based on TAMT radicals were synthesised and the properties of these clusters and the corresponding polyether precursors were studied.^{87–89}

The polyether precursors of the polyradicals were obtained by a multistep block-synthesis in which the key step was the Negishi cross-coupling of four monofunctional dendritic blocks with modules and a tetrafunctional calix[4]aryl-containing macrocyclic core for (compounds **68** and **72**), of difunctional calix[4]arene-containing macrocycles (for annulated structures **61**, **69** and **70**) and of mono-, di- and tetrafunctional calix[4]arene-containing macrocycles with (aryl)bis(4-halophenyl)methoxymethyl linking units (for polyradicals **71**, **73** and **74**). The target polyethers were isolated from the reaction mixtures by chromatography. The corresponding polycarbanions were then synthesised and oxidised to polyradicals in THF-*d*₈. The polyradicals thus formed were classified as spin clusters, their structures are given near the formulas. Some properties of these clusters and the starting polyethers are summarised in Table 2. The saturation magnetisation and the magnetic susceptibility values for all polyradicals reported in the studies cited^{87–89} indicate that $\sim 40\%$ – 60% of unpaired electrons are present at low temperatures ($T = 1.8$ – 5 K) and confirm the presence of high-spin ground states. Analysis of the S values and the mole fractions of the unpaired electrons (M_{sat}) suggests that ferromagnetic coupling predominates in these polyradicals. Nevertheless, significant antiferromagnetic coupling is also present and, together with chemical defects, it decreases the S and M_{sat} values with respect to the theoretical ones. It is believed that detailed interpretation of magnetic measurements becomes more complicated due to the possible presence of conformations with different exchange (ferro or antiferro) interactions, different methods of averaging for the measured values (S , M_{sat} and χT) and the possibility of incomplete transfer of the sample mass during experiments. In some cases (for polyradicals **68** and **72**), the magnetic data are described satisfactorily by the Heisenberg model for magnetic interactions in the cluster. For polyradical **70**, the magnetic characteristics



varying with temperature also comply with the model based on the Heisenberg Hamiltonian; however, this model is no longer applicable to the description of low-temperature data varying with

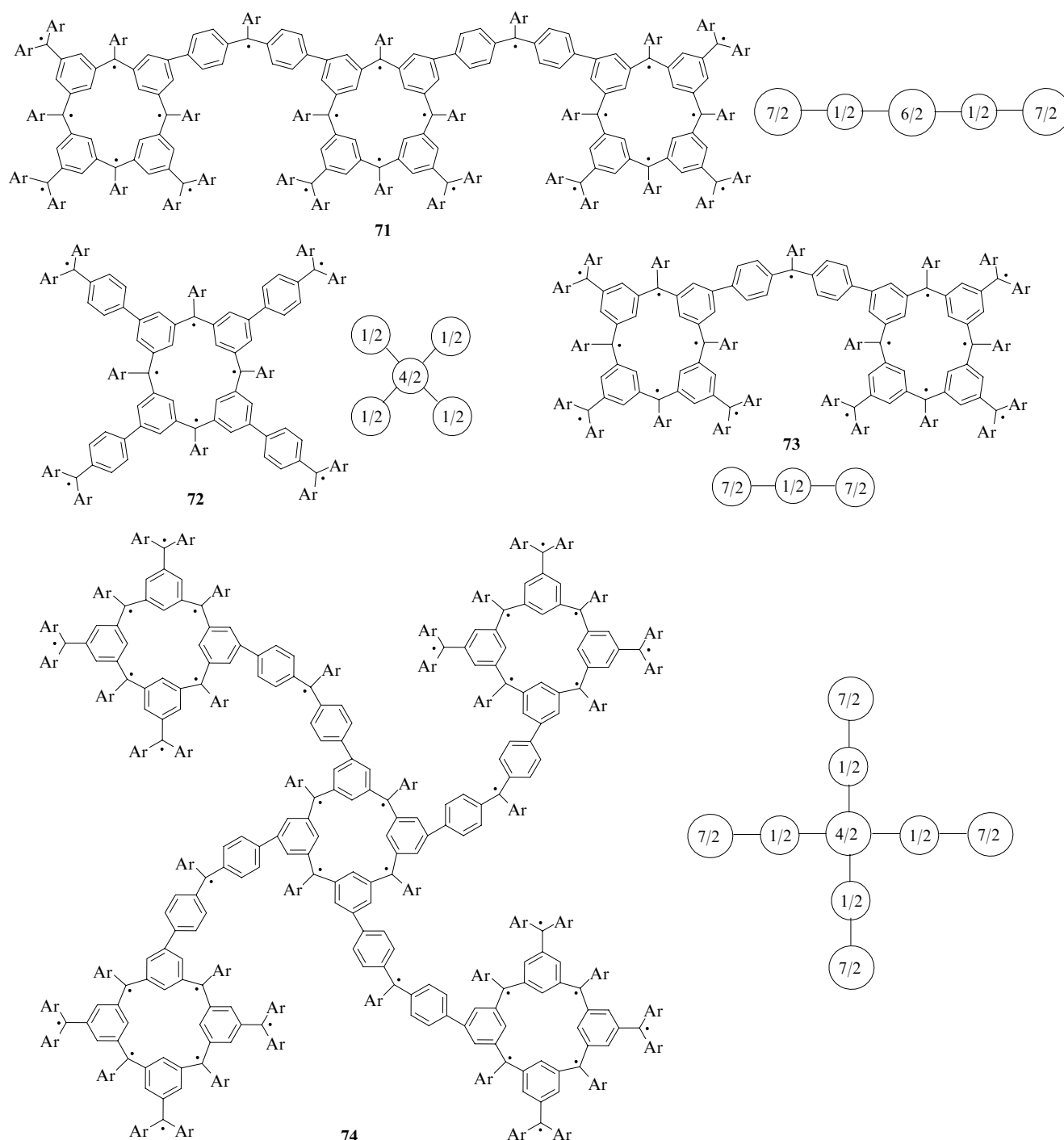
the magnetic field. In relation to spin trimer **73** and pentamer **71**, a two-parameter percolation model of organic spin clusters with a chaotic distribution of chemical defects and alternation of ferro-

Table 2. Some physicochemical and magnetic characteristics of spin clusters and their polyether precursors.

Cluster	$[M-\text{OMe}]^+$ /Da	R_g /nm ^b	S_{exp}^c	S_{theor}^d	M_{sat}/μ_B^e	$\chi T_{\text{max}}/\text{emu K mol}^{-1}$ (see ^f)	M_w /kDa ^g	J/k /K ^h	Ref.
68	7001	1.5	10	12 (24)	0.5–0.7	35–45	—	7	86, 88
69	~7780	1.7	~10	14 (28)	~0.56	~46	10.5	—	89
70	3874	—	~6–7	7 (14)	~0.6	~16	4.9	12 (–9)	89
71	6117	1.3	7–9	11 (22)	~0.6	~30	7.5	—	87
72	—	—	3.6–3.8	4 (8)	0.81	7.3	—	34	88
73	4165	1.2	5–6	7.5 (15)	0.6	15–16	~5	—	87
74	10022	1.8	11–13	18 (36)	0.4–0.6	21–86	12	—	87
78 ⁱ	—	3.2	~18	>28 (>56)	~0.5	~2	29–33	—	89

^a $[M-\text{OMe}]^+$ is the mass of the positive ion formed upon abstraction of one ether group in the fast atom bombardment mass spectrum of the polyether;

^b R_g is the rotation radius of the polyether molecule determined in small angle neutron scattering (SANS) experiments; ^c S_{exp} is the average total spin of the polyradical determined mainly from representation of the SQUID magnetometry data by a linear combination of the Brillouin functions; ^d S_{theor} is the maximum possible total spin of the polyradical under ferromagnetic coupling of unpaired electrons, the values in parentheses represent the numbers of possible triarylmethyl fragments in the polyradical, i.e., the greatest number of unpaired electrons; ^e M_{sat} is the saturation magnetisation (a 1 μ_B value corresponds to one unpaired electron per triarylmethyl fragment); ^f χT_{max} is the maximum value of the product of the magnetic susceptibility into temperature in the χT vs. temperature curve; ^g M_w is the weight average mass of the polyether determined by gel permeation chromatography with large angle light scattering; ^h J/k is the spin–spin coupling constant corresponding to pair interaction of spin cluster components in the Heisenberg model; for polyradical **70**, the possibilities of both fully ferromagnetic and fully antiferromagnetic coupling (data in parentheses) were considered; ⁱ for information about this compound, see Section IV.5.e.



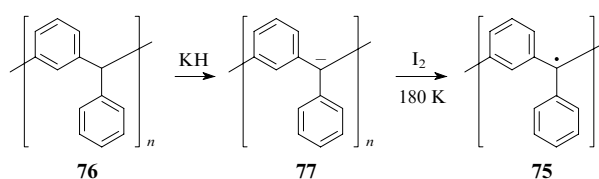
magnetic and antiferromagnetic coupling has been developed.⁸⁷ This model ensures a quantitative agreement between the experiment and the theory both for the clusters in question and for other spin clusters studied previously.^{87–89}

The value $S = 13$ achieved for nonamer **74** is now the record value for organic molecules.

For polyradical **68** (with the average spin $S = 10$), the size and the shape were estimated by the SANS method (see Table 2); the barrier to magnetisation reversal [Eqn (1)] determined by the shape anisotropy is rather low (about 0.001 K). It has been assumed⁸⁷ that macromolecular polyradicals with S values of about 10^3 – 10^4 similar to polyradical **68** as regards the shape and spin density distribution would behave as SMM at easily attainable temperatures $T > 2$ K.

e. Polymeric polyradicals of the triarylmethyl type

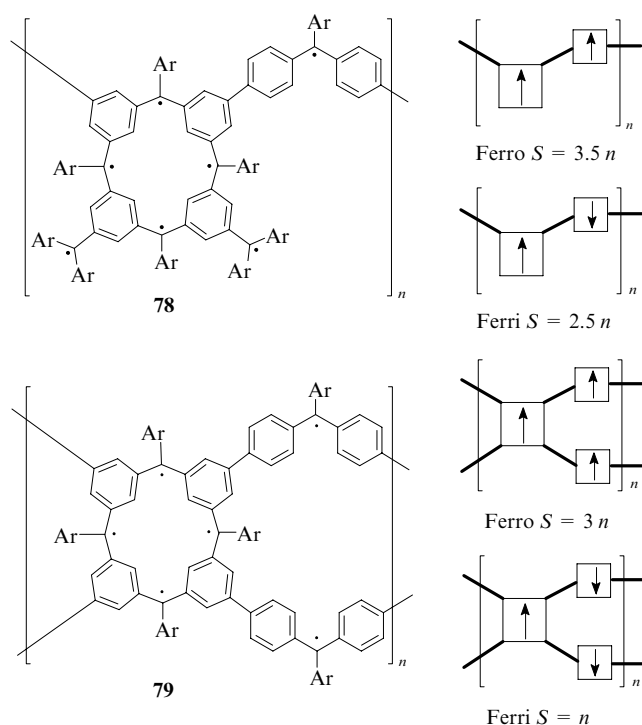
It is clear from the preceding sections that Rajca's group achieved great progress in the synthesis of diradicals and clusters; however, the synthesis of macromolecular polyradicals like the Mataga polymer **19** still remained the main goal of researchers. In 1993, high-spin linear polymer **75** was obtained.⁹⁰



Polyradical **75** was generated by the carbanionic method from polyarylmethane polymer **76** containing ~ 30 triarylmethane centres per macromolecule. The EPR spectrum of compound **75** recorded in MTHF or THF at 4 K in the region of $\Delta m_s = 1$ is a singlet; a weak signal is observed at $\Delta m_s = 2$, which implies the presence of high-spin species with $S \geq 1$. Magnetisation measurements for solutions of polyradical **75** at 10 K give $S = 2$, which indicates ferromagnetic interaction of at least four unpaired electrons, although some length distribution of exchange-coupled segments exists most likely in the polymer chain. The interruption of spin interactions in the chain is due to defects, which may be caused by partial protonation of polycarbanion **77**, its oxidation, intra- or intermolecular cross-linking of polyradical **75**, etc. This case clearly demonstrates the sensitivity of linear chains to chemical defects; it is this fact that stimulated Rajca to turn subsequently to dendritic and macrocyclic polyradicals. It was also found that at 5 and 2 K, $S < 2$. The decrease in the 'effective' spin of the polymer at low temperatures was attributed to the antiferromagnetic coupling between polymer chains. The same coupling results in a negative deviation of the plot for the product of magnetic susceptibility and temperature vs. temperature from a straight line at $T < 10$ K. This was the only attempt of Rajca's group to synthesise a linear one-dimensional triarylmethyl type polyradical.

A ferromagnetic–ferrimagnetic coupling scheme based on the non-equivalence of spin modules in the clusters has been used⁸⁹ to prepare two high-spin polymers **78** and **79** containing calix[4]arene macrocycles.

Polymer **78** in which macrocycles with $S = 3$ are linked by bridges with $S = 1/2$ can be regarded as a 'quasi-linear' chain of inequivalent spins with $S = 3$ and $S = 1/2$. It was found that polyradical **78** obtained from polyether with $M = 30\,000$ is characterised by an average S 18 at low temperatures. This value differs substantially from S of about 50–60, which would be expected if all the unpaired electrons were involved in ferromagnetic coupling and if no chemical defects were present. However, $S \approx 18$ is still higher than the best value $S \approx 5$ attained for other high-spin organic polymers. Some characteristics of polymer **78** are also presented in Table 2.



f. The first plastic magnet

Similarly to polymer **78**, the cross-linked polymer **79** can be considered as a network of non-equivalent spins, in particular, macrocyclic modules with $S = 2$ and linking modules with $S = 1/2$. The polyradical **79** synthesised⁹¹ from the soluble fraction of the polyether with $M = 300\,000$ – $500\,000$ has on average $S \geq 40$. The S value for polymer **79** obtained from insoluble polyether fractions which form a gel with THF- d_8 depends on the polymerisation time after gelation. If polymerisation stops near the gelation point (10–30 min), polymer **79** has $S = 600$ – 1500 ; for longer polymerisation times (5 h), the values $S = 3000$ – 7000 were attained.⁹² It was found that at low temperatures, $\sim 50\%$ of unpaired electrons are present. This fact is consistent with the views on inevitable presence of chemical defects and with the scheme of combination of ferro- and ferrimagnetic coupling. It should be borne in mind that structure **79** is rather arbitrary, as macrocyclic modules may form diverse structures during condensation and detailed analysis of the final insoluble polymer is almost impossible. In particular, polyradicals **61**, **69**–**74** have been considered^{87–89} as possible fragments of a plastic magnet **79**.

Conjugated organic polymer **79** was the first to exhibit magnetic properties other than merely paramagnetism. The magnetic ordering in this polyradical is switched on at ~ 10 K; for a typical sample with $S = 5000$, a sharp increase in the magnetisation (by two orders of magnitude) is observed. Below 10 K, magnetisation increases very rapidly with strengthening of the applied magnetic field and almost reaches saturation at relatively low fields. The saturation magnetisation for polymer **79** is ~ 10 emu g^{-1} , which is close to the paramagnetic saturation magnetisation for the poly(arylmethyl) polyradicals prepared previously. At a zero and low magnetic fields (about the Earth magnetic field), magnetic blocking was found, i.e., a substantial barrier to the magnetisation reversal was observed. Magnetic susceptibility studies in alternating fields gave a barrier of ~ 15 K and showed that very high magnetic moments ($S \approx 5000$) are frozen at low (≤ 10 K) temperatures with some degree of ordering (cooperativity). Generally, the magnetic properties of polymer **79** can be classified as being intermediate between the properties of non-conducting spin glasses and blocked superparamagnets but they are closer to spin glasses.⁹² As regards the magnetic behaviour, polymer **79** resembles known organic low-molecular-mass magnets, although the temperature of ordering in the polymer is higher.

6. Perchlorinated triarylmethyl type di- and polyradicals

Ballester^{93,94} has shown that perchlorinated di- and triphenylmethyl radicals synthesised by his group are fully monomeric both in solution and in the solid state and have high thermal stability and unique chemical stability, due to the essential localisation of the unpaired electron on the central carbon atom and considerable steric shielding of this atom. The first perchlorinated diradicals **80**⁹⁴ and **81**,⁹⁵ which are as chemically inert as the monoradicals, were also obtained.

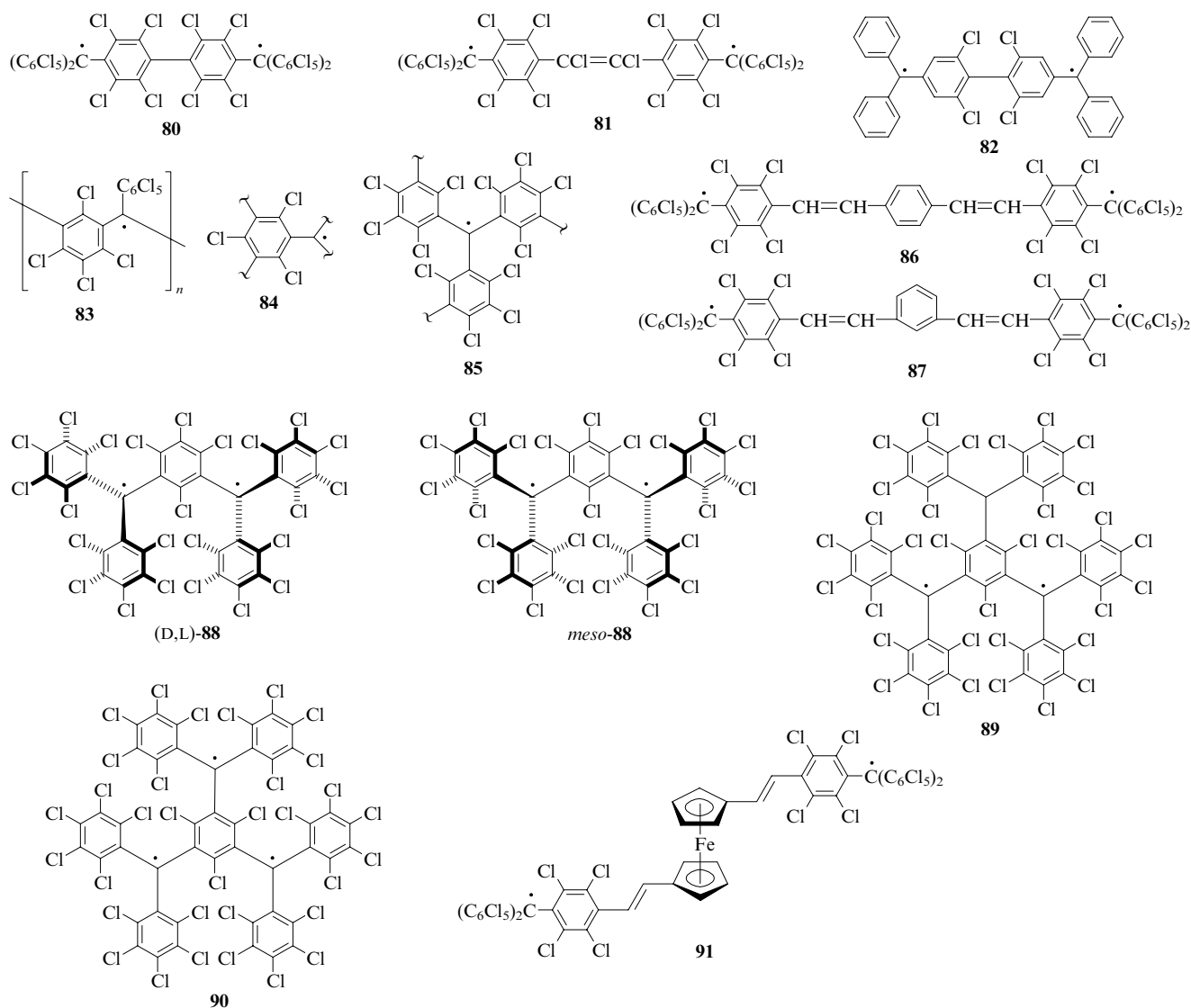
The electronic spectrum and the EPR spectrum of compound **80** do not virtually differ from the corresponding spectra of the perchlorinated TPMR; in particular, the EPR spectrum of this diradical does not manifest the magnetic dipole–dipole coupling. Thus, the radical centres in diradical **80** do not interact with each other, despite their relative geometric proximity. This fact can be attributed⁹⁶ to the perpendicular arrangement of the benzene rings in the biphenyl bridge and, correspondingly, complete elimination of the conjugation between the unpaired electrons. Apparently, the localisation of unpaired electrons highly pronounced for perchlorinated radicals also plays a role, because partially chlorinated diradical **82** in which the benzene rings in the bridge are also nearly perpendicular has a singlet ground state (Table 3) and its EPR spectrum does exhibit⁹⁷ magnetic dipole–

Table 3. Some properties of perchlorinated and mixed di- and triradicals of the triarylmethyl type.

Diradical	$10^3 D/hc /\text{cm}^{-1}$; $10^3 E/hc /\text{cm}^{-1}$	Ground state ^a	Ref.
80	—	—	94
81	—	—	95
82	7.2; ≤ 0.3	S	97
86	≤ 10 ; ~ 0	—	98, 99
87	≤ 3 ; ~ 0	—	98, 99
<i>meso</i> - 88	15.2; 5.1	T (> 0.2)	100
(D,L)- 88	8.5; ≤ 0.3	T (> 0.2)	100
89 ^b	16.5; 4.7 (A)	T	100
	7.4; ~ 0 (B)	T	
	9.2; ~ 0 (C)	T	
90 ^b	3.6; ~ 1 (A)	Q	101
	5.0; ~ 0 (B)	Q	
91	5.5; 0	T (0.02)	102

^a The energy differences between the singlet and the triplet states $|\Delta E_{ST}|$ (kcal mol⁻¹) are given in parentheses. ^b Letters A–C designate different conformers of these radicals.

dipole interaction for thermally excited molecules in the triplet state.



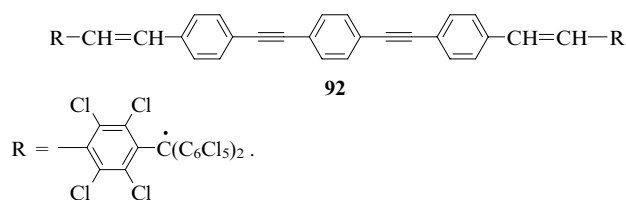
The interaction between the ‘halves’ of diradical **82** is also manifested in a bathochromic shift of the absorption bands in its electronic spectrum with respect to the spectrum of the model monoradical. In the vinylene perchlorinated diradical **81**, the steric restrictions are less pronounced (the benzene rings in the bridge are not perpendicular) and in this case, spin–spin exchange can be observed as a twofold decrease in the coupling constant of the unpaired electrons with the ¹³C nuclei.

Naturally, Ballester’s followers (Veciana’s group) proposed^{98, 100, 103} a strategy for the synthesis of linear and dendritic perchlorinated polyradicals of types **83–85** as a possible base of organic magnets.

Radicals **86–90** have been synthesised and studied by spectroscopic and magnetic methods (see Table 3). Mixed diradicals **86** and **87** in which perchlorinated triphenylmethyl radical centres are connected by hydrocarbon bridges retained the thermal and chemical stability typical of perchlorinated radicals but the intramolecular magnetic dipole and exchange interactions of the unpaired electrons in them proved to be fairly weak.^{98, 99} The nature of the ground state for diradical **87** has not been elucidated;⁹⁸ for diradical **86**, the ground state is singlet, however, according to another publication,⁹⁹ the nature of the ground state cannot be regarded as definitely established for both diradicals. The greater *D* value and the greater bathochromic shifts of the absorption bands in the electronic spectrum of diradical **86** compared to diradical **87** are believed⁹⁸ to be due to more pronounced delocalisation of unpaired electrons with *para*-bridg-

ing. The weak spin coupling in these diradicals is obviously due to the large length of the bridges, which actually comprise three benzene rings and two double and four single bonds. In the AM1-optimised structures of the diradicals, the through-space and through-bond distances between the radical centres are 18.8 and 24.1 Å, respectively for diradical **86** and ~16 and 22.7 Å, respectively, for diradical **87**. It is worth noting that the distance between the spins determined from the parameter D in the point dipole approximation is 19 Å for diradical **86** and 22 Å for diradical **87**, *i.e.*, electron delocalisation in the *para*-coupled divinylphenylene bridge reduces the effective separation of spins in **86**.⁹⁹ Subsequently, diradicals **88**, **89** and triradical **90** in which the unpaired electrons were located much more closely to each other than in **86** and **87** have been prepared.^{100, 101} Radicals **88–90** were prepared by oxidation with chloranil of the corresponding carbanions, which were generated by treatment of hydrogen-containing precursors with $\text{Bu}_4\text{N}^+\text{OH}^-$. The presence of bulky *ortho*-chlorine atoms in the di- and triradicals thus formed brings about great steric restrictions to the rotation of pentachlorophenyl groups, which results in coexistence of various stereoisomers separated by high energy barriers (~24 kcal mol⁻¹). Full stereochemical analysis of compounds **88–90** was carried out; signals of separate conformers were identified in the experimental EPR spectra. Interpretation of the spectra was possible by virtue of isolation of the conformers by chromatography or recrystallisation. EPR spectroscopy and magnetic susceptibility and magnetisation measurements have shown that all conformers of these radicals have high-spin ground states, which are separated from the low-spin excited states by energy barriers substantially exceeding 200 cm⁻¹. For example, diradical **89** has a triplet ground state and is stable in air up to 250 °C. Thus, intramolecular exchange interactions in these radicals are ferromagnetic, *i.e.*, in this case, the perturbation by electronegative heteroatoms, the loss of planarity and symmetry changes have only a slight influence on the exchange interaction. It was concluded^{100, 101} that the topological model developed for planar and unsubstituted alternant hydrocarbons may be applicable to highly distorted and substituted systems. However, as we have demonstrated above for the hydrocarbon diradical **6**, this is not always the case. Later, the limitations of this conclusion have been manifested in an attempt to synthesise a perchlorinated tetradiradical (see below).

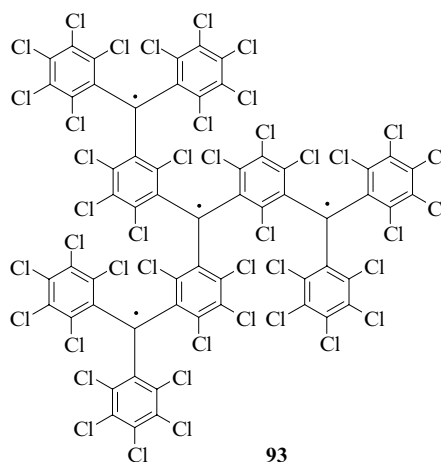
Veciana's group has synthesised and studied¹⁰² diradical **91** consisting of two perchlorinated triphenylmethyl radicals linked by a ferrocene-1,1'-diyldivinyl bridge. A study of the temperature dependence of the intensity of the EPR signal of this diradical showed that it has a triplet ground state; the triplet–singlet splitting was determined using the Bleaney–Bowers equation.¹⁰⁴ Rather unexpectedly, weak antiferromagnetic coupling was manifested even in diradical **92** (Ref. 105) in which the distance between the radical centres reaches ~4 nm.



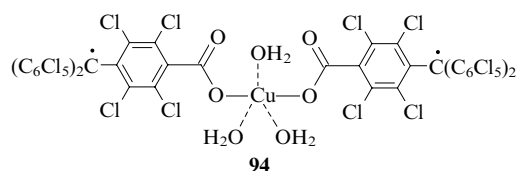
Attempts to synthesise perchlorinated polyradicals with $S > 3/2$ have faced so far inextricable difficulties due to steric overcrowding of polychlorinated compounds. The precursor of the dendritic perchlorinated TAMT tetradiradical **93** was synthesised with great difficulty;¹⁰³ however, the attempts to obtain appreciable amounts of the tetradiradical from this precursor have failed due to the formation of numerous chemical defects.

Subsequently, these results were critically re-evaluated¹⁰⁶ and it was concluded that a tetradiradical in the chemical sense, *i.e.*, as a species containing four unpaired electrons, was actually synthesised in a high yield, but its quintet state with $S = 2$ was not

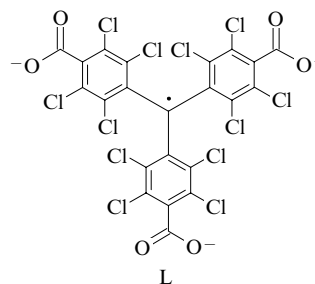
manifested due to the magnetostructural (topological) defects, *i.e.*, transformation of a large portion of *meta*-phenylene FCU into ACU, which took place due to steric crowding of molecules **93**. This is why magnetic measurements for these compounds reveal mainly (96%) triplet species with $S = 1$ (Ref. 106).



Unfortunately, the works on the synthesis of perchlorinated polyradicals have not been further developed as yet. Instead, another line of the use of polychlorinated stable radicals in the design of new magnetic materials is being actively developed. According to one more approach existing in the design of molecular magnets,¹⁰⁷ paramagnetic metal ions are combined with purely organic radicals, most often, iminoxyl radicals, as ligands. Four copper(II) complexes containing perchlorotriphenylmethyl radicals with carboxyl substituents as ligands have been prepared.¹⁰⁸ Magnetic susceptibility and magnetisation measurements for all complexes have shown the presence of fairly strong antiferromagnetic coupling between Cu(II) ions and two coordinated radicals. For example, for complex **94**, presentation of the magnetic data in the three-spin linear model gave $J/k_B = -24.9$ K.



Moreover, perchlorotriphenylmethyl radicals with three carboxyl groups as substituents were used to create¹⁰⁹ a polymeric magnetic nanoporous material $[\text{Cu}_3\text{L}_2(\text{py})_6(\text{EtOH})_2(\text{H}_2\text{O})]_n$ in which the presence of large pores with linear dimensions of ~3 nm was combined with ferrimagnetic ordering at low temperatures (the structure of ligand **L** is shown below).

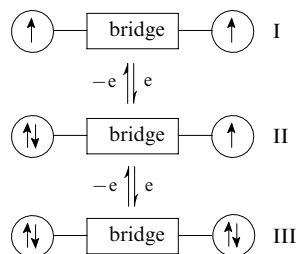


7. Mixed-valence compounds based on triarylmethyl type radicals

As shown above, almost all methods for the preparation of TAMT di- and polyradicals are related to the reduction of molecular precursors and oxidation of the resulting carbanions. These reactions often yield mixed-valence organic compounds in

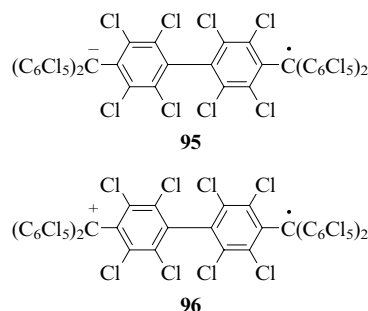
which intramolecular electron transfer (IET) is possible. The problem of intramolecular electron transfer in mixed-valence compounds and examples of this transfer in coordination and purely organic compounds have been discussed in a review.¹¹⁰

The transition from the diradical to doubly charged anion (and back) upon consecutive addition (abstraction) of electrons can be represented as follows:



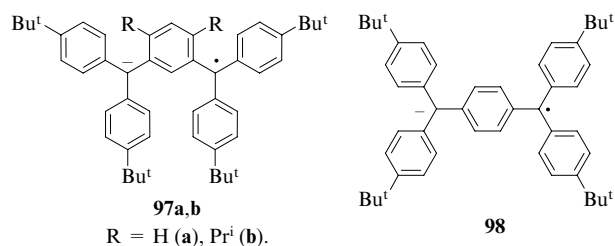
In the case of carbon-centred radicals in compound II on the left (anion), carbon is tetravalent while on the right (radical) it is trivalent, *i.e.*, this is a mixed-valence compound.

Ballester *et al.*^{96,111} prepared the reduced (**95**) and oxidised (**96**) forms of diradical **80**, which retained the thermal and chemical stability.



The twofold decrease in the ¹³C coupling constants in the EPR spectra of compounds **95** and **96** with respect to the spectra of mono- and diradical shows the spin and charge delocalisation on an EPR time scale, *i.e.*, in these mixed-valence compounds, the perpendicular arrangement of the benzene rings in the biphenyl bridge does not prevent electron delocalisation.

A study of the HFS of the EPR signals of radical anions **97a** and **98** in the temperature range of 100–300 K indicates¹¹² that the unpaired electron spin density in the 1,3-coupled radical anion is localised on one triarylmethyl fragment, while in the 1,4-coupled radical anion it is delocalised over two triarylmethyl fragments. It was concluded that the arylmethyl fragments are strongly coupled through 1,4-phenylene and weakly coupled through 1,3-phenylene. The problem of the nature of the absorption bands in the electronic spectra of compounds **97a,b** at 740 and 770 nm, respectively, remains open, although it cannot be ruled out that they refer to electron transfer bands. Some properties of radical anions **97** and **98** are presented in Table 4.



R = H (a), Prⁱ (b).

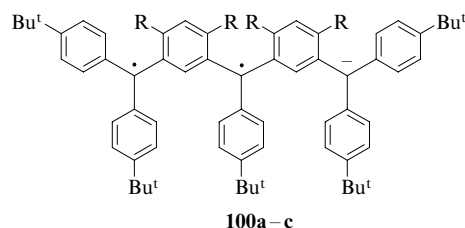
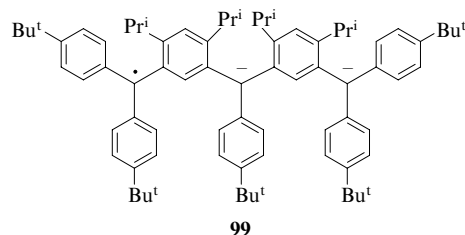
A question has been raised¹¹³ of how an electron added to a chain of exchange-coupled (ferro- or antiferromagnetically) spins affects the interaction of the remaining unpaired electrons. This type of anionic defects can evidently occur in 'incompletely

Table 4. Properties of radical ions based on triarylmethyl type diradicals.¹¹²

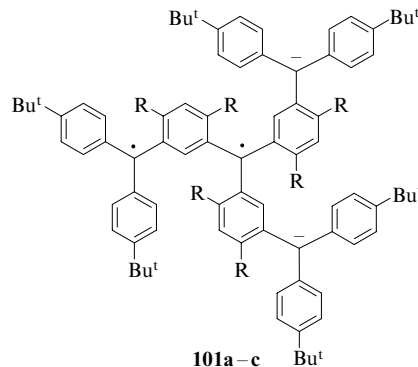
Compound	Ground state	a_H / G (see ^a)	$\lambda_{\text{max}} / \text{nm}$
97a	D	2.65 (6H) 1.15 (5H) 2.85 (1H)	740
97b	D	—	770
98	D	1.3 (12H) 0.65 (8H)	—

^a Hyperfine coupling constant in the EPR spectra.

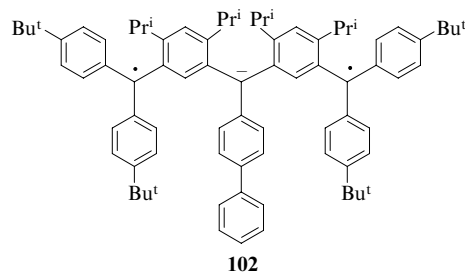
oxidised' polyradicals obtained from polyanions. To answer this question, oligomeric radical anions **99–102** were specially prepared and studied (Table 5).



R = H (a), Me (b), Prⁱ (c).



R = H (a), Me (b), Prⁱ (c).



First, it was found that in all these compounds, the charge and the spin are localised on particular triarylmethyl fragments, as in compound **97a**. Second, it was demonstrated that if the charge (electron pair) is localised on a terminal fragment (compounds **100**, **101**), ferromagnetic coupling of the remaining unpaired

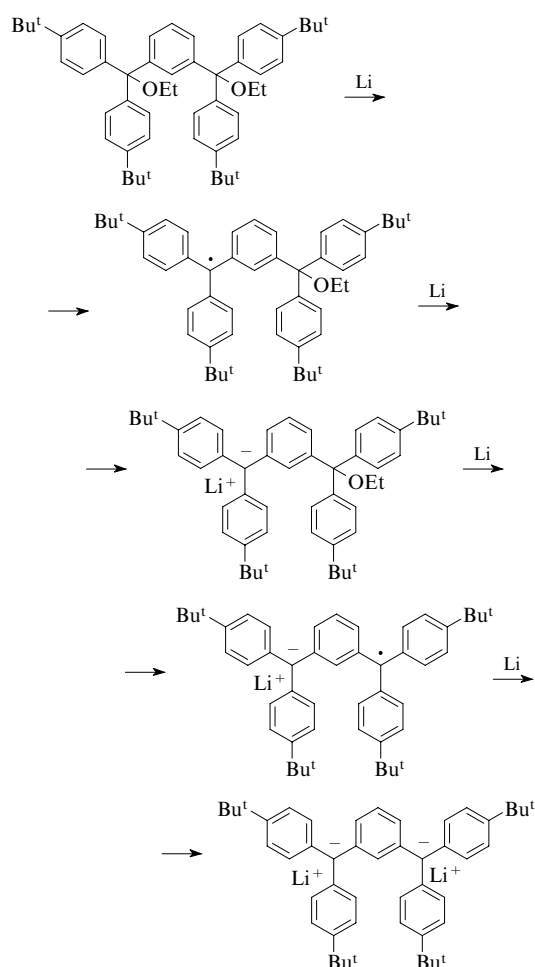
Table 5. Model oligomeric radical anions of the triarylmethyl type.¹¹³

Compound	$10^3 D/hc / \text{cm}^{-1}$	Ground state ^a	$\lambda_{\text{max}} / \text{nm}$
99	—	D	—
100a	6.9; 5.0 (2 isomers)	T	—
100b	8.6	T	—
100c	9.6	T	~350 ~465
101a	7.1; 5.2	T	—
101b	9.5	T	—
101c	9.4	T	—
102	2.7	S (0.018)	~350 ~370 (shoulder)

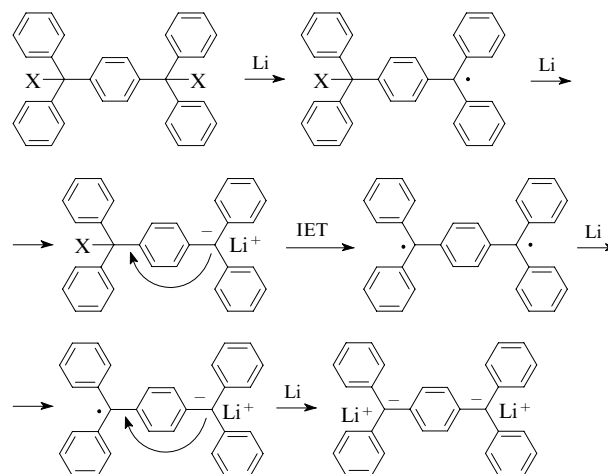
^a The $|\Delta E_{\text{ST}}|$ value (kcal mol^{-1}) is given in parentheses.

electrons is retained. However, if the charge is concentrated on the central fragment (compound **102**), the remaining unpaired electrons are involved in antiferromagnetic coupling. Thus, spin coupling can be controlled by controlling charge localisation. Having summarised his own results and Ballester's data on radical ions **95** and **96**, Rajca put forward a hypothesis³ that ferromagnetic or antiferromagnetic coupling in the starting polyradicals leads to electron localisation or delocalisation, respectively, in the obtained radical ions.

In view of the electron localisation in the 1,3-coupled compounds, Rajca proposed¹¹² the following mechanism for their reduction with metallic lithium:



Presumably, intramolecular electron transfer processes would play an important role in the reduction of 1,4-coupled compounds.



X is an electron-withdrawing leaving group.

This scheme does not show the formation of the quinonoid structure from the diradical. For the radical anion, the IET results in spin and charge delocalisation over two positions. Note that this scheme does not contradict the putative mechanism of the electroreduction of dihalo-*p*-xylenes.¹¹⁴ In particular, the IET should apparently be taken into account when investigating the reduction of poly(arylenesulfophthalides) and poly(arylenephthalides) containing biphenyl-4,4'-diyl and fluorenediyl bridges.

The IET processes were found for compounds **103–105** (Table 6) in which the perchlorinated triphenylmethyl carbanion acts as the electron donor, while the perchlorinated triphenylmethyl radical is the electron acceptor.

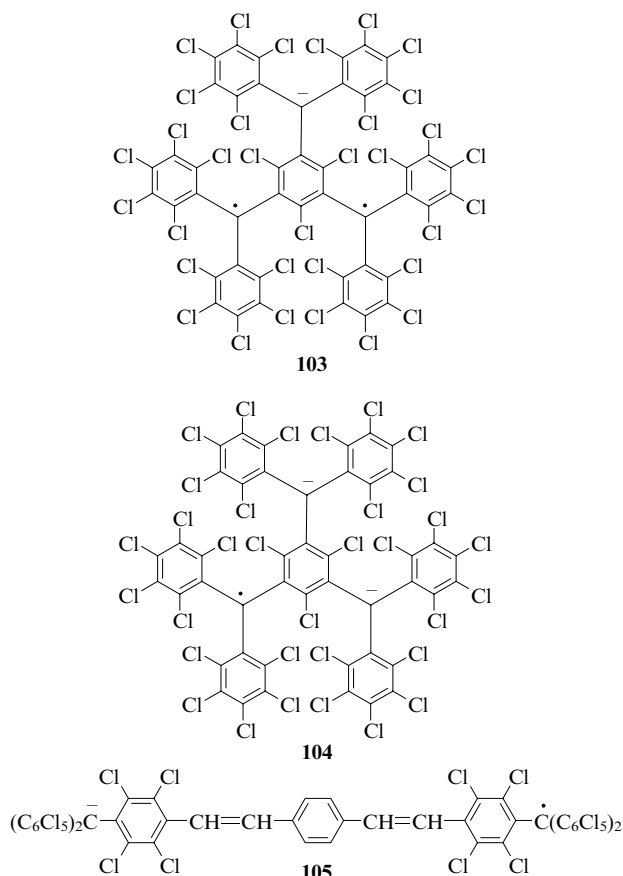
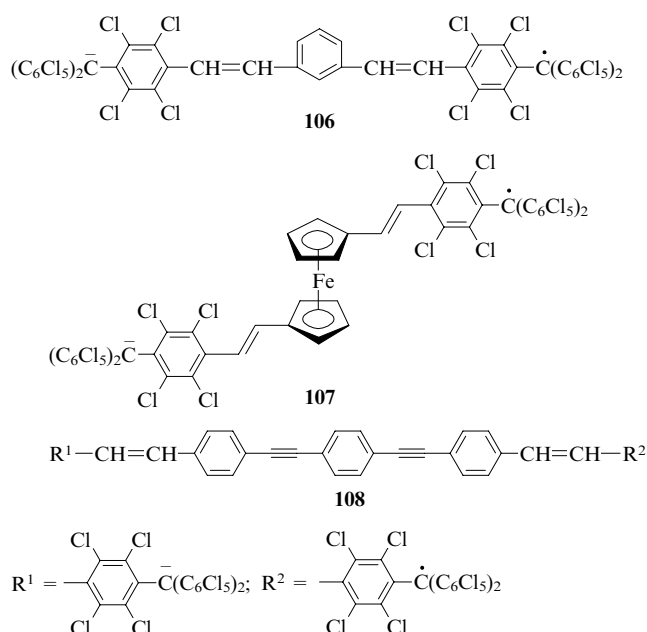


Table 6. Properties of the radical anion systems based on perchlorinated triarylmethyl type radicals.

Com-pound	Ground state	a_{H} and a (^{13}C)/G	λ_{max} /nm	λ_{ET} /nm	V_{ab} /cm $^{-1}$	Ref.
103	T	—	368 508	~2900	320	115
104	D	—	368 508	~2900	390	115
105	D	1.9 (1H)	—	1400	121	99
106	D	1.8 (2H) 0.6 (2H)	—	none	—	99
107	D	—	—	none	—	116
108	D	1.6 (1H) 29.3 (C_α)	—	none	—	103, 116

In the near-IR region, broad intensive electron transfer bands typical of mixed-valence compounds were observed.¹¹⁰ With known peak position (λ_{ET}) and the extinction coefficient at the peak, one can find the electron coupling parameter V_{ab} using the Hush formula. Compound **103** is the first example of a purely organic mixed-valence compound in which intramolecular electron transfer was found in addition to the high-spin ground state. In the case of compound **105**, a thermally activated IET was also observed⁹⁹ by EPR in the temperature range of 200–300 K, the activation barrier being 0.117 eV. For radical anions **106–108**, no intramolecular electron transfer was found.



It can be seen from a comparison of compounds **105** and **106** that a *p*-phenylene fragment present in the bridge facilitates the electron transfer, while a *m*-phenylene fragment hampers the electron transfer, which is consistent, to some extent, with Rajca's data presented above. It is noteworthy that the problem of intramolecular electron transfer is tightly connected with the search for appropriate molecular wires for the various molecular devices;^{110, 116} meanwhile, the bridges in compounds **103–105** can be regarded as molecular wires.

V. Conclusion

Polymeric polyradical **79** can apparently be considered to be the world first polymeric organic magnet. It took almost a hundred years to create such a magnet based on the first discovered stable hydrocarbon radical (the Gomberg radical). Generally, the

achievements of Rajca's research group represent an example of deliberate consecutive work and the use of the whole power of the advanced methods of organic chemistry and physical techniques for substance investigation; however, these would be impossible without the preceding research into the TAMT mono-, di- and polyradicals.

Of course, Rajca's plastic magnet has only feebly pronounced magnetic properties and is far from being suitable for practical purposes. However, the ordering temperature of ~10 K is relatively high for organic magnets and confirms the great potential of the macromolecular approach to their design. The unavoidable presence of chemical and topological defects in the TAMT polyradicals also precludes the formation of ensembles of identical single-molecule magnets from these polyradicals. It is clear that the design of practically useful magnets requires the use of more stable radicals and the existence of magnetic ordering at room (or higher) temperature. A consistent application of Rajca's strategy to the synthesis of inert perchlorinated TAMT polyradicals may give organic magnets stable at room temperature; however, no data concerning any studies along this line are available to date.

As we have seen, the unsolved problems remain also in the studies of TAMT diradicals, even the best known ones such as the Chichibabin, Muller and Schlenk–Brauns hydrocarbons.

As regards the problem of organic magnets as a whole, it is quite possible that practically valuable organic magnets will be obtained in a quite unexpected way, for example, in the way the magnetic order was found at room temperature for the tetracyanoethylene complex with polyaniline.¹¹⁷ However, it must be remembered that the magnetic properties of organic compounds are often due to ferromagnetic impurities (known examples can be found in a review¹).

The author is sincerely grateful to Academician A L Buchachenko for attentive reading and useful discussion of the review.

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^a — *Russ. Chem. Bull., Int. Ed. (Engl. Transl.)*

^b — *Dokl. Chem. (Engl. Transl.)*

Formazans and their metal complexes

G I Sigeikin, G N Lipunova, I G Pervova

Contents

I. Introduction	885
II. Structure of formazans	885
III. Synthesis and properties of formazan derivatives	889
IV. Formazan complexes with metals: structures and applications	893
V. Formazan-containing polymers	897

Abstract. The current data on the structure of formazans in crystals and in solutions are considered and some problems of tautomeric and conformational equilibria are discussed. Some novel classes of formazans synthesised over the past decade are presented. The results of structural studies of formazan complexes with various types of metal coordination are generalised. Examples of synthesis of formazan-containing polymers are given. Special emphasis is placed on analytical and practical applications of formazan derivatives. The bibliography includes 155 references.

I. Introduction

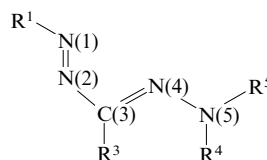
Studies into tautomerism and complexation of heterocyclic compounds are among the main lines of research at the Urals school of organic chemists founded by I Ya Postovsky. The main results and achievements in the chemistry of formazans have been surveyed.^{1,2}

Formazans were first synthesised over a century ago, but still attract attention of chemists, biologists, technologists and other specialists. The presence in formazans of a mobile π -system, the ease of redox reactions typical of these compounds, their ability for isomerisation and tautomeric transformations and enhanced acidity and basicity have determined the main areas of their practical applications. Formazan derivatives are widely used as dyes for different purposes, charge-generating compounds, biochemical markers for redox processes, analytical reagents, photo- and thermochromic materials and synthons for the synthesis of heterocyclic compounds. The data on the structures, properties

and applications of the known formazans and methods for their synthesis published before 1992 are generalised in a monograph.² However, the results of recent studies allow the consideration of problems of tautomerism and isomerism of this class of compounds at a higher level. Despite the large number of novel formazan derivatives synthesised over the last years, the number of publications devoted to the examination of chemical properties of these compounds is very limited. The interest of investigators was mainly focused on the description of different modes of coordination of formazans with metals and their novel applications. Therefore, the aim of the present review is to elucidate the state-of-the-art in theoretical and applied aspects of the chemistry of formazans.

II. Structure of formazans

Formazans represent compounds with an azohydrazone system of bonds:



This review is confined exclusively to the consideration of formazan derivatives with $R^4 = H$ among which 1,3,5-trisubstituted formazans have been studied in especially great detail. Traditionally, substituents at the N(1) and N(5) atoms are designated as R^1 and R^5 , and those at C(3) (which is also referred to as the *meso* position), as R^3 . Substituents in the formazan fragment are enumerated in the ascending order of the atom numbers in the azohydrazone chain; if the position of the substituents at the N(1) and N(5) atoms is not exactly known, they are additionally designated by numbers in parentheses. These rules will be followed in this review.

The molecules of all currently known formazans manifest extremely high conformational and tautomeric mobilities, the types of their isomerism being dependent on the nature of the substituents, first of all, those at the N(1) and N(5) atoms. Thus *N,N'*-diarylformazans **1** are characterised by prototropic tautomerism of the type R^5NH (compound **1a**) $\rightleftharpoons$ R^1NH (**1b**).

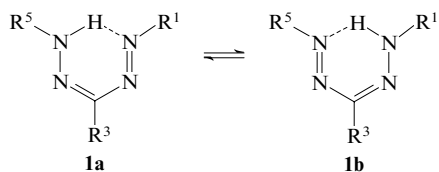
G I Sigeikin Interdepartmental Centre of Analytical Research in Chemistry, Physics and Biology at the Presidium of the Russian Academy of Sciences, ul. Vavilova 44/2, 119333 Moscow, Russian Federation. Fax (7-495) 135 88 25, tel. (7-495) 135 20 58, e-mail: mzairan@ipiran.ru

G N Lipunova Urals State Technical University, ul. Mira 19, 620002 Ekaterinburg, Russian Federation. Fax/tel. (7-343) 374 04 58, e-mail: lipunov@r66.ru

I G Pervova Urals State Forest Engineering University, Sibirskii trakt 37, 620100 Ekaterinburg, Russian Federation. Fax/tel. (7-343) 262 96 50, e-mail: biosphera@usfeu.ru

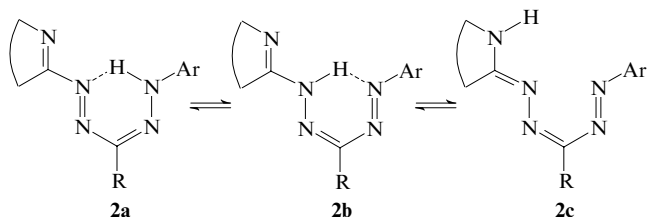
Received 15 May 2006

Uspekhi Khimii 75 (10) 980–997 (2006); translated by R L Birnova



$R^1, R^5 = \text{Ar}$.

If an α -azaheterocyclic substituent is linked to one of the nitrogen atoms of a formazan (compound **2**), an additional amine–imine tautomerism is observed, which involves the nitrogen atom of the heterocycle (**2a** $\rightleftharpoons$ **2b** $\rightleftharpoons$ **2c**).



Some types of formazans, *e.g.*, the well-known analytical reagent dithizone (1,5-diphenyl-3-mercaptoformazan), are subject to autoprotonation. *N*(5)-Acylformazans are also characterised by the presence of rotamers due to hindered rotation around the $N(5)–C=O$ amide bond. Besides, the system of double and single nitrogen–nitrogen and carbon–carbon bonds is responsible for different spatial arrangement of the fragments relative to one another, which determines the existence of geometric isomers.

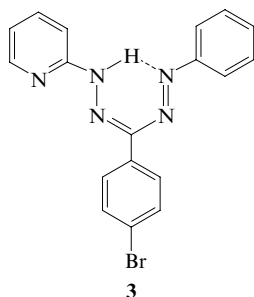
Thus, structural studies of formazans consist in elucidating the prototropic equilibrium between possible tautomeric forms and analysing configurational isomerism.

1. Spatial structure of formazans

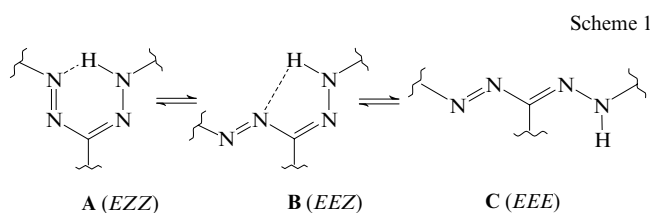
The presence in the formazan chain of two multiple bonds and the $N(5)$ atom with a lone electron pair brings about the formation of an overall conjugated system. This leads to an increase in the order of the $N(2)–C(3)$ and $N(4)–N(5)$ bonds and in the height of the rotation barrier around them. Therefore, the configurations of all the bonds in the formazan fragment are designated in terms of the *Z,E* nomenclature.²

X-Ray diffraction studies of a large series of formazans revealed³ three configurational combinations in the azohydrazone chains in the crystals, *viz.*, *EZZ*, *EEZ* and *EEE* [hereinafter, this refers to the bond sequences $N(1)–N(2)$, $N(2)–C(3)$ and $C(3)–N(4)$, respectively] (Scheme 1).

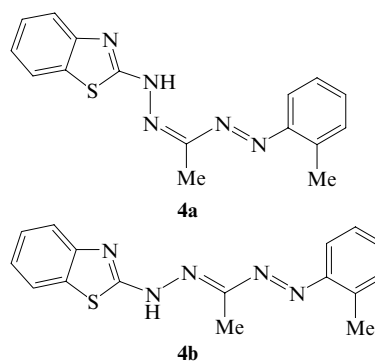
The configuration of formazans is largely determined by the steric effect of the substituent at the *meso*-carbon atom. Thus *EZZ* isomers (structure **A**) are characteristic of formazans with a bulky substituent R^3 (Ph, Bu^t, NO₂, *etc.*).^{3,4} For example, the chain of 1-phenyl-3-(4-bromophenyl)-5-(2-pyridyl)formazan (**3**) in crystals has an *EZZ* configuration.⁵



If the *meso*-carbon atom of formazan contains an alkyl substituent, the crystals can adopt both the *EEE* (structure **C** in Scheme 1) and *EEZ* (structure **B**) configurations. This can be attributed to the fact that the steric demands of these substituents and the phenylazo group are comparable. X-Ray diffraction data



for formazans³ suggest that these compounds exist in crystals exclusively as individual geometric isomers. However, co-crystallisation of 1-(*o*-tolyl)-3-methyl-5-(benzimidazol-2-yl)-formazan **Z** (**4a**) and *E* isomers (**4b**) relative to the $C=N$ bond (Fig. 1) has been observed.⁶



In the crystal lattices, both isomers form dimers, where the molecules are linked by an intermolecular H-bond between the hydrogen atom at the $N(5)$ atom and the nitrogen atom of the heterocycle; in addition, the molecule of compound **4a** contains an intramolecular H-bond with a length of 2.234 Å (see Fig. 1).

It is of note that formazans devoid of substituents at the $C(3)$ atom exist in crystals exclusively in the form of *EEE* isomers.²

The configuration of the azohydrazone chain in crystals of formazans is determined not only by the bulk of the substituent at the carbon atom, but, to a large extent, by the possibility of hydrogen bonding which stabilises their geometric structures.

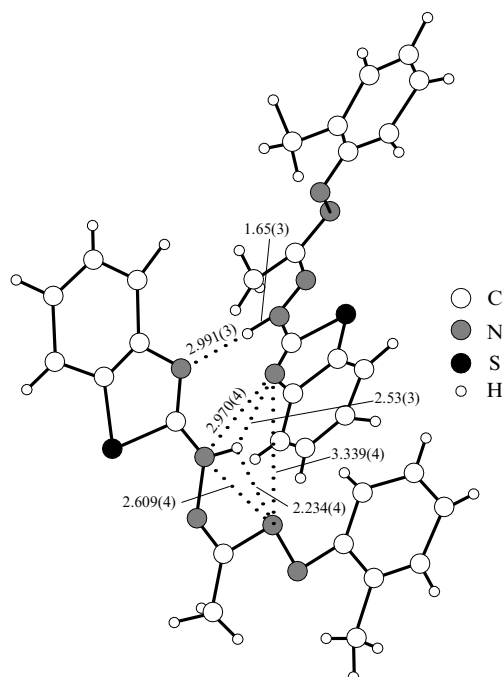
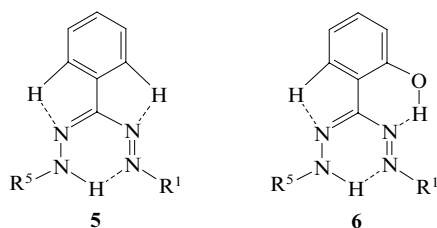


Figure 1. Molecular structure of compound **4**.

Thus the *EZZ* configuration of formazans is stabilised by the intramolecular N(1)⋯HN(5) hydrogen bond in the six-membered ring (see structure **A** in Scheme 1), the *EEZ* isomer is stabilised by the N(2)⋯HN(5) bond in the five-membered ring (see structure **B**), while the *EEE* form is stabilised by intermolecular H-bonds. In *N*-azaheterocyclic formazans, which crystallise in the imino tautomeric form, the intramolecular N(4)⋯HN(heterocycle) H-bond provides additional stabilisation.⁷

A prominent role in stabilisation of one or another configuration of the formazan molecule is played by H-bonds with atomic groups in peripheral substituents. These include not only NH, OH or SH groups, but also CH groups. π -Interactions of aromatic rings with the heteroatom are also possible. For example, a significant role in stabilisation of the *EZZ* form of 3-arylformazans is played by two CH⋯N hydrogen bonds between the *ortho*-protons of the aryl fragment and the nitrogen atoms of the formazan chain (structure **5**). The replacement of the naphthalene rings ($R^1 = R^5 = 1$ -naphthyl) at positions 1 and 5 of compound **5** ($R^1 = R^5 = \text{Ph}$) with benzene rings did not influence the configuration of the molecule (the *EZZ* form), while the passage from 3-phenyl- to 3-naphthylformazans resulted in a shift of the tautomeric equilibrium towards the formation of an open form.² At the same time, the introduction of a hydroxy group into the *ortho* position of the *meso*-phenyl substituent (compound **6**) provided additional stabilisation of the *EZZ* isomer due to formation of an intramolecular H-bond.⁸



It is noteworthy that no compounds with the *EZE* configuration of the formazan chain are known so far. Apparently, such isomers would be energetically unfavourable due to repulsion between the lone electron pairs at the N(1) and N(4) atoms, whereas this configuration is rather common in metal complexes of formazans.²

Recently, theoretical data on the structures of unsubstituted and 3-nitro-substituted formazans, which are unstable under ordinary conditions and could not be prepared experimentally, have been obtained.⁹ The results of *ab initio* quantum-chemical calculations of all possible conformations of these compounds suggest that the *EZZ* configuration is the most stable (at least, in the gas phase). To a large extent, this structure is stabilised by a bridging N—H⋯N hydrogen bond in the six-membered chelate ring where proton transfer is possible. However, according to X-ray diffraction data, 3-unsubstituted 1,5-diphenylformazan (**7**) has the *EEE* configuration in crystals.³ Evidently, the formation of the crystal lattice is controlled by other factors the effects of which have not been taken into account in the quantum-chemical calculations.

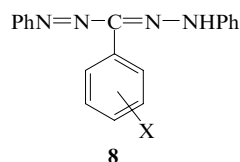
The knowledge of spatial structures of arylformazans in solutions had long been confined to recognition of the ability of these compounds to exist in two forms which can conventionally be designated as 'red' (chelated) and 'yellow' (open) forms. It is the transitions from one form to another that underlie the well-established red–yellow photochromism of 1,3,5-triarylformazans. However, until very recently their structures have been a debated topic.²

Structural analysis of the 'red' form proved unequivocally this to be the *EZZ* isomer. The majority of formazans with this structure are characterised by the lack of absorption bands (ν_{NH}) in their IR spectra at 3100–3500 cm^{-1} , but manifest the presence of a low-field signal of NH in the ^1H NMR spectra and an intense absorption band around 480–500 nm in the electronic spectra

irrespective of the nature of the solvent. The chemical shift of the *meso*-carbon atom in ^{13}C NMR spectra of these compounds is at δ 148–151.¹⁰

In the absence of irradiation, 'yellow' forms of 1,3,5-triarylformazans are unstable, the long-wavelength band at 410–420 nm in the electronic spectra being their only spectral characteristics. Other spectral features of 1,3,5-triarylformazans do not allow their unambiguous structural identification.

Conformations of arylformazans were calculated using different quantum-chemical methods including DFT (density functional theory).¹¹ The effects of substituents on the spectral characteristics of 1,5-diphenylformazans **8** with a substituted phenyl group at position 3 have been described.¹²



X = 2-NO₂, 3-NO₂, 4-NO₂, 2-CO₂H, 3-CO₂H, 4-CO₂H.

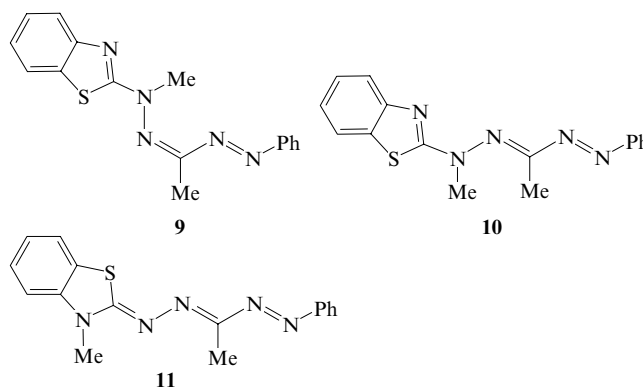
A good correlation was found between the absorption maxima in the electronic spectra and the Hammett constants of the substituents in the benzene ring; however, this correlation was not related to the spatial structures of the formazans under study.

The 'chelate' structure of the *EZZ* isomer is also typical of 1,3-diaryl-5-hetarylformazans. However, the chelate ring with the intramolecular N(1)⋯HN(5) hydrogen bond appeared to be less stable in solution in comparison with 1,3,5-triarylformazans. The ring is easily opened in proton-acceptor solvents, which resulted in an equilibrium between the *EZZ* and *EEZ* forms; their ratio depends on the nature of the heterocycle and the solvent.¹³ This was manifested in the dependence of the position of the δ_{NH} signal in the ^1H NMR spectrum on the solvent polarity as well as in the presence of weak and moderate ν_{NH} bands at 3300–3340 cm^{-1} in the IR spectra.

1,5-Diarylformazans devoid of aryl substituents at the C(3) atom are often unable to preserve the configuration of the azohydrazone chain upon dissolution. The transition between their isomeric forms occurs spontaneously and is catalysed by Brønsted acids or by irradiation of solutions with visible light. Such a conformational lability of 1,5-diarylformazans hampers the elucidation of their structures in solutions and identification of spectral 'diagnostic' markers.²

The electronic spectra of substituted diarylformazans in organic solvents of different polarity and the effects of solvents on the position of the intramolecular charge-transfer band have been studied.¹⁴ The results of calculations of molecular orbitals (MO) by the MPDP/PM3 method point to the *EEZ* configuration of the formazan chain as the most preferable geometry of the diarylformazan molecule.

The problem of establishing spatial structures of 1-aryl-3-alkyl-5-(benzothiazol-2-yl)formazans in solutions was successfully solved¹⁵ using *N*-alkylated 3-methylformazans **9–11** as the



model compounds. The fixed configurations of the double bonds in these formazans rule out the formation of intra- and intermolecular H-bonds and their tautomerism.

In-depth studies of these compounds using a combination of modern physicochemical methods (X-ray diffraction, ^1H and ^{13}C NMR, electronic spectroscopy, dipole moment measurements) with consideration of the published spectral data for 1,5-diaryl-3-alkylformazans enabled establishing 'diagnostic' markers for determination of the configuration of the azohydrazone chain:

(1) The *EEZ* Isomers absorb visible light in a longer-wavelength region than compounds with the *EEE* configuration. The bathochromic shift of the absorption maxima (λ_{max}) of formazans containing an alkyl substituent at the *meso*-carbon atom on going from polar to nonpolar solvents (the so-called negative solvatochromism) is due to an increased content of *Z* isomers as regards substituents at the $\text{C}(3)=\text{N}(4)$ bond ($Z^{3,4}$). The *EEE* isomer with the absorption maximum around 400 nm is predominant in polar solvents.

(2) The chemical shift ($\delta^{13}\text{C}$) of the *meso*-carbon atom in the ^{13}C NMR spectra of *EEE* isomers is observed at lower field ($\delta^{13}\text{C} = 155.0\text{--}162.9$) in comparison with the *EEZ* isomers ($\delta^{13}\text{C} = 150.3\text{--}156.0$). The carbon atoms of alkyl substituents at the $\text{C}(3)$ atom (R^3) of the *EEE* isomers resonated at higher field in comparison with the *EEZ* isomer, the difference between them being equal to 5.4–9.5 ppm.^{16,17} The dependence of the chemical shift on the concentration of the solute is characteristic of only the carbon atoms that are directly linked to the $\text{C}(3)$ atom.

Analysis of the spectral data for 1-aryl-3-alkyl-5-(benzothiazol-2-yl)formazans with consideration of the observed regularities made it possible to calculate the ratio of the *EEE* to *EEZ* isomers in solution. An increase in the length of the alkyl substituent at the $\text{C}(3)$ atom results in the predominance of the $Z^{3,4}$ -isomer in solution, while an increase in its bulk (e.g., for $\text{R}^3 = \text{Pr}^i$) stabilises the *EEZ* configuration with a five-membered chelate ring (structure **B** in Scheme 1) irrespective of the nature of the solvent. The ratio of the $E^{3,4}$ to $Z^{3,4}$ isomers of compounds studied in solution depends on both the nature of the solvent (polar protic solvents stabilise the *Z* form, while non-polar solvents stabilise the *E* form) and on conditions of isolation and purification of formazans.¹⁶

The configurations and electronic structures of several novel 3-furyl-, 3-thienyl- and 3-pyrrolylformazans have been studied.¹⁸ The electron density distribution in these molecules was studied by the PPDP/2 method and related to the electronic structures of the substituents and the nature of the heteroatom in the heterocycle.

2. Tautomerism of formazans

It is believed that the tautomerism of triarylformazans containing identical substituents at the $\text{N}(1)$ and $\text{N}(5)$ atoms ($\text{R}^1 = \text{R}^5$) is an intramolecular process occurring between two degenerate forms. In 1,3,5-triphenylformazan with the *EZZ* configuration (structure **A** in Scheme 1), the proton forms covalent bonds alternately with the $\text{N}(1)$ and $\text{N}(5)$ atoms in the course of intrachelate proton transfer with the lifetime of the tautomers of about 10^{-3} s. The position of the hydrogen atom in the azohydrazone chain is important for formazans with different substituents R^1 and R^5 .

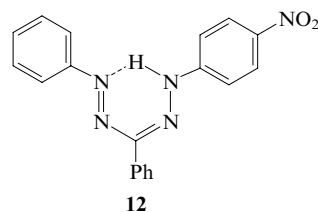
The tautomeric ratio in solution of a formazan is determined by the electronic characteristics of the substituents at the $\text{N}(1)$ and $\text{N}(5)$ atoms. The introduction of a strong electron-withdrawing (e.g., acyl, nitro or dinitrophenyl) or an electron-donating group may lead to only one tautomer. The levelling of the electronic characteristics of the terminal substituents (e.g., if R^1 and R^5 are different aromatic groups) results in a tautomeric equilibrium $\text{R}^1\text{NH} \rightleftharpoons \text{R}^5\text{NH}$; the position of the latter is judged upon by a number of features established from the analysis of ^1H and ^{13}C NMR spectra (see Refs 2 and 3).

The changes in the chemical shifts of the signals for the carbon atoms of the aryl substituent linked to the $\text{N}(1)$ or $\text{N}(5)$ atom in the ^{13}C NMR spectrum relative to the signal for the carbon atom of benzene or its derivative ($\Delta\delta^{13}\text{C}$) are the most informative. A method for the quantitative evaluation of the tautomeric equilibrium of formazans^{3,19} allowed determination of the percentage of one of the tautomers [e.g., that containing a proton at the $\text{N}(5)$ atom] according to the formula:

$$P_{\text{R}^5\text{NH}} = \left(\frac{\Delta\delta_{\text{R}^5} - \Delta\delta_{\text{R}^5\text{N}=\text{N}}}{\Delta\delta_{\text{R}^5\text{NH}} - \Delta\delta_{\text{R}^5\text{N}=\text{N}}} \right) \times 100\%,$$

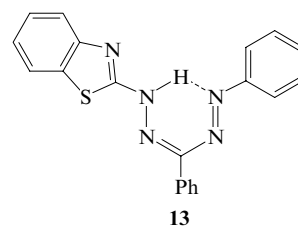
where $\Delta\delta_{\text{R}^5}$ is the experimental change of the chemical shift ($\delta^{13}\text{C}$) of the carbon atoms of substituent R^5 relative to that in substituent R^5H ; $\Delta\delta_{\text{R}^5\text{NH}}$ is the change of the $\delta^{13}\text{C}$ of the carbon atoms of substituent R^5 relative to that in R^5H calculated for the R^5NH tautomer and $\Delta\delta_{\text{R}^5\text{N}=\text{N}}$ is the difference calculated for the R^1NH tautomer.

The nitrophenylhydrazone group of 1,3-diphenyl-5-(*p*-nitrophenyl)formazan (**12**) was used as a model of the R^5NH tautomer, while its azophenyl fragment, as a model of the R^1NH tautomer. It is considered¹⁹ that compound **12** exists in solution in the form of nitrophenylhydrazone.

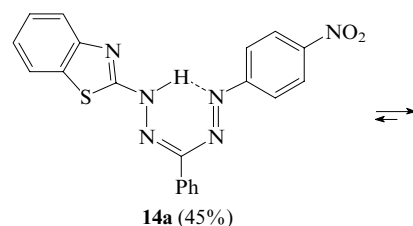


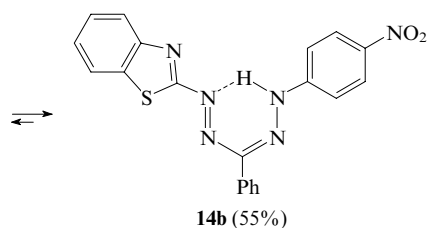
The most characteristic changes in $\delta^{13}\text{C}$ induced by the azo or the hydrazone fragment were observed for the carbon atoms in the *ipso*, *ortho* and *para* positions. The calculations took into account the changes in the chemical shifts of these atoms.

At present, this method is considered to be the most convenient and reliable procedure for determining the percentage of tautomeric forms of different types of formazans. For example, a comparison of $\delta^{13}\text{C}$ in R^1NH and R^5NH tautomers of 1,3-diphenyl-5-(benzothiazol-2-yl)formazan (**13**) suggests that this compound exists almost exclusively in the form of a $\text{PhN}(1)$ tautomer irrespective of the solvent polarity.³



The enhancement of the electron-withdrawing properties of the aryl substituent at the $\text{N}(5)$ atom (introduction of the *p*-nitrophenyl group, formazan **14**), leads to co-existence of azoaryl tautomer **14a** with a considerable amount of the arylhydrazone tautomer **14b**.

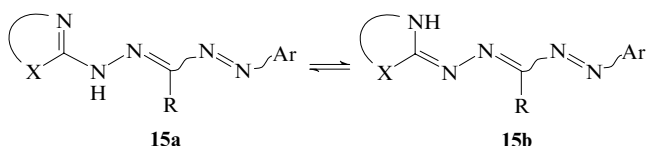




Quantitative evaluation of the tautomeric equilibrium in solutions of formazan revealed that, unlike the gas phase, the effect of the electronic characteristics of substituents R^1 and R^5 on the position of the tautomeric equilibrium is very pronounced. In 1,3,5-triarylformazan solutions, the equilibrium is fully shifted towards the form where the proton is localised at the nitrogen atom linked to the substituent with the strongest electron-withdrawing properties.^{2,3}

Similar conclusions were made in studies on the tautomerism of 3-furyl(thienyl, pyrrolyl)formazans by mass spectrometry.^{18,20}

In addition to the aforementioned prototropic equilibrium ($R^1NH \rightleftharpoons R^5NH$), the amino–imino (formazan–formazene) tautomerism, which involves the nitrogen atom of the azaheterocyclic substituents, is observed for 1-aryl-5-hetarylformazans.² Quantitation of the isomer ratio in the gas phase of hetarylformazans by mass spectrometry presents a problem due to identical masses of the fragment ions of the imino (**15a**) and amino (**15b**) tautomers of the heterocycles.



However, the predominant localisation of the proton at the endocyclic nitrogen atom (the imine form of the type **15a**) of 1,3-diphenyl-5-(benzothiazol-2-yl)formazan (**13**) could be established on the basis of electron impact and chemical ionisation mass spectrometry and using semiempirical calculations.²¹

The position of the ν_{NH} band in the IR spectra of *N*-hetarylformazans has long remained the only spectral criterion of the amino–imino tautomerism in solutions. The imino form manifests a characteristic band around $3420\text{--}3460\text{ cm}^{-1}$, while the band around $3330\text{--}3360\text{ cm}^{-1}$ is more typical of the amino form.

^{13}C NMR spectroscopy is the most informative method for studying the amino–imino tautomerism in solutions. These conversions strongly affect the chemical shifts of the carbon atoms in azaheterocycles. The use of fixed models of different isomeric forms of 1-phenyl-3-methyl-5-(benzothiazol-2-yl)formazans **9–11** as examples revealed¹⁵ that the differences in the chemical shifts ($\delta^{13}\text{C}$) of individual atoms in the benzene rings of the heterocycle range from 7 to 11 ppm. A comparison of the $\delta^{13}\text{C}$ values in the ^{13}C NMR spectra of model compounds and the corresponding formazans enabled quantitative determination of the ratios of amino to imino tautomers in solutions of trisubstituted 1(5)-aryl-5(1)-(benzothiazol-2-yl)formazans.^{13,16} It was found that the concentration of the imino tautomer in a non-polar solvent decreases with an increase in the bulk of the substituent at the C(3) atom and the ability of formazans to exist in a ‘folded’ state stabilised by intramolecular H-bonds. Thus in CDCl_3 the contribution of the imino tautomer of formazans **13** (the *EZZ* isomer) and **4b** (the *EEZ* isomer) could not be reliably established because its percentage did not exceed 5%, whereas that of the imino tautomer of *EEE* formazan **4a** was 20%–25% [calculated from signals for the C(4), C(8) and C(9) atoms of the heterocycle]. In proton-acceptor solvents, the percentage of the imino tautomer increases (in some cases, up to 44%–76%).

A comparison of the tautomeric compositions of solutions of 1-aryl-3-phenyl-5-hetarylformazans differing in the substituents

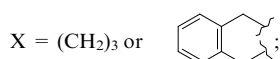
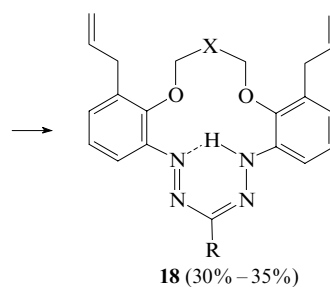
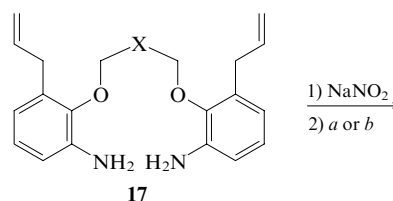
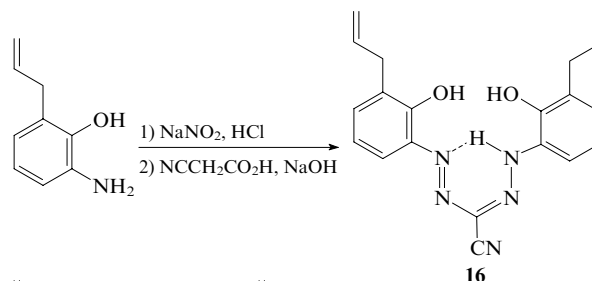
at the N(5) atom demonstrated that the contribution of the imine structure increases with an increase in the basicity and a decrease in the aromaticity of the heterocycle. Thus in formazans containing thiazole, benzothiazole and benzoxazole rings the position of the tautomeric equilibrium in non-polar solvents was close to that for triarylformazans, *i.e.*, both classes of compounds exist predominantly in the amine form. In contrast, their benzimidazole analogues exist exclusively as imino tautomers with the *EEE* configuration.³

The preferable tautomeric forms of *N*-pyrazolyl-*C,N*-diarylformazans were established on the basis of a comparative analysis of quantum-chemical calculations and spectroscopic data.²²

III. Synthesis and properties of formazan derivatives

The majority of recent studies aimed at the synthesis of novel formazans are directed at the design of substances with valuable properties. Most often, the known approach to the synthesis of formazans is used, which is based on reactions of aryl(hetaryl)hydrazones with diazo compounds, non-traditional compounds being used as amine, hydrazine or aldehyde components in recent years. Thus the introduction, into the azohydrazone chain, of new heterocycles that play the role of additional addends for complexation and such metal-coordinating groups as podands, crown ethers, *etc.*, allows preparation of metal chelates with improved characteristics.

Allyl-substituted macrocyclic crown-formazans as non-traditional intermediates for the design of polymeric macrocycles have been synthesised.¹⁷ Thus bisphenol **16** was prepared by a reaction of diazotised 6-allyl-2-aminophenol with cyanoacetic acid. Diazotisation of diamine **17** and its subsequent azo coupling with compounds containing a reactive CH group have led to a vast variety of the corresponding macrocyclic formazans **18**.

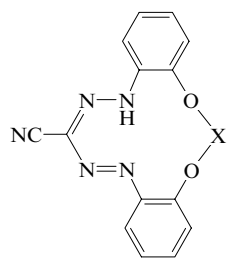


(a) $\text{NCCH}_2\text{CO}_2\text{H}$, Py, Cu(II) (for $R = \text{CN}$);

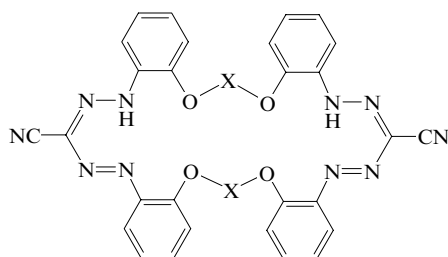
(b) $\text{PhCH}_2\text{C}(\text{O})\text{CO}_2\text{H}$, NaOH, H_2O (for $R = \text{Ph}$).

The synthesis of 14- and 15-membered crown-formazans and estimation of the prospects of their use for spectrophotometric determination of lithium have been described.²³ These compounds were shown to be highly selective chelating agents for this ion. Some of these formazans were assayed as selective neutral conductors for caesium ion-selective electrodes.²⁴ Thus formazan containing a 4-pyridine *N*-oxide residue at the C(3) atom manifested the highest selectivity with respect to caesium ions with low selectivity for potassium and ammonium ions.

Crown formazans **19a–c** as well as 28- and 30-membered bisformazans **20a–c** have been synthesised in low yields.²⁵



19a–c



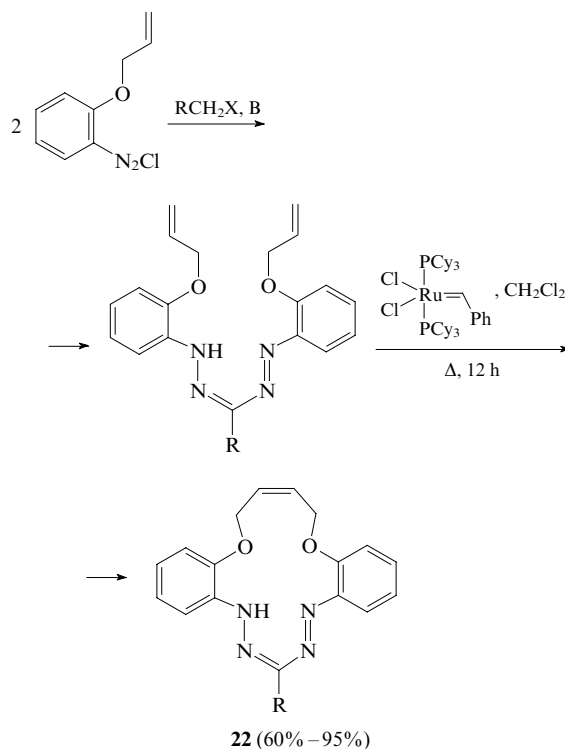
20a–c

X = CH₂C(=CH₂)CH₂ (**a**), (CH₂)₃ (**b**), (CH₂)₄ (**c**).

Mixtures of formazans **19** and **20** were separated into individual components by TLC.

Ozonolysis of compound **19a** at low temperature yielded ketone **19d**; reduction of the latter with sodium borohydride gave alcohol **19e**. The condensation of ketone **19d** with 1,3-diaminopropane yielded bisformazan **21** (Scheme 2).

A highly stereoselective synthesis of 15-membered macrocyclic crown formazans **22** with *Z* configuration of the C=C bond (the *Z*:*E* ratio varied from 90:10 to 97:3) has been carried out.²⁶



22 (60%–95%)

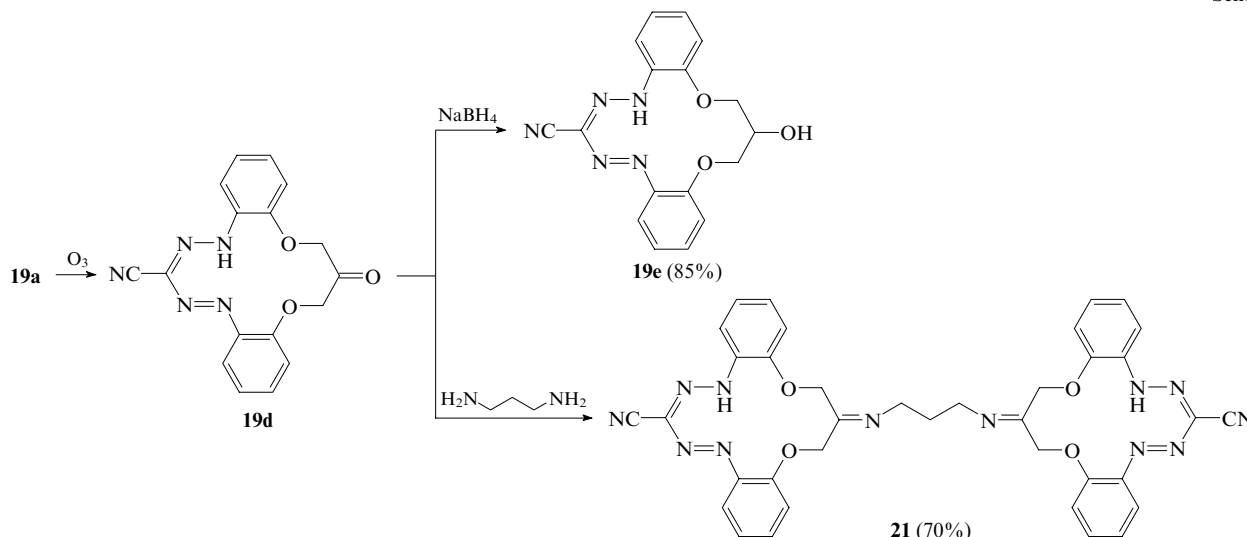
R = CN, Ph, 4-ClC₆H₄, 4-MeC₆H₄, 4-MeOC₆H₄, 4-C₅H₅N⁺O[−], PhSO₂; X = CO₂H or C(O)CO₂H; Cy = cyclo-C₆H₁₁.

The introduction of podands containing oligooxyethylene bridges of various lengths between two formazan fragments afforded new classes of bisverdazyls (**23**) and bisverdazylum salts (**24**) (Scheme 3).²⁷

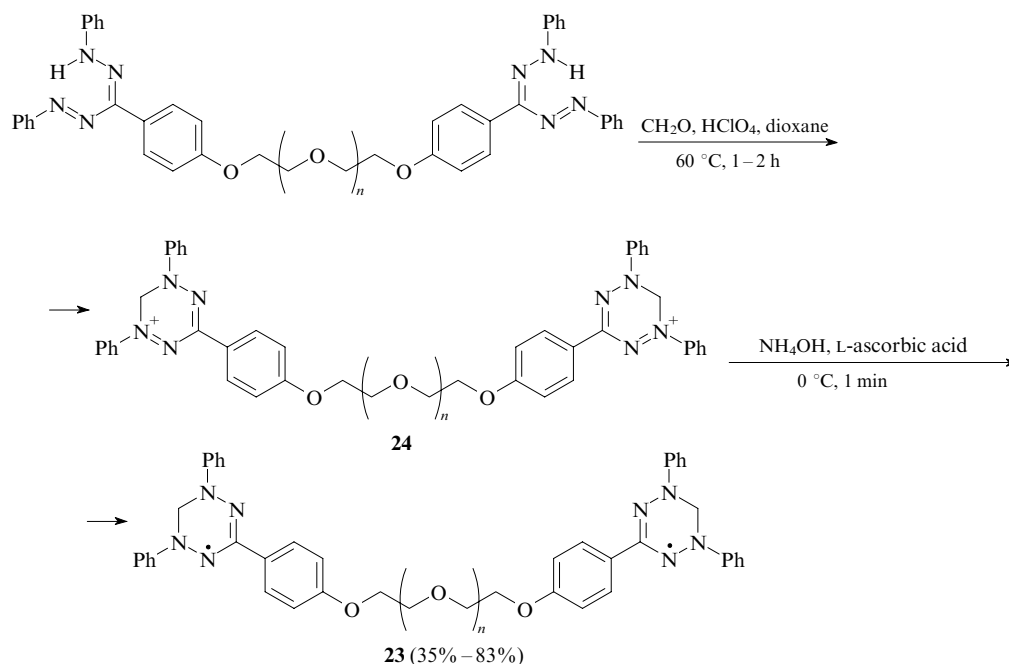
Bisverdazyls **23** represent a novel class of stable biradicals: solid samples decompose at room temperature only after several days, while their solutions in organic solvents do not change optical densities over a course of several weeks. The calculated distances between the spin centres agree well with experimental values.²⁸ These compounds are good models for the study of 'host–guest' interactions.

Podands can be used as amine (like the aforementioned compounds **18–22**) or aldehyde components in the synthesis of formazans (in the latter case, the role of the azo component is played by diazonium salts). The synthesis of benzothiazolylfor-

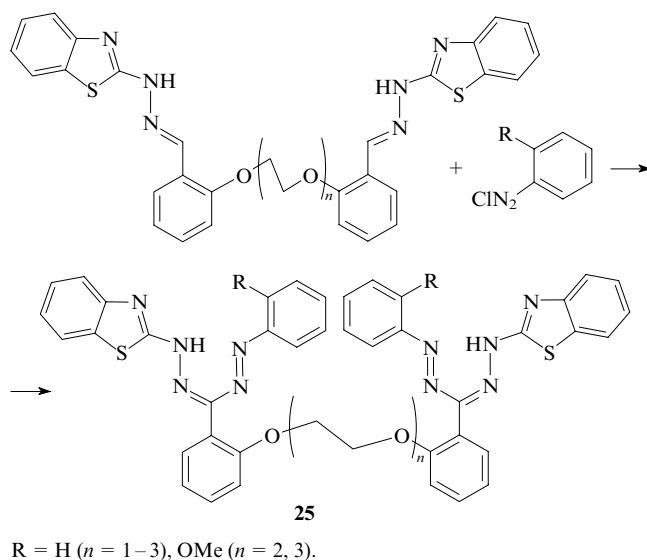
Scheme 2



Scheme 3



mazans **25** containing oxyethylene groups ($n = 1–3$) has been described.²⁹ Cross-linked salicylaldehyde benzothiazol-2-ylhydrazones and diazonium salts prepared from aniline or *o*-anisidine served as the starting compounds in the synthesis of podands **25**.



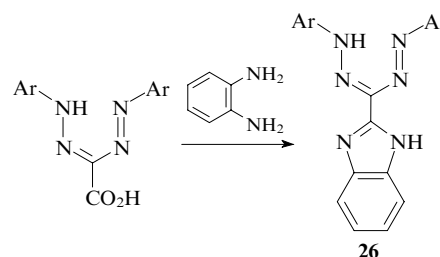
The complexation ability of nickel(II), cadmium(II), zinc(II) and lead(II) ions toward compounds **25** has been investigated. Formazans **25** formed mono- and binuclear complexes with these metals. The introduction of an oxyethylene bridge not only expanded the range of the coordinated metals, but also conferred novel properties on the formazan complexes. Thus the binuclear lead(II)–formazan **25** complex (R = OMe, $n = 2$) shows photochromic properties.²⁹ After sunlight irradiation, the blue colour of a solution of the complex in ethanol changed into orange; the original colouring was restored in the dark. Such interconversions occur repeatedly with no change in the absorption intensity in the electronic spectra. The reaction of formazan **25** (R = H, $n = 3$) with solid metal salts yielded coloured complexes only with zinc(II) and cadmium(II) ions, which can be used for the extraction of these metals from mixtures. Some specific features of the

behaviour of zinc and cadmium formazanates with respect to sunlight were established.

A recently published review³⁰ devoted to macrocyclic formazans describes methods for the synthesis and properties of crown formazans, discusses elucidation of their structures by NMR, IR and UV spectroscopy and mass spectrometry and presents data on their reactivities and applications.

The synthesis of 1,5-diphenylformazans carrying a substituted benzene ring at the C(3) atom has been described.³¹ The structures of formazans were studied by IR, ¹H and ¹³C NMR spectroscopy. A good correlation was found between the absorption maxima in the electronic spectra and the Hammett constants of the substituents in the benzene ring. Tetrazolyl-substituted formazans were prepared from (tetrazol-1-yl)acetohydrazide and *p*-chloro- or *m*-nitrobenzaldehyde.³² The condensation was induced by microwave irradiation. The hydrazone formed was then treated with a diazonium salt to give a high yield of 1,3-diaryl-5-[(tetrazol-1-yl)acetyl]formazan.

The condensation of 1,5-diaryl-3-carboxyformazan with *o*-phenylenediamine yielded 1,5-diaryl-3-(benzimidazol-2-yl)formazans **26**.³³



Reductive cleavage of these compounds yielded benzimidazole-2-carboxamide arylhydrazones.

The ability of formazans to form complexes with metal ions is among their most salient properties. Thus 1,5-bis(2-carboxyphenyl)-3-(2-furyl)formazans gave complexes with zinc(II), cadmium(II), mercury(II) and lead(II) ions and mixed-ligand complexes of these formazans and 2,2'-bipyridyl with cadmium(II), mercury(II) and lead(II).³⁴ The structures and properties of the synthesised compounds were studied by IR, electronic and ¹H NMR spectroscopy; their thermal analyses were carried out.

The synthesis and spectroscopic analysis of 1-aryl-3-(*n*-heptyl)-5-benzothiazolylformazans and their complexes with metal

ions have been carried out.³⁵ It was found that these formazans form 1 : 1 complexes with silver(I) ions and 1 : 2 complexes with nickel ions. The ligands of some compounds of this series formed stable complexes with lead and rare-earth ions. In aprotic solvents (*e.g.*, acetonitrile), formazans manifested specific, *e.g.*, complexing, properties. For example, the *m*-nitro group in an aryl substituent at the N(1) atom is involved in the coordination to the metal.

The dependence of complexation of formazans with metals on the nature of the solvent has been studied.³⁶ A comparison of complexing properties of aryl- and hetarylformazans in acetonitrile revealed that the efficiency of the complexation depends on the ionic strength of the solutions and the donor-acceptor properties of the substituents in the ligand molecule.

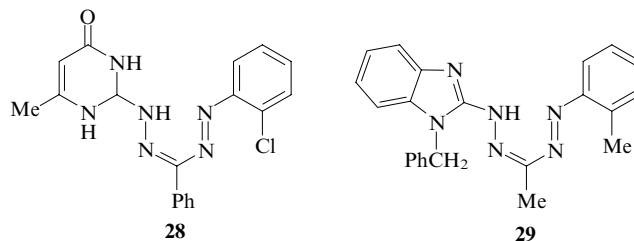
Some recently published papers were devoted to practical applications of formazans as analytical reagents for the determination of microquantities of metals in various objects. Thus 1,5-bis(2-carboxyphenyl)-3-phenylformazan was used for spectrophotometric determination of copper ions in the presence of other metal ions.³⁷ The highly sensitive colour reaction of 1-(2-hydroxy-5-sulfophenyl)-3-(2-hydroxyphenyl)-5-(3,5-dibromo-2-pyridyl)formazan with copper ions for the determination of the copper content in ores has been studied.³⁸ Simple, rapid and accurate methods for the spectrophotometric determination of divalent cobalt, copper and palladium ions based on the formation of coloured complexes of these metals with 1-(2-arsenophenyl)- (Ref. 39) and 1-(2-carboxyphenyl)-3-benzoyl-5-phenylformazan (**27**) have been developed and employed for the quantitation of copper ions in alloys.⁴⁰ Carboxyphenylformazan **27** was recommended as an indicator in spectrophotometric titration of cobalt, copper and palladium by ethylenediaminetetraacetic acid (EDTA). In the series of hetarylformazans, 1-(2-hydroxy-5-nitrophenyl)-3-isopropyl-5-(benzoxazol-2-yl)formazan was found as a new extractant for preconcentration and determination of scandium(III) ions.⁴¹ This compound was highly selective with respect to Sc(III) in the presence of different metals. Its lower homologue, *viz.*, 1-(2-hydroxy-5-nitrophenyl)-3-ethyl-5-(benzoxazol-2-yl)formazan, proved to be a selective reagent for the photometric determination and preconcentration of lead.⁴²

Formazans are used more and more often in flow injection analysis (FIA). This method in combination with spectrophotometric detection of multicomponent mixtures can be used for simultaneous determination of cobalt, copper and zinc ions (in the concentration range 0.2–1.9 $\mu\text{g ml}^{-1}$) with 1-(2-carboxyphenyl)-3-phenyl-5-(2-hydroxy-5-sulfophenyl)formazan as the chromogenic reagent.⁴³ This procedure was employed for the determination of copper and zinc in blood sera, veterinary preparations⁴³ and plants.⁴⁴ Formazans were also proposed as sorbents for flow sorption–atomic absorption determination of metals in solutions.⁴⁵

A spectrophotometric procedure for the determination of copper ions in water using 1,5-bis(2-hydroxy-5-sulfophenyl)-3-cyanoformazan has been developed.⁴⁶ A rapid spectrophotometric method was described⁴⁷ for the determination of zinc in biological materials and pharmaceutical preparations using 3-acetyl-1,5-diarylformazans as ligands in the presence of cetylpyridinium chloride.

The ability of formazans to form complexes with metals is also used in some electrochemical analytical techniques. Thus the electrochemical behaviour of seven hetarylformazans used as components of carbon-containing inks of thick-film screen-printed electrodes was studied.^{48, 49} The compositions of complex compounds formed on the electrode surface and their stability constants were determined. It was shown, for example, that 1-(2-chlorophenyl)-3-phenyl-5-(6-methyl-4-oxo-3,4-dihydropyrimidin-2-yl)formazan (**28**) provides high sensitivity of graphite-containing modified electrodes, low detection limits with respect to Cu(II), Pb(II), Cd(II) and Zn(II) ions and high reproducibility of the results of analysis.

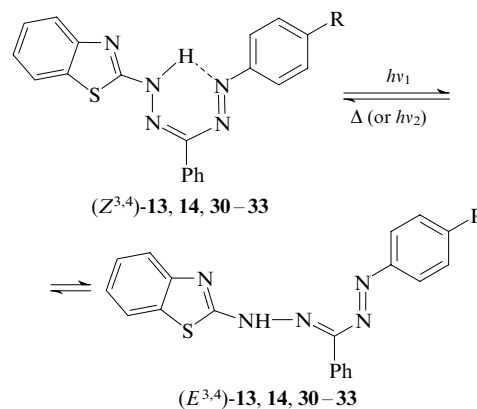
A mercury-free thick-film graphite-containing electrode modified with 1-(*o*-tolyl)-3-methyl-5-(1-benzylbenzimidazol-2-yl)formazan (**29**) was proposed for the determination of Mn(II) ions by the cathodic inverse voltammetric method.⁵⁰ The determination limit of manganese(II) with this electrode was 0.04 $\mu\text{g litre}^{-1}$; the preconcentration time was 60 s. The dependence of the analytical signal of Mn(II) on its concentration in solution was linear in the range from 0.1 to 30 $\mu\text{g litre}^{-1}$. This procedure was used for the analysis of natural and drinking waters for the detection of manganese(II) ions.



Gas-phase oxidation and reduction of 1-(benzothiazol-2-yl)-3,5-diphenylformazans as well as complex formation with transition metals under laser ionisation were studied.⁵¹ The data obtained suggest that formazan molecules are photoionised to molecular radical ions, which are further involved in ion-molecular reactions. Formazans give singly charged metal formazanates with the composition 1 : 2. Anionic metal complexes of formazans were also studied by capillary electrophoresis–mass-spectrometry.⁵²

Photochromic properties of formazans have been known since long ago and were repeatedly discussed in the literature. However, detailed mechanisms of their photochromic conversions still remain obscure. Therefore, the number of publications on this subject is steadily increasing. For instance, the dependence of spectral-kinetic characteristics of photochromic arylformazans on their structures was investigated.⁵³ It was found that enhancement of the electron-donor properties of substituents was accompanied by a bathochromic shift of the absorption bands of the original chelate structure, the positions of the absorption maxima of the photoinduced form being determined by the properties of the tautomeric structures. As for the kinetic characteristics, they depend exclusively on the thermal relaxation of the photoinduced form into the original state, the rate of this process being related to the nature of the substituents.

The photothermochromic conversions of 1-aryl-3-phenyl-5-(benzothiazol-2-yl)formazans **13**, **14** and **30–33** were studied under conditions of steady-state photolysis.⁵⁴



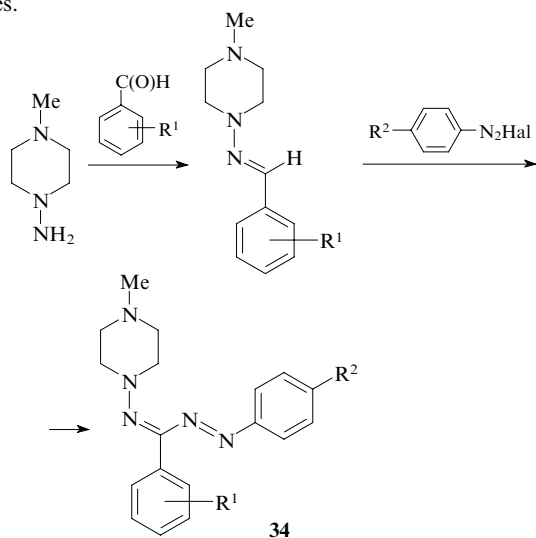
R = H (**13**), NO₂ (**14**), Cl (**30**), Br (**31**), NMe₂ (**32**), CO₂Me (**33**).

Irradiation of solutions of these compounds in toluene at $\lambda = 578 \text{ nm}$ resulted in changes of the colour of the solution from red and blue (for R = NO₂ and CO₂Me) to yellow. The relaxation of the photoinduced form into the original state takes place both as a result of either thermal dark reaction or irradiation

($\lambda = 436$ nm). In this case, the *E,Z* isomerisation of the C=N bond becomes the major photochemical reaction. The reverse reaction proceeds at a higher rate in comparison with triphenylformazan due to the presence of a weaker intramolecular hydrogen bond in the original forms of formazans **13**, **14** and **30–33**. Kinetic studies of photo conversions and thermal conversions of compounds **14** and **33** revealed the presence of an isosbestic point in their absorption spectra. This suggests that the lifetimes of their intermediate forms were significantly shorter than those of the starting compounds and the final products. The photothermal conversions of formazans **13**, **30–32** were accompanied by the formation of long-lived intermediate species.

Variation of substituents in the formazan molecule was aimed at a search for biologically active substances. Thus a series of 1-aryl-3-(3,4,5-trimethoxyphenyl)-5-(3-nitrobenzoyl)formazans were synthesised and assayed for antibacterial, antituberculosis and antifungal activities.⁵⁵ It was found that formazans comprising 2-chlorophenothiazine could be employed as antiinflammatory agents.⁵⁶

The synthesis of formazans **34** containing the piperazine fragment was described and their biological activities were investigated.⁵⁷ Compounds **34** were prepared by a reaction of *N*-amino-4-methylpiperazine with salicylaldehyde or vanillin with subsequent condensation of the hydrazones with aryldiazonium halides.

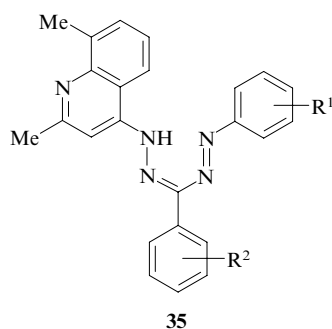


R¹ = 2-OH, 3-OMe-4-OH; R² = 2-OMe, 3-OH, 4-OH, 4-OMe.

Some formazans **34** manifest bactericidal activity against *Staphylococcus aureus* and *Mycobacterium* H₃₇R_v.

The synthesis of formazans containing the 1,8-naphthyridinyl fragment was described and the antibacterial effects of these compounds against Gram-positive and Gram-negative bacteria were investigated.⁵⁸

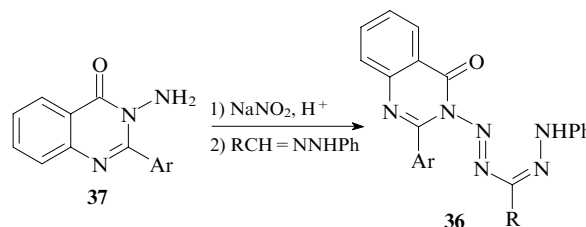
Several quinolinyl-diarylformazans **35** were assayed for tuberculostatic (*Mycobacterium* H₃₇R_v) and antibacterial (*E. coli*, *B. subtilis*, *S. paratyphi* B) activities.⁵⁹



R¹ = 4-OMe, 2-Cl; R² = 2-OMe, 4-OMe, 4-OEt, 4-OH, 3-OH.

Some of recently synthesised formazans containing a *p*-toluenesulfamide fragment possess high fungicidal activity.⁶⁰

A series of 1-[2-aryl-4-oxo-(3*H*)-quinazolin-3-yl]-5-phenylformazans **36** have been synthesised.⁶¹ *N*-Aminoquinazolinones **37** prepared by condensation of the corresponding benzoxazinone with hydrazine hydrate served as the starting compounds in the synthesis of formazans **36**. Diazotisation of compounds **37** and condensation of the diazonium salts with aldehyde phenylhydrazones gave quinazolinylformazans **36**. The latter manifest moderate activity against *Vaccinia* virus.



R = Ph, PhCH=CH.

Antiviral, antibacterial and fungicidal effects of formazan derivatives and the respective tetrazolium salts[†] have been studied.^{62–64}

In some cases, directed synthesis of formazans designed for biological studies was achieved through introduction of various pharmacophore groups into formazan molecules. 1-Phenyl-3-[2-methoxy-4-*N,N*-bis(2-cyanoethyl)aminophenyl]-5-arylformazans were assayed for anticancer and anti-HIV activities.⁶⁵ In a more recent study,⁶⁶ a series of 3-[2-methyl-4-*N,N*-bis(2-cyanoethyl)aminophenyl]-containing formazans were assayed for the same activities. Formazans containing *p*-tolylhydrazine residues were also synthesised,^{67,68} but they were found to be inactive.

A series of formazans containing benzenesulfamido groups were synthesised⁶⁹ and their properties including the fungicidal activity were investigated.

It was found⁷⁰ that hetarylformazans containing the indole fragment at position 3 possess contraceptive properties. Reactions of 6-substituted indole-3-carbaldehydes with (1-naphthyl)aceto-hydrazide and their subsequent coupling with aryldiazonium salts yielded indol-3-ylformazans⁷¹ possessing weak antiviral activity.

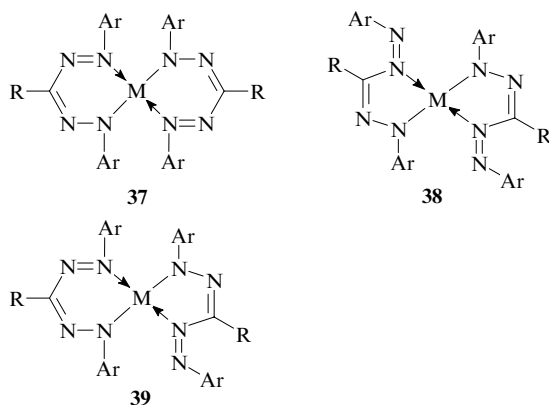
The above-mentioned examples unequivocally demonstrate that formazans hold little promise as basic materials for medicinal drugs. Unfortunately, the papers cited did not provide any information about the relationship between the results obtained and the nature of the substituents in the formazan fragment.

IV. Formazan complexes with metals: structures and applications

Complex compounds based on formazans constitute a well-known class of tetraaza-coordinated metal chelates.^{2,72} These ligands attract attention by virtue of stable intense colour of their metal complexes. Variation of substituents at positions 1, 3 and 5 of the formazan fragment enables the introduction of additional complexing groups which increases the denticity of the formazan ligands.

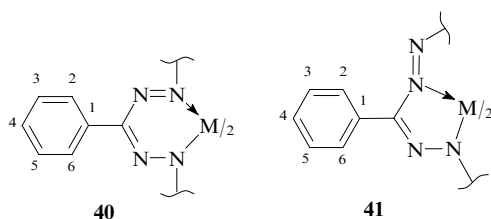
Reactions of 1,5-diarylformazans with metals yield three types of bicyclic compounds. Those containing two six-membered metallacycles (structure **37**) belong to the first type, two five-membered rings (structure **38**), to the second and one six-membered and one five-membered rings (structure **39**), to the third type.

[†] Tetrazolium salts are formed upon oxidation of 1,5-di- and 1,3,5-trisubstituted formazans.²



The calculation of relative stabilities of systems **37–39** by the molecular mechanics method using the PCMODEL software revealed⁷³ that their strain energies are very close, *viz.*, –915, –859 and –976 kJ mol^{–1}, respectively. It is noteworthy that six-membered metallacycles implemented in crystals are far from being energetically favourable. The loss of strain energy of these rings is compensated by intermolecular interactions. If metallacycles contain the same number of fragments, the type of the coordination polyhedron of the complex is determined by the structure of the substituent at the C(3) atom and the nature of the metal complexing agent.

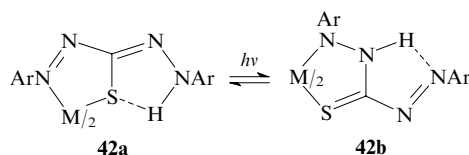
Five- and six-membered rings in diamagnetic formazan complexes with transition metals can be identified by ¹³C NMR spectroscopy.⁷² The transition from the ligand to the metal complex (structure **40**) is accompanied by shielding of the C(1) atom of the phenyl ring at position 3 with a concomitant change in the chemical shift $\Delta\delta = 2.4–5.5$ ppm and deshielding of the C(2) and C(6) atoms ($\Delta\delta = 2.9–4.0$ ppm). Contrariwise, deshielding of the C(1) atom ($\Delta\delta = 1.6–3.0$ ppm) and virtually unchanged chemical shifts of the atoms in the *ortho* position of the benzene ring are more characteristic of structure **41**.



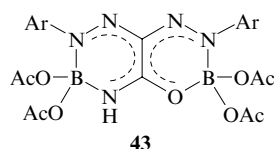
In the majority of metal formazanates, the ligand exists as an anion. Only in the Cu(I)–1,5-diphenylformazan complex (compound **7**) is the copper atom coordinated by a neutral molecule (X-ray diffraction data).⁷² This complex presents interest as a new example of a molecular adduct based on a chelating formazan ligand.

The introduction of additional complexing groups into the formazan molecules not only expands the range of metals able to form complexes with formazans, but also results in formation of new coordination sites. Thus the coordination units of the majority of metal chelates of 1,5-diaryl-3-mercaptoformazans (**42**) contain both nitrogen and sulfur atoms.^{2,72}

Metal complexes **42** are characterised by intrachelate bond isomerism, which underlies their photochromism. The changes in the colour of a substance from orange (or red) to blue (violet) upon irradiation are due to proton transfer and subsequent rearrangement of the π -electron system. It is structure **42b** that corresponds to the photocoloured form. Novel photochromic materials were designed based on such metal complexes.

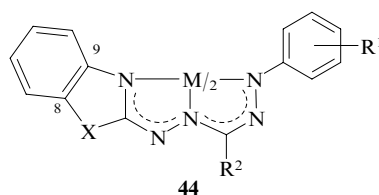


Boron chelates with 1,5-diarylformazans that contain amide groups at position 3 able to bind to the boron atom have been described.^{74,75} For example, in compounds **43** the formazan molecule is involved in the formation of two six-membered heterocycles.



The ability of formazans containing hydroxy, carboxy, *etc.*, groups in the *ortho* position of the aryl substituents at the N(1) and N(5) atoms to coordinate metals, which is accompanied by the formation of five- or six-membered metallacycles, is especially pronounced. Such formazans play the role of tri- or tetradentate ligands.⁷²

The introduction of an α -azaheterocycle into the formazan molecule is equivalent to the presence of an aryl substituent with an additional coordinating group; as a result, the ligands acquire a tridentate character. The structures of hetarylformazan complexes were established by ¹³C, ¹⁵N, ¹⁹⁹Hg and ^{113,111}Cd NMR spectroscopy and X-ray diffraction.^{76–78} These studies demonstrated that Zn-, Cd- and Hg-containing benzazolyformazanates have pseudo-octahedral structures in solutions. The ligand in such complexes is coordinated through the N(1) and N(4) atoms of the formazan fragment and the nitrogen atom of the heterocycle. The changes in the chemical shifts of the heterocyclic substituent (similar to those observed for the transition from the amino to the imino tautomer) and the values of the spin-spin coupling constants of the carbon atoms in the benzene ring fused to the heterocycle [C(8) and C(9) atoms in structure **44**] were used as characteristic criteria for the identification of this coordination mode.⁷⁶



X = S, O; M = Ni, Co, Zn, Cd, Hg, Fe, Mn.
R¹ = H, OMe, Buⁿ; R² = Prⁱ, Buⁿ, Ph.

The chemical shifts in the ¹⁹⁹Hg and ^{113,111}Cd NMR spectra and the spin–spin coupling constants of these nuclei with the ¹³C nuclei of the ligand were measured.⁷⁸ For the first time, ¹⁴N NMR spectroscopy was used⁷⁷ in structural studies of zinc and cadmium complexes **44**, in the first place, with regard to the ¹⁴N nuclei in the coordination units.

It should be noted that independently of the isomeric form of the starting formazan, the complexes formed contained only an imino tautomer in the *EZZ* configuration. The results of X-ray diffraction studies of complexes **44** [M = Ni, X = S, R¹ = 4-Buⁿ, R² = 4-Buⁿ; M = Co, X = S, R¹ = 4-Buⁿ, R² = Ph; M = Fe(II), X = O, R¹ = H, R² = Prⁱ; M = Fe(II), Mn(II): X = S, R¹ = H, R² = Ph]^{79–82} suggest unequivocally the involvement of the nitrogen atom of the benzazole system in the formation of the metallacycle. The configuration of the metal bonds in these

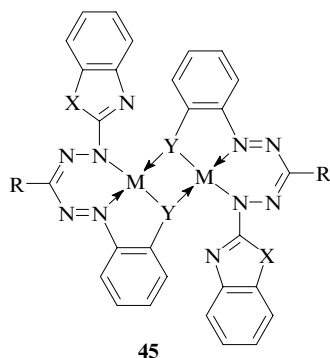
complexes represents a distorted octahedron with an MN_4 coordination unit.

Complexes similar to compounds **44** were also prepared on the basis of formazans containing azine fragments.^{2, 72}

The geometry of metal hetarylformazanates is represented by only one type of a polyhedron, *viz.*, a distorted octahedron; the degree of distortion and the coplanarity of the metallacycles depend on the nature of the metal and the structure of the ligand. In contrast to their aromatic analogues, hetarylformazan complexes contained predominantly five-membered metallacycles.⁸³

It was found⁸² that reactions of 1,3-diphenyl-5-(benzothiazol-2-yl)formazan (**13**) with Fe(III) and Mn(III) ions result in the reduction of metal ions to the oxidation state 2+ and, as a consequence, in the oxidation of the formazan to the tetrazolium salt. The complex compounds formed had a composition L_2M ; the iron complex was diamagnetic. The structures of the formazanates were confirmed by X-ray diffraction data. At the same time, Fe(III) and Mn(III) ions retained a high oxidation state in reactions with 1-(2-carboxyphenyl)-3-alkyl-5-(benzothiazol-2-yl)formazan; the corresponding iron complex was paramagnetic. In the authors' opinion, in the latter case this was due to the involvement of the carboxy group in the complexation with the metals.

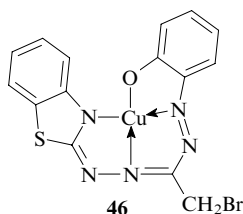
Indeed, 1-hetaryl-5-arylformazans with a hydroxy or a carboxy group in the *ortho* position of the aryl substituent at the N(1) atom can be regarded as tetradentate ligands that form complexes **45** with metals.^{72, 84}



X = NH, NAlk, S; Y = O, OC(O); M = Ni, Zn; R = Alk, Ar.

It is noteworthy that depending on the position of the nitro group in the *N*-aryl fragment in complexes **45** (M = Zn) with 1-[2-hydroxy-4(5)-nitrophenyl]-5-(benzazol-2-yl)formazan the ligand is coordinated to the zinc atom either in the hydroxyazo (similar to nickel complexes) or in the quinone–hydrazone form.⁸⁴ In contrast to nickel formazanates, zinc complexes readily undergo ligand exchange reactions with amines. Owing to this property, such complexes have been used for the design of thermochromic systems with positive and negative thermoinduction effect.

The compositions and structures of coordination units in Cu(II)–benzothiazolylformazan complexes were studied by EPR spectroscopy.⁸⁵ It was found that depending on the nature of the substituents at the N(1) atom, the copper atom acquires a square-planar or a pseudo-tetrahedral configuration. For L_2Cu complexes prepared in an excess of a ligand, the coordination unit CuN_4 formed contained the N(1) and N(5) atoms of formazan (see structure **37**). 1-(2-Hydroxyphenyl)-5-(benzothiazol-2-yl)formazan gave copper complex **46** (LCu) the copper atom in which is



coordinated to the nitrogen atoms of the heterocycle, to the N(1) and N(4) atoms of the formazan chain and to the oxygen atom of the hydroxy group (the coordination CuN_3O unit).

Mono- and binuclear metal formazanates present interest as catalysts for diverse chemical reactions. Thus benzazolylformazan–nickel complexes manifest high catalytic activity in the dimerisation of ethylene.⁸⁶ The synthesis of novel homo- and heterobimetallic catalysts based on 1,5-diaryl-3-ferrocenylformazan complexes has been described.⁸⁷

The structures and properties of thorium(IV), uranium(VI) and REE 3-acetyl- and 3-cyano-1,5-diarylformazanates have been studied.^{88–91} It was found that the stabilities of REE 1,3,5-triphenylformazanates correlated with the basicity of the ligand as well as with the ionisation potential, electronegativity and the ionic radius of the metal.

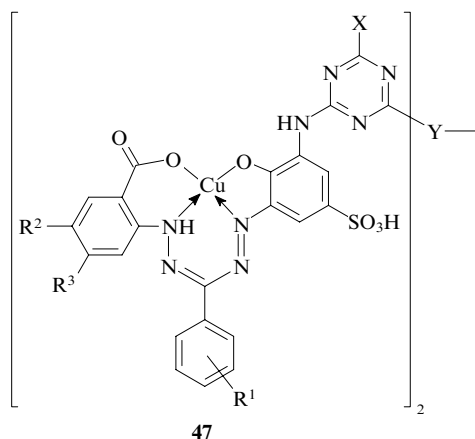
Ligands containing two formazan fragments were used in the synthesis of polymetallic complexes.⁹² Tetranuclear complexes with cobalt, nickel, copper, manganese, zinc, cadmium and mercury ions were prepared from bis[1-phenyl-3-(2-hydroxyphenyl)formazan]phenyl ether. The results of spectroscopic and magnetic studies suggest that Co(II)-, Cu(II)- and Mn(II)-containing complexes have an octahedral or a distorted octahedral structure; Ni(II) derivatives have a planar structure, while Zn(II), Cd(II) and Hg compounds have a tetrahedral structure. Palladium complexes with formazans containing a heterocyclic fragment (pyrrole and 1-methylpyrrole) were synthesised⁹³ and their properties were investigated.

Potentiometry, conductometry, IR spectroscopy, thermogravimetry and measurements of electroconductivity and magnetic susceptibility were used for the study of complexation of praseodymium, neodymium, samarium, gadolinium, holmium, erbium, thulium and ytterbium ions with symmetric 1,5-diphenyl-3-cyanoformazan.⁹⁴ In a study⁹⁵ of complexation of benzazolylformazans with uranyl ions and some REE, it was demonstrated that uranyl complexes have mainly the composition $L(UO_2)$ in solution and in the crystalline state, while benzazolylformazan–REE coordination complexes have the composition L_2M .

The same authors⁹⁶ studied the complexing properties of 1-(2-hydroxyphenyl)-5-benzazolylformazans with respect to scandium(III) ions in the pH range 3–10. The composition of scandium formazanates (L_2Sc) was confirmed by IR and electronic spectroscopy and the ligand exchange method, while the structure of the coordination unit depends on the nature of the heterocycle.

The fluorescence properties of formazan–REE complexes were studied in solutions and in monolayers.⁹⁷ For the first time, fluorescence in the IR spectral region of complexes of 1-aryl-3-alkyl-5-benzothiazolylformazans devoid of additional complexing groups was detected. It was found that the efficiency of fluorescence depends on the structure of formazans, nature of the metals and state of the surface of Langmuir–Blodgett films as supports.

Many properties of formazan–metal complexes (in the first place, their catalytic, photochemical and thermochromic properties) are connected with conversions that involve the metal chelate unit. However, only functional groups of the ligand can be involved in reactions of metal formazanates without affecting the nearest environment of the metal centre. These reactions include acylation of peripheral groups by acid derivatives (including those of the heterocyclic series), alkylation, reactions with azines (most commonly, introduction of pyrimidine and *sym*-triazine), *etc.*² These reactions are usually employed for the preparation of active metal-containing formazan dyes, which have long been used for the dyeing of miscellaneous materials. The main advantages of such dyes include high water and light resistance, good colour characteristics, *etc.* The methods for their preparation and dyeing technologies are usually covered by patents.⁹⁸ For example, a vast variety of copper complexes based on polydentate triarylformazans (structure **47**) are used as dye-stuffs for cellulose materials.⁹⁹



$R^1 = \text{H}, \text{SO}_3\text{H}, \text{OH}, \text{Cl}, \text{OMe}, \text{C}(\text{O})\text{Alk}$; $R^2, R^3 = \text{H}, \text{SO}_3\text{H}$;

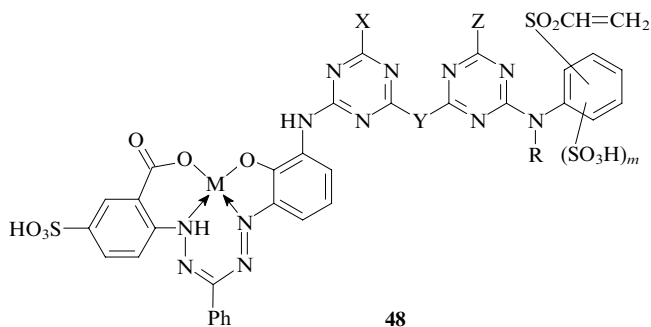
$X = \text{N} \begin{array}{c} \diagup \diagdown \\ \text{O} \end{array}, \text{NHCH}_2\text{CH}_2\text{OH}, \text{N}(\text{CH}_2\text{CH}_2\text{OH})_2$;

$Y = \text{HN} \begin{array}{c} \text{---} \text{C}_6\text{H}_4 \text{---} \text{C}_6\text{H}_4 \text{---} \text{NH} \end{array}, \text{HN} \begin{array}{c} \text{---} \text{C}_6\text{H}_3(\text{OMe}) \text{---} \text{C}_6\text{H}_3(\text{OMe}) \text{---} \text{NH} \end{array}$.

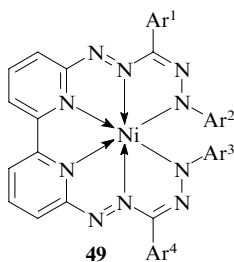
The synthesis of metal complexes with aryl- and hetarylformazans containing a vast variety of substituents in different positions as promising pigments for cellulose tissues, cotton and synthetic fibres was patented.^{100–103} All these dyes contain sulfo groups and triazine fragments able to bind to fibres, whereas copper, nickel or cobalt ions usually play the role of metal centres, which made it possible to attain various shades of blue or green colour.

The use of formazan complexes **48**, which represent active dyes with good colour properties, as dyestuff for natural and synthetic cotton and hemp has been patented.¹⁰⁴

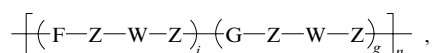
The use of a mixture of nickel – 1,3-diaryl-5-(2-pyridyl)formazan complexes **49** as a dye has been studied.¹⁰⁵ By varying aryl substituents, one can obtain dyes with different colour gamut.



$M = \text{Cu}, \text{Ni}$; $X, Z = \text{F}, \text{Cl}, \text{Br}$; $Y = \text{NH}(\text{CH}_2)_m\text{NH}$, etc.



Dyeing entails the use of mixtures of various classes of dyes. For example, formazan–cyanine copolymer dyes for the preparation of optical self-recording layers and sensors contain up to 70%–100% of molecular fragments of the general formula:



where F is the fragment of the formazan dye; G is the fragment of the cyanine dye; W is the (cyclo)alkylene, arylene, etc., bridging group and Z is the residue of a carbonic acid derivative, urea, an ester or an amide.¹⁰⁶

The use of composites containing formazans, azo dyes and benzoxazines carrying different substituents in each fragment, has been patented.¹⁰⁷ Such mixtures are distinguished for high colourability and high stability and are used as dyestuff for cellulose fibres. Mixtures of azo and formazan dyes, or pure formazan dyes manifest a synergistic effect in the formation of the colour gamut.^{108, 109}

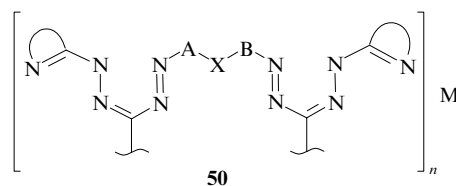
A mixture based on cellulose triacetate, a formazan derivative and an organic solvent was proposed for the manufacture of light- and thermally inhibited films.¹¹⁰ Here, the nickel complex of 1-(1-methylbenzimidazol-2-yl)-3-methyl-5-(*p*-sulfamidophenyl)-formazan was used as the dyestuff.

The use of formazans, e.g., Zincon [1-(2-hydroxy-5-sulfo-phenyl)-3-phenyl-5-(2-carboxyphenyl)formazan], for staining proteins in polyacrylamide gels¹¹¹ demonstrated their advantages over traditional staining reagents, e.g., Brilliant Green.

An increasing attention in the past decade was given to the development and application of environmentally safe dyes. Formazan complexes with metals were synthesised where chromium, cobalt and copper ions were replaced by, e.g., iron ions.^{112, 113} Iron complexes based on 1,5-diaryl-3-cyanoformazans with the composition $\text{Fe} : \text{L} = 1 : 2$ were also synthesised.¹¹⁴ The structures of these compounds and their colour characteristics were studied by ¹H NMR, FAB (Fast Atom Bombardment Mass Spectrometry) and electronic spectroscopy. The complexes were used as acid dyestuffs for wool and polyamide fibres. A recently published review¹¹⁵ is devoted to the chemistry of this type of dyes.

Yet another trend in the practical application of metal complexes based on formazans is their use as materials for registration, recording and storage of information.^{116–118} The structures and properties of metal formazanates as optical recording media are described in a series of Japanese patents.^{119–122} It is of note¹¹⁹ that the recording layer contains a dye with the absorption maximum at 700–750 nm, is characterised by high photo and storage stability and is used for recording information on CD carriers.

Metal complexes **50**, which contain two formazan fragments with residues of nitrogen heterocycles, are described in a patent.¹²³ They were synthesised from formazans directly linked through methylene or sulfonyl bridges.



A, B is arylene; X = CH₂, SO₂; M is a divalent metal.

The material based on complexes **50** manifests high light resistance and good storage stability and is used for recording DVD.

There is an increasing number of patents devoted to the use of metal formazanates as optical elements (see, e.g., Refs 124–130). The use of a mixture consisting of cyanine or phthalocyanine and formazan derivatives for the manufacture of materials with high photo and storage stability has been described.^{124, 130} Such elements are usually employed in the commercial production of CD.

Yet another area of application of formazan-based metal chelates is worth noting, viz., a method for the manufacture of thermosensitive materials for lithographic boards based on complexation of formazans.¹³¹

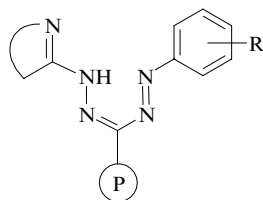
V. Formazan-containing polymers

The advent and development of modern technologies brought forth the necessity of a search for novel materials endowed with desired properties. To such materials one can relate, in particular, formazan-containing polymers including high-molecular-mass metal complexes that have already found wide practical application. Several approaches to the synthesis of such polymers have been developed.

The simplest method includes introduction, into the formazan molecule, of polymerisable fragments. The preparation and properties of polymeric materials containing formazan units are described in a review.¹³² Formazans containing a styrene residue at positions 1 and 3 were subjected to anionic (or radical) polymerisation.¹³² The polyformazans thus prepared were used for the preparation of polymeric metal complexes, polyverdazyl radicals and polytetrazolium salts. The main advantage of this approach to the synthesis of polyformazans and their complexes is that the composition of the polymer formed and the structure of the metal chelate unit correspond to those of the original monomer. However, its practical application is limited due to possible complications during polymerisation.

The synthesis of polyformazans by polymer-analogous transformations was more successful. Thus numerous formazans containing polymeric fragments at position 1 were obtained from poly(*m*-aminostyrene). Polyacrolein and poly(*p*-formylstyrene) were used for the synthesis of formazans containing polymeric fragments at position 3. Such polymeric formazans were used for the synthesis of chelates with the coordination unit MN_4 .¹³² Some poly(acroleinphenylformazans) are efficient selective ion-exchangers for extraction of heavy metals: under certain conditions they bind Cu(II) and $UO_2(II)$ ions and do not react with Ni(II) and Co(II) ions. Analogously, poly(styrene-divinylbenzene) with an aldehyde group was transformed to hetarylformazan employed for the preparation of novel adsorbents.¹³³ The sorption properties of such polymers with respect to heavy metals and the possibility of selective extraction of copper ions were investigated.

Modification of cellulose by hetarylformazans is described in a monograph by V. M. Ostrovskaya *et al.*¹³⁴ This work deals with the description of different methods for immobilisation of formazan-containing reagents and provides examples of their practical applications. Many cellulose derivatives of hetarylformazans **51** were prepared by a reaction of aldehyde-cellulose with hetarylhydrazones and subsequent coupling with aromatic diazo compounds.



51

(P) is cellulose; R = H, OMe, SO_3H , CO_2H , Cl;

 2,6- and 4,6-disubstituted pyrimidines, thiazole, pyrazole, benzazoles, *etc.*

It was found¹³⁵ that the cellulose backbone exerts the same effect on the chromaticity of formazans as the alkyl substituent at position 3. The bathochromic colour reactions of formazans attached to modified α -cellulose at position 6 with ions of some heavy, precious and rare-earth metals were studied. Irregular polydentate 1-aryl-5-(benzazol-2-yl)formazan-6- α -celluloses were used for the manufacture of reagent test papers (RTP).¹³⁵ Formazans covalently grafted to cellulose exceed formazans

adsorbed on cellulose in both selectivity and stability, presumably due to higher structural rigidity. Cellulose benzoxazolylformazans are promising analytical reagents for determination of metals by test methods.

Several approaches have recently been developed to the quality control of copper(II) test reagents based on irregular polydentate α -celluloses including those containing 1-(4-methyl-6-methoxypyrimidin-2-yl)-5-phenyl-, 1-(4-methyl-6-methoxypyrimidin-2-yl)-5-(2-carboxyphenyl)- and 1,5-bis(4-methyl-6-methoxypyrimidin-2-yl)formazan units.¹³⁶ The efficiency of such materials used as tubes and multilayer test reagents is usually determined from the contrast of their colour reactions with copper(II), which are accompanied by liberation of equivalent amounts of hydrogen ions and formation of chelates.

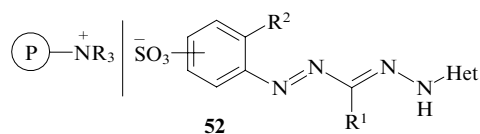
Celluloses modified by benzothiazolyl-, benzoxazolyl- and 4,6-dimethylpyrimidinylformazans were studied in detail^{137–140} and characterised by diffuse reflectance spectroscopy. The complexation of these polymers with copper, nickel, cadmium, zinc, lead, silver and mercury ions revealed certain differences in their sorption capacities. The efficiency of extraction of metal ions depends on both the structure of the immobilised formazan group and the complexation conditions. Certain formazan-containing polymers can be used as reagents for the concentration of metal ions, *e.g.*, Cu(II), Ni(II), Pd(II), Hg(II); these polymers served as the basis for the development of novel RTP for the analysis of drinking water.

Sorption of heavy metals by membranes prepared by modification of sheet cellulose with formazan derivatives is accompanied by profound colour transitions.¹³⁸ Such membranes have the shape of coloured paper discs and are used, in particular, for purification of distilled and tap water from trace amounts of heavy metals and iron (the metal content in the membranes is determined by visual inspection and X-ray fluorescence analysis). Studies of sorption and chromogenic complexing properties of these membranes with respect to palladium and silver ions and some REE resulted in the development of a procedure for measuring palladium(II) concentrations in process solutions using 1-phenyl-5-(4,6-diphenylpyrimidin-2-yl)formazan-6- α -cellulose.¹³⁹ Hetarylformazan-6- α -celluloses, which supplemented the database of novel indicator materials, are among promising highly sensitive chromogenic ion-exchange polymeric reagents.¹⁴⁰ They are characterised by a combination of reversible complexation colour and redox reactions.

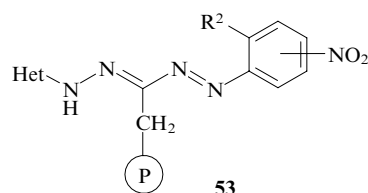
At present, formazans fixed on solid substrates by physical or chemical forces have found wide application as sorbents. The fixation is achieved by covalent immobilisation, ion exchange or physical sorption.¹³² The first experiments aimed at immobilisation of formazans on polymeric substrates employed compounds containing amide fragments at position 3 of the formazan chain. Sorbents obtained by immobilisation of aminophenyl-containing formazan on chloromethylated polystyrene manifested anion-exchange properties and high selectivity with respect to noble metals. They allowed isolation of trace amounts of Pd(II) from ammoniacal solutions containing a 10-fold excess of Ni(II). A modified ion-exchange sorbent for the separation of Ag(I) from a 1000-fold excess of Cu(II) was prepared by immobilisation of sulfoformazans on an aminomethylated polystyrene support. The use of silica gel as a substrate for immobilisation of sulfoformazans allowed preparation of an efficient ion-exchanger for pre-concentration and separation of Ag(I) ions from Pd(II) and Pt(II) ions.

Selective sorbents for Hg(II) from aqueous media were prepared by fixation of sulfoformazans on cellulose and immobilisation of dithizone on a polyurethane foam.¹³² These sorbents are used for the isolation of mercury from domestic and industrial waste waters in a broad range of pH.

Several papers^{141–145} describe the results of immobilisation of hetarylformazans on anion-exchangers. Modified ion-exchangers **52** and **53** were prepared by ion-exchange and condensation.



52



53

(P) is a polymer; $R^1 = \text{Me, Et, Pr}^i, \text{Ph}$; $R^2 = \text{H, OH}$.

The cross-linked amino-containing ion-exchanger AN-20 and commercial ion-exchangers AV-17, AN-18 and AN-31 differing in basicities were used as polymeric supports. Benzothiazole, benzoxazole and benzimidazole fragments and 4,6-disubstituted pyrimidine were used as heterocyclic components of formazans. The stabilities of the reagents synthesised in different media were found to depend on the basicity of the anion-exchanger. The sorption characteristics of the modified ion-exchangers with respect to a broad range of metals were investigated. They were used for the qualitative detection of trace elements in natural and waste waters and selective isolation of copper and scandium ions from solutions containing accompanying elements. For example, benzoxazolylformazan-modified anion-exchangers **52** selectively bind Sc(III) ions from solutions also containing Ti(IV) and Zr(III). The sorption properties of modified ion-exchangers depend on the structure of formazans immobilised, nature of the metal and sorption conditions. Representatives of compounds **52** and **53** can be used for efficient separation of copper and nickel in low-concentration acidic solutions, for selective isolation of mercury(II) in the presence of zinc(II) and cadmium(II) and for separation of silver(I) from nickel(II) and cobalt(II) and of zinc(II) from cadmium(II). Some of these polymers were proposed for separation of REE mixtures and preconcentration of lead(II) ions.

Analytical sorption-spectroscopic and test methods are based on the use of the known formazans in a new quality, *viz.*, in immobilised form, are actively developed of present. Fibrous materials and ion-exchange tissues are popular solid-phase supports for their immobilisation. Especially promising is a flow-through method for the preconcentration of chromium(VI) compounds on polyacrylonitrile discs filled with finely dispersed strongly basic anion-exchangers. Treatment of the disc with a solution of 1,5-diphenyl-3-hydroxyformazan in a dynamic mode ensures binding of chromium in a complex in the solid phase; metal ions are detected by the diffuse reflectance method.¹⁴⁶ Reagents preimmobilised on the surface of the support have got the name flow sensor systems.

Dithizone is widely used for this purpose. A test method for semi-quantitative determination of zinc by its sorption from alkaline borate solutions onto tissue discs has been developed.¹⁴⁷ Subsequent detection of zinc ions was carried out by visual inspection following treatment with dithizone solutions from the appearance of crimson colour. In another study,¹⁴⁸ the same authors studied colour reactions of zinc ions with dithizone on vinylpyridinium-containing tissues and fibrous materials filled with anion-exchangers using diffuse reflectance spectroscopy. Sensitive optical sensors based on immobilised dithizone for the presence of uranium(VI), mercury(II) and lead(II) compounds have been developed.¹⁴⁹ The use of these materials for direct determination of mercury in various waters revealed that the most sensitive reaction was observed in the case of immobilisation of dithizone on polyamide (*e.g.*, caprone, capropore or halipore) membranes.

Non-covalent immobilisation of benzazolyl- and pyrimidinyl-formazans on polyacrylonitrile fibres filled with the anion-exchange resin AV-17 was carried out and the effects of various

factors on the sorption properties of the polymers synthesised with respect to some heavy metal ions were investigated.¹⁵⁰ Among these compounds, selective sorbents were found for the isolation of copper ions in the presence of nickel, zinc and cadmium ions. Different hetarylformazans were immobilised on polyacrylonitrile fibres filled with the anion-exchanger AN-31 by covalent binding, ion exchange and physical sorption.¹⁵¹ Studies of the properties of these sorbents demonstrated that they can be used for sorption-spectroscopic determination of heavy metals.

Metallopolymeric systems have been prepared on the basis of immobilised formazans. High efficiency of such products is due to strong multipoint fixation of the metal as the complex with a formazan. Thus the aforementioned hetarylformazan-modified anion-exchangers **52** and **53** were used as ligands in the synthesis of polymeric metal complexes.¹⁵² Copper complexes of these materials prepared by sorption of Cu(II) ions from copper sulfate solutions were studied by EPR.¹⁵³ By varying the conditions of synthesis (chemical nature of the formazan, concentration ratio, method of synthesis of metal complexes on solid supports), one can obtain formazanates with different compositions (CuN_4 , CuN_3 or CuN_3O) and structures of the coordination metal centre. Polymeric metal complexes were also synthesised⁸⁴ by immobilisation of preformed Cu(II) or Fe(II) complexes with sulfobenzothiazolylformazan on an ion-exchanger. In this case, structural features of the coordination sphere of the monomeric analogues are retained.

Formazan-containing polymers were examined as catalysts of decomposition of aqueous solutions of H_2O_2 and liquid-phase oxidation of sulfides and hydrogen sulfide. The analysis of catalytic properties of copper- and iron-containing sorbents based on benzazolylformazan-modified anion-exchangers demonstrated^{154, 155} that the best results were obtained at the maximum saturation of the coordination unit of the metal chelate. In the case of copper complexes, the catalytic activity depends on both the content of copper ions and the structure and composition of the metal chelate unit. For example, the activity with respect to decomposition of H_2O_2 decreased on going from copper complexes (CuN_4) with a distorted square-planar coordination mode to mixed nitrogen-oxygen-containing complexes with a square-planar coordination mode.

* * *

The formazan systems considered in this review manifest extremely high tautomeric and conformational flexibilities. The use of such chelating ligands makes it possible to obtain complex compounds that present interest as subjects for solution of the problem of competitive coordination and effect of the nature of the polyhedra on the number of units in the metallacycle. It is noteworthy that in parallel with traditional applications of formazans and their metal chelates as dyes and photochromic agents some new areas emerge, *e.g.*, for their application as optical filters, thermosensitive elements, catalysts, optical sensors, test reagents and modified polymeric materials.

This review has been written with the financial support of the Russian Foundation for Basic Research (Project Nos 05-03-32023 and 06-03-08040).

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^a — *Sci. Appl. Photogr. (Engl. Transl.)*

^b — *Crystallogr. Rep. (Engl. Transl.)*

^c — *J. Struct. Chem. (Engl. Transl.)*

^d — *Russ. J. Gen. Chem. (Engl. Transl.)*

^e — *Chem. Heterocycl. Compd. (Engl. Transl.)*

^f — *Russ. J. Org. Chem. (Engl. Transl.)*

^g — *Russ. J. Inorg. Chem. (Engl. Transl.)*

^h — *Russ. J. Anal. Chem. (Engl. Transl.)*

ⁱ — *Russ. Chem. Bull., Int. Ed. (Engl. Transl.)*

^j — *Mendeleev Chem. J. (Engl. Transl.)*

^k — *Russ. J. Coord. Chem. (Engl. Transl.)*

^l — *Polym. Sci. (Engl. Transl.)*

^m — *Russ. J. Appl. Chem. (Engl. Transl.)*

Molecularly imprinted materials: synthesis, properties, applications

G V Lisichkin, Yu A Krutyakov

Contents

I. Introduction	901
II. Classification of molecular imprinting methods	902
III. Physicochemical fundamentals of molecular imprinting	907
IV. Molecular imprinting on mineral supports	909
V. The applications of materials capable of molecular recognition	915
VI. Conclusion	916

Abstract. This review is devoted to the method of molecular imprinting. The physicochemical fundamentals and mechanisms of covalent and non-covalent molecular imprinting aimed at the development of organic polymeric sorbents capable of molecular recognition are considered. Attention is focused on the preparation of molecular imprints on mineral supports. The mechanisms of molecular recognition in adsorption are discussed. Application fields of materials with molecular imprints are briefly surveyed. The bibliography includes 112 references.

I. Introduction

The molecular imprinting method consists of the synthesis of organic or inorganic polymers capable of recognising molecules that were used as templates during their synthesis.^{1–10} The recognition becomes possible because the structure of such polymers includes areas (the so-called imprints) that can specifically interact (complementary interactions) with the template molecules or compounds with similar structures. The concept of complementarity includes the shape and size matching of an imprint to the template as well as the presence in the imprint of auxiliary functional groups capable of interacting with functional groups in the template.

The procedure of preparation of polymeric materials with molecular imprints includes three stages. In the first stage, a mixture of functional monomers and a template molecule is prepared. The so-called pre-assembling, *i.e.*, the formation of a molecular pre-polymerisation complex between the monomer and the template molecule takes place in this stage (Fig. 1). These complexes can be formed as a result of either the covalent bonding (covalent molecular imprinting) or non-covalent intermolecular interactions (hydrogen bonding, ion–ion and ion–dipole interactions, *etc.*). In the latter case, we deal with non-covalent molecular imprinting. In the second stage, polymerisation (polycondensation) of pre-polymerisation complexes with a large

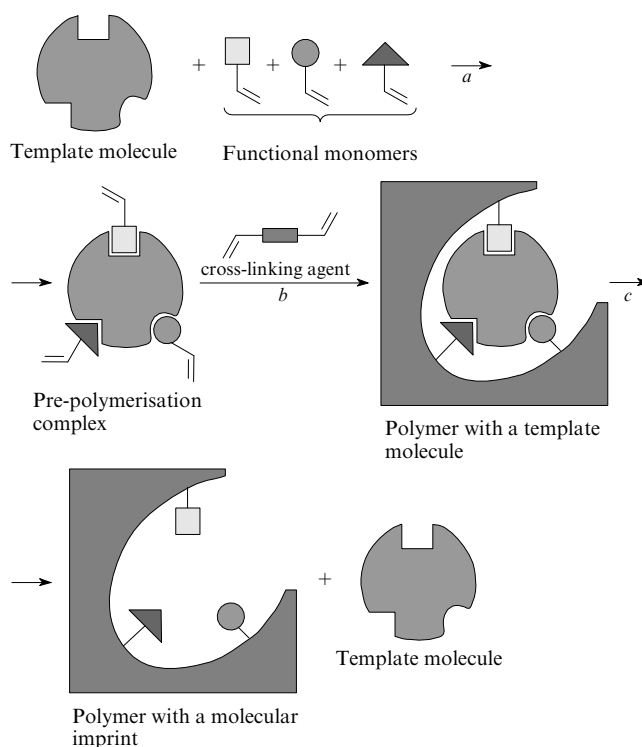


Figure 1. Synthesis of polymeric materials with imprints.

(a) Formation of a pre-polymerisation complex of functional monomers with a template; (b) formation of a polymeric matrix incorporating the template molecules; (c) removal of the template molecules from the polymeric matrix and the formation of cavities complementary to the template molecule.

G V Lisichkin, Yu A Krutyakov 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 46 38, e-mail: lisich@petrol.chem.msu.ru
(G V Lisichkin), tel. (7-495) 939 36 66,
e-mail: yurii@petrol.chem.msu.ru (Yu A Krutyakov)

Received 24 November 2005

Uspekhi Khimii 75 (10) 998–1017 (2006); translated by T Ya Safonova

excess of a cross-linking agent results in the formation of a polymeric matrix that contains areas with functional groups arranged in positions determined by the template molecules. The third stage consists of either the removal of template molecules from the polymeric matrix by liquid extraction methods (for non-covalent imprinting) or the cleavage of chemical bonds between the template molecule and the polymer (for covalent imprinting). As a result, the material acquires cavities that, in ideal, should match the template molecule in their size, shape and the arrangement of functional groups.

It can be expected that the synthesised material will exhibit high specificity with respect to template molecules or molecules of compounds with similar structures. In nature, such specificity is typical of antibodies; this is why the materials prepared by molecular imprinting are often referred to as 'antibody mimics'.

II. Classification of molecular imprinting methods

The methods of synthesis of polymeric materials capable of molecular recognition can be classified according to the following criteria: (1) the nature of the polymeric matrix, (2) the method of preparation of a complex between the functional monomer and the template molecule, (3) the structure of imprints obtained.

Depending on the nature of functional monomers used in the synthesis of polymeric matrices, all materials capable of molecular recognition can be divided into organic and inorganic. The synthesis of organic matrices with molecular imprints involves the use of organic functional monomers and cross-linking agents containing C=C bonds. Inorganic matrices are usually prepared by polycondensation. Most often, functionalised silanes serve as the monomers and tetraethoxysilane as the cross-linking agent.

Depending on the method of preparation of pre-polymerisation complexes between a functional monomer and a template molecule, the methods of synthesis of materials capable of molecular recognition are conventionally divided into the imprinting in pre-assembled systems (the pre-polymerisation complex is synthesised beforehand) and the imprinting in self-assembling systems (the pre-polymerisation complex is synthesised immediately during the polymerisation). Imprinting in pre-assembled systems is referred to as covalent imprinting, because the complex is formed as a result of covalent interactions. Molecular imprinting in self-assembling systems is called non-covalent. In the latter case, the pre-polymerisation complex is formed as a result of non-covalent intermolecular interactions between template molecules and functional monomers.

Finally, molecular imprints can be formed either on the surface (2D-imprinting) or in the bulk (3D-imprinting) in the presence of appropriate solvents. In addition, the polymeric layers capable of molecular recognition can be applied onto pre-fabricated supports (the latter usually represent inorganic oxide supports with hydroxyl groups uniformly distributed over the surface[†]). Hence, the third classification is based on the structure of obtained imprints.

1. Non-covalent molecular imprinting

In the method of non-covalent imprinting, the polymerisation of functional monomers with a great amount of a cross-linking reagent in the presence of template molecules affords a highly cross-linked polymer incorporating template molecules. Template molecules are fixed within the polymeric matrix by non-covalent interactions (hydrogen bonding, electrostatic or π - π -interactions) with the functional groups of the monomers. Following removal of the template, which is usually carried out by solvent extraction, regions emerge in which functional groups are arranged complementary with respect to the functional groups in the template molecule. Being relatively simple and universal, the non-covalent approach is used to date most widely among the methods of molecular imprinting.

The first adsorbents with enhanced specificities with respect to molecular templates were synthesised by Polyakov¹¹ in the early 1930s. He demonstrated that silica gels formed in the presence of various alkylbenzenes exhibited enhanced (by approximately 15%) selectivity with respect to the adsorption of those particular hydrocarbons that have been used in their synthesis. Later, these experiments were continued with involvement of a wider range of

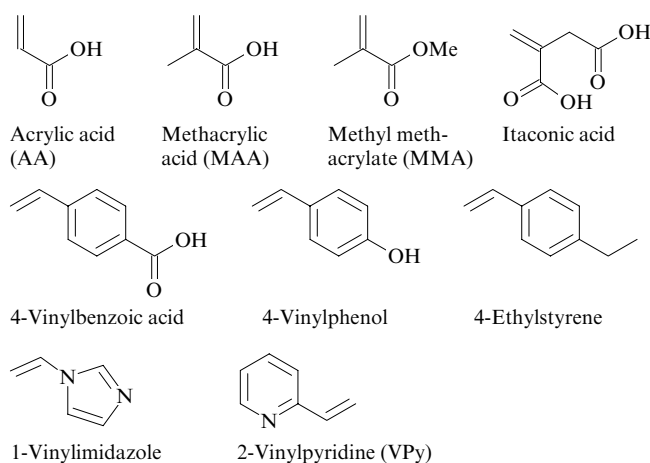
template molecules.^{12,13} In 1960, Patrikeev, Balandin *et al.* published a paper¹⁴ in which they showed that the pore size and adsorption properties of silica gels depend on the type of the substance introduced as a template at the stage of their synthesis. Silica gels thus obtained play the role of molecular sieves with respect to the template molecules.

The idea of changing the adsorption properties of solid adsorbents by the introduction of template substances at the stage of their synthesis was independently advanced by Pauling. He entrusted its experimental verification to his disciple Dickey. By allowing the solid structure of a sorbent to form in the presence of a compound for which this specific sorbent was intended, Dickey showed¹⁵ that the material synthesised can indeed selectively retain the substance that has been used as the molecular template in the synthesis of this material. In the synthesis of an adsorbent for Methyl Orange (1) and Ethyl Orange (2) dyes, in one of experiments the solution of sodium silicate was acidified in the presence of Methyl Orange (1) to afford a hydrogel, which contained molecules of this dye in its structure (Scheme 1). The material formed upon drying of the hydrogel and removal of the dye by extraction turned out to adsorb a double amount of Methyl Orange (1) as compared with Ethyl Orange (2).

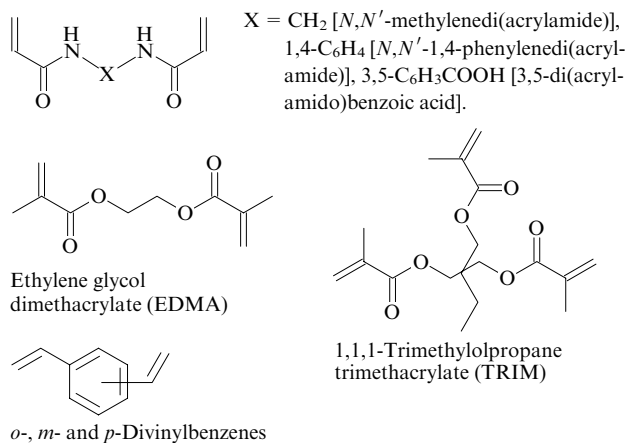
Later, Dickey's concepts on the mechanism of molecular recognition were corrected by Wulff *et al.*^{16,17} who have shown that it is the complementarity between functional groups in the template molecule and in the recognition site that is the driving force of molecular recognition rather than the shape and size matching of the polymeric-matrix cavity to the template.

Below, we show examples of functional monomers and cross-linking agents that are used in the synthesis of selective sorbents by the non-covalent molecular imprinting method.¹⁸

A. Functional monomers

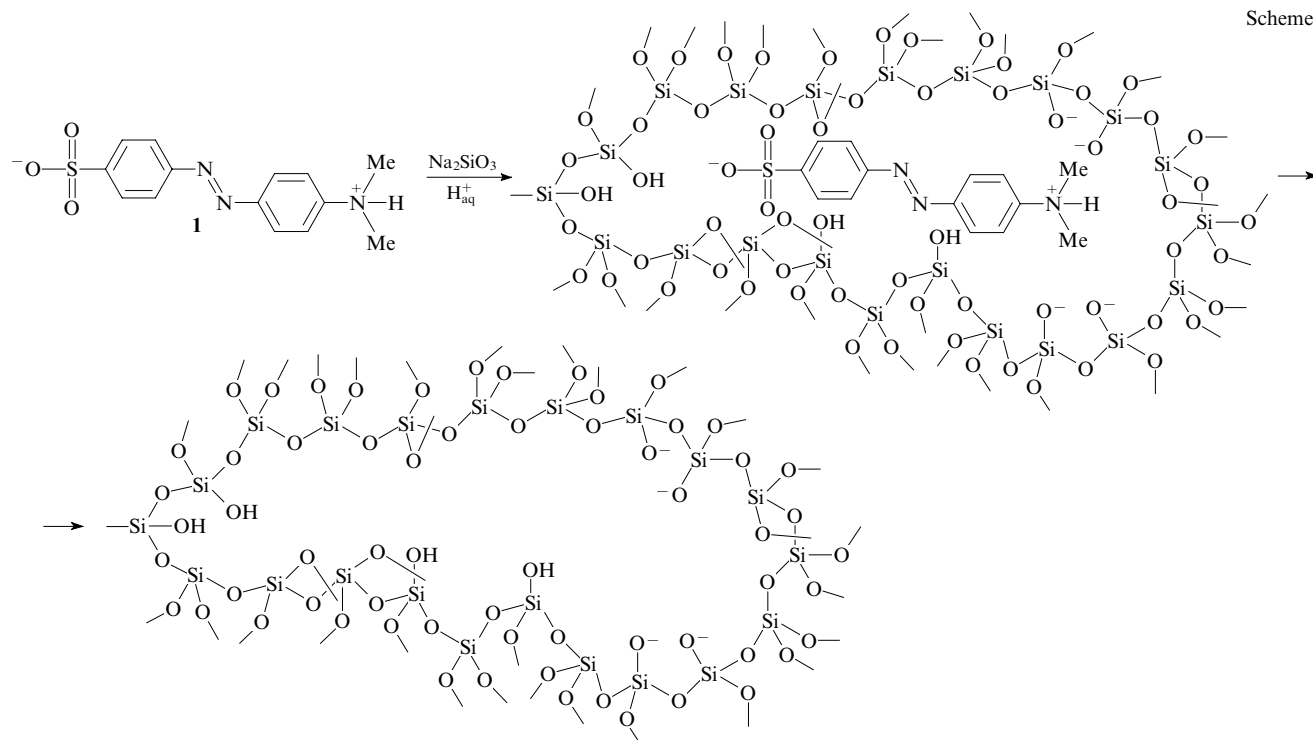


B. Cross-linking reagents



[†] For silica, the surface concentration of hydroxyl groups is 4.6 nm^{-2} . On the metal surface, hydroxyl groups are formed as a result of oxidation followed by hydroxylation.

Scheme 1

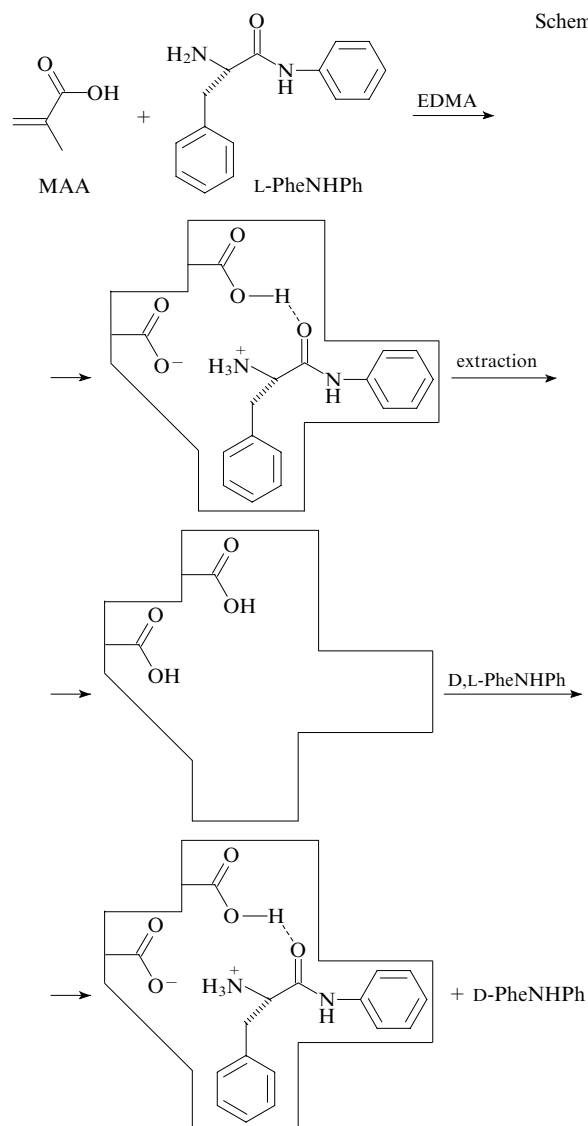


Functional monomers are selected in such a way as to provide their interaction with the functional groups of the template molecule at the stage of synthesis of the polymer. Methacrylic acid is used most often as the functional polymer because it can form complexes with many template molecules, *viz.*, with amines by forming an ionic bond and with amides, carbamates, alcohols, *etc.* by forming a hydrogen bond. It is known that electrostatic interactions are stronger than van der Waals interactions (particularly, hydrogen bonds); hence, the polymers that form ionic bonds with template molecules exhibit higher selectivity than those that form only hydrogen bonds. This was taken into account in the preparation of chiral stationary phases for the separation of racemates by HPLC (High-Performance Liquid Chromatography) (*e.g.*, for the separation of anilides of D- and L-phenylalanine, Scheme 2).^{19–21}

Studying the nature of molecular recognition of template molecules by polymers synthesised with involvement of non-covalent imprinting is a complex task. The literature contains relatively few publications devoted to the mechanism of such recognition.

The formation of non-covalent intermolecular monomer–template complexes in pre-polymerisation systems was proved by UV and NMR spectroscopy^{19,22} as well as by chromatographic methods. In particular, the effect of the functional monomer : template molar ratio in the pre-polymerisation mixture on the chromatographic characteristics of the resulting sorbents was investigated.²³ A series of polymers based on methacrylic acid (functional monomer) and ethylene glycol dimethacrylate (cross-linking agent) were prepared in the absence (control sample **P0**) and in the presence of a molecular template (template samples **P1–P6**). (–)-Nicotine served as the molecular template. The functional polymer : template molar ratio was varied from 4 : 1 to 1 : 10. The methacrylic acid : nicotine molar ratio was shown to have a substantial effect on the amount and quality of specific adsorption sites formed during the polymerisation, which followed from the results of chromatographic separation of a mixture of (–)-nicotine and 4,4'-bipyridyl on these polymers.

Scheme 2



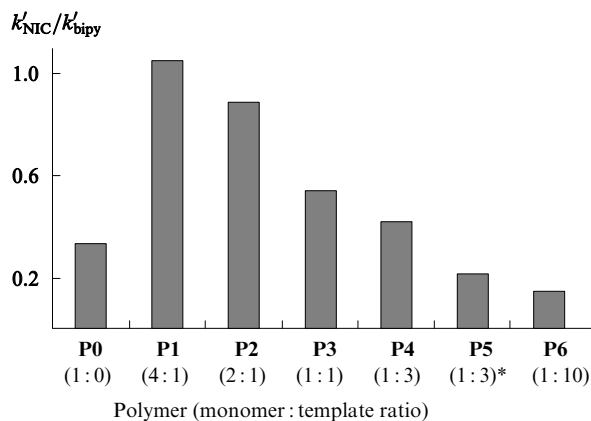
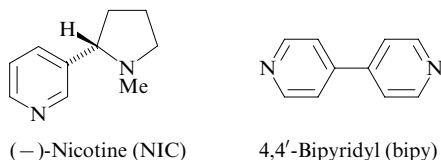
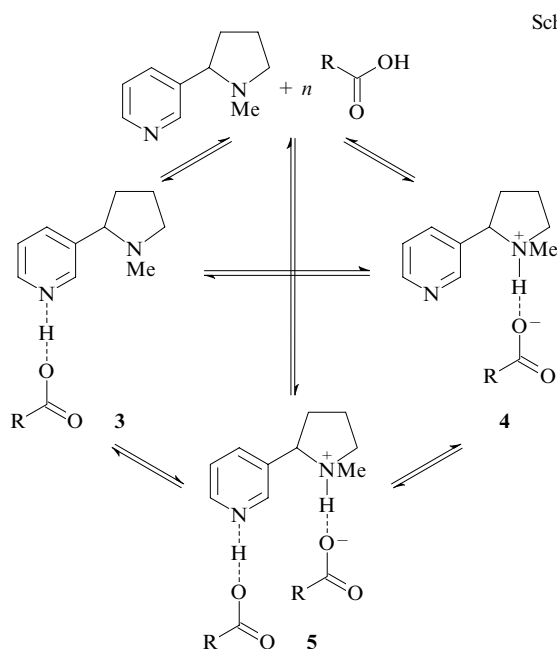


Figure 2. The ratio of selectivity factors in chromatographic separation of (–)-nicotine and 4,4′-bipyridyl on sorbents **P0**–**P6**.²³ For the description of polymers **P0**–**P6**, see text.



It was shown that the excess of (–)-nicotine in the pre-polymerisation mixture has an adverse effect on the selectivity of the resulting sorbent with respect to nicotine (Fig. 2, polymers **P4**–**P6**), which followed from the low selectivity ratios of the separation of nicotine and 4,4′-bipyridyl ($k'_{\text{NIC}}/k'_{\text{bipy}}$) on polymers **P4**–**P6** (see Fig. 2) and also from the fact that the addition of acetic acid to the reaction mixture during the synthesis of polymer **P5** decreased the selectivity of separation of the above compounds on this polymer as compared with **P4** due to the competition between methacrylic and acetic acids for the binding of nicotine. This can be explained by the shift of equilibrium between pre-polymerisation complexes **3**–**5** to the formation of complexes **3** and **4** (Scheme 3). On the other hand, a small excess of the monomer favours the increase in the selectivity of sorbents (polymers **P1** and **P2**), which is associated with the preferential formation of complex **5**. However, a large excess of methacrylic

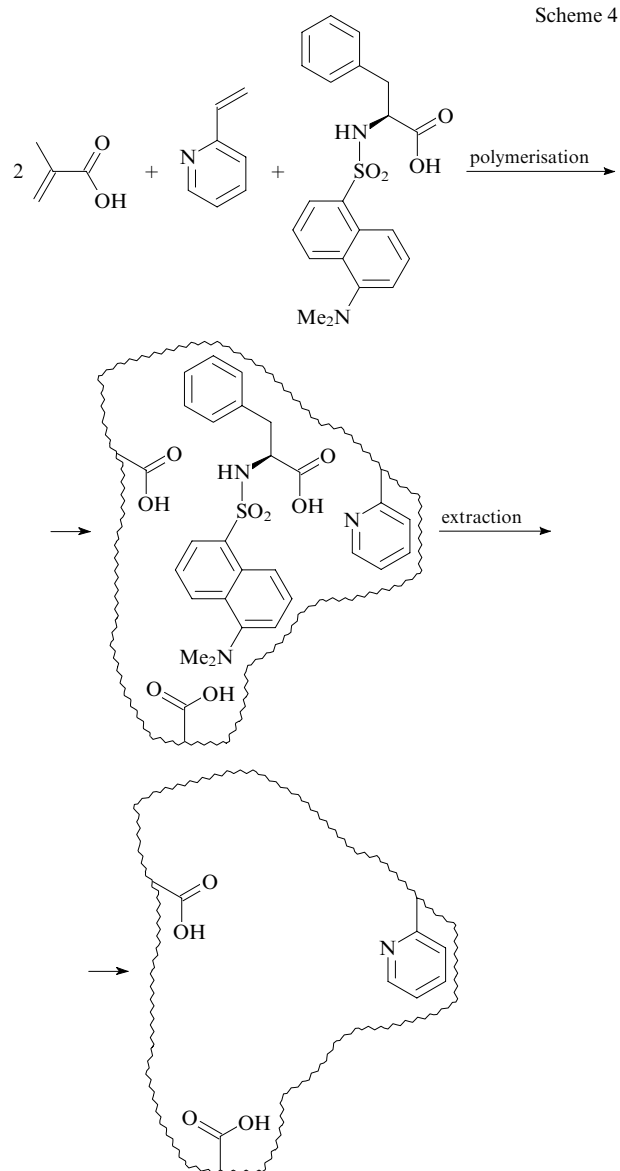


acid gives rise to a great number of non-specific binding sites in the polymeric sorbent, which decreases its selectivity.

Insofar as selectivity of obtained sorbents is the result of pre-assembling of monomer molecules with template molecules, it can be assumed that the formation of complex **5** is most favourable for the formation of highly selective adsorption sites in the polymeric network. Polymerisation of complexes **3** and **4** obviously results in the formation of regions with lower affinity to the template molecule, although it should be borne in mind that weak interactions of template molecules with the cross-linking agent (ethylene glycol dimethacrylate) can partly compensate the deficiency of methacrylic acid.

The idea of using vinylpyridines as the functional basic monomers was first forwarded in 1993 (Ref. 24). Three types of sorbents were prepared, namely, from 2-vinylpyridine (sorbent **A**), from methacrylic acid (sorbent **B**) and from both monomers taken in the molar ratio of 1:1 (sorbent **C**). Synthesis of these sorbents in the presence of Boc-L-tryptophan (as the molecular template) and their use in the chromatographic separation of Boc-L,D-tryptophan racemate have shown that the most efficient separation was achieved on sorbent **C**. Sorbent **A** was inferior, and sorbent **B** demonstrated the lowest separation ability.

Similar results were obtained with the use of dansyl-L-phenylalanine as the template (Scheme 4). Presumably, the formation of a pre-polymerisation complex, which would favour the formation



of selective sites, requires the simultaneous presence of both monomers in the reaction mixture, *viz.*, methacrylic acid for binding amino groups and 2-vinylpyridine for binding COOH groups in the amino acid.

Chromatographic properties of sorbents obtained in the presence of a non-polymerisable analogue of 2-vinylpyridine or methacrylic acid, namely, either pyridine or acetic acid, were analysed in order to confirm this hypothesis. In both cases, these sorbents proved inefficient in the separation of racemates as compared with sorbents prepared in the presence of two functional monomers simultaneously. This suggests that the formation of the pre-polymerisation complex involves the molecules of both monomers.

2. Covalent molecular imprinting

In covalent imprinting, the complex between a template molecule and a functional monomer, which can undergo co-polymerisation with a cross-linking agent in an appropriate solvent, is synthesised beforehand. Polymerisation of such a complex with an excess of the cross-linking agent affords a polymer incorporating chemically bound template molecules. In the final stage, under the action of the corresponding chemical reagents, the chemical bonds of template molecules with the matrix are broken and they are liberated. The cavities formed upon the template removal are characterised by a more definite (complementary to the template molecule) position of the functional group, which took part in the complex formation, than it can be achieved in non-covalent imprinting.

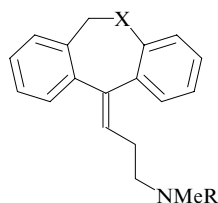
As compared with non-covalent imprinting, the imprinting in pre-assembled systems is much more laborious as regards both the choice of the template molecule and the experimental procedure. Hence, it is not surprising that the literature contains much fewer examples of the implementation of this approach as compared with the non-covalent imprinting.

The covalent imprinting method was first applied by Wulff *et al.*²⁵ They used phenyl α -D-mannopyranoside functionalised with 4-vinylphenylboronic acid as the template molecule. This compound was polymerised. The removal of the glycoside from the polymer afforded cavities that contained boronate functional groups.

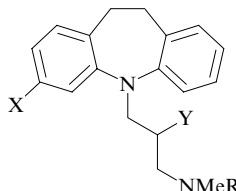
The use of covalent imprinting in the synthesis of sorbent **P4** (Table 1), which is highly sensitive to nortriptyline and other tricyclic antidepressants, was reported.²⁶

Table 1. Methods of synthesis of polymeric sorbents studied in Ref. 26.

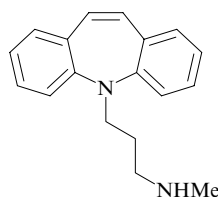
Polymeric sorbents (abbreviation)	Template (mol.%)	Cross-linking agent TRIM (mol.%)	Functional monomer (mol.%)
Sorbents without NOR molecular imprints			
P1	—	96	4-vinylphenol (4)
P2	—	64	methacrylic acid (24) + styrene (12)
P3	—	63	4-vinylphenol (12) + styrene (12) + methacrylic acid (13)
Sorbents containing NOR molecular imprints			
P4	NOR-alkene (4)	96	none
P5	NOR (4)	60	4-vinylphenol (12) + styrene (12) + methacrylic acid (12)
P6	NOR (2)	98	none
P7	NOR (2)	62	methacrylic acid (24) + styrene (12)



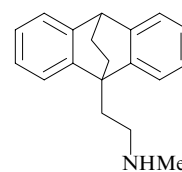
Nortriptyline (NOR): X = CH₂, R = H;
Amitriptyline (AMI): X = CH₂, R = Me;
Doxepin (DOX): X = O, R = Me.



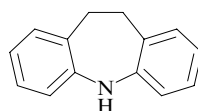
Desipramine (DES): X = Y = R = H;
Imipramine (IMI): X = Y = H, R = Me;
Trimipramine (TRI): X = H, Y = R = Me;
Clomipramine (CLO): X = Cl, Y = H, R = Me.



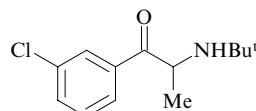
Protriptyline (PRO)



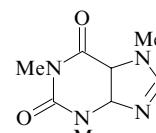
Maprotiline (MAP)



Iminodibenzyl (IDB)



Bupropion (BUP)



Caffeine (CAF)

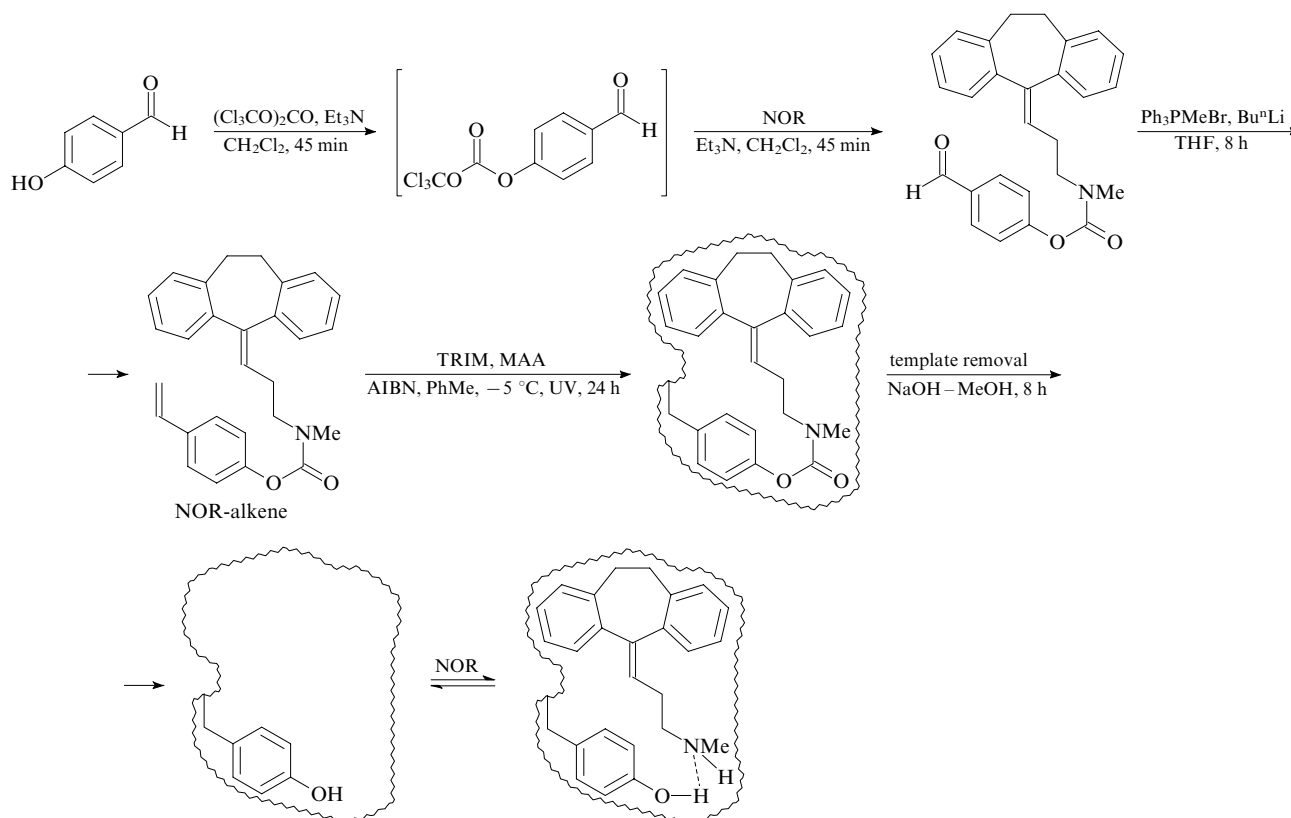
Functionalisation of nortriptyline and preparation of specific sorbent **P4** were carried out as shown in Scheme 5. Sorption properties of sorbent **P4** synthesised by covalent imprinting were compared with the properties of other polymeric sorbents used for sorption of these tricyclic compounds. To this end, a series of sorbents based on methacrylic acid and trimethylolpropane trimethacrylate were synthesised. Sorbents **P1**–**P3** were prepared by conventional polymerisation in the absence of a template, sorbents **P5**–**P7** were obtained by non-covalent imprinting in the presence of NOR (see Table 1).

The chromatographic properties of the obtained sorbents were studied. Several tricyclic antidepressants and compounds with similar physiological properties were screened. Table 2 shows the retention factors (*k*) for these compounds on sorbents **P4**–**P7**, which contained imprints of NOR molecules. As expected, the retention factor of nortriptyline on sorbents **P4**, **P5** and **P7** was substantially larger than those of other compounds

Table 2. Retention factors of compounds on different sorbents.

Compound	Retention factors (<i>k</i>) of compounds on sorbents			
	P4	P5	P6	P7
NOR	2.83	4.55	0.16	2.68
DES	2.59	3.53	0.20	2.48
PRO	2.35	3.58	0.18	2.24
MAP	2.49	3.96	0.20	2.44
DOX	1.43	0.75	0.14	1.13
TRI	1.33	0.53	0.15	1.03
AMI	1.57	0.85	0.14	1.11
IMI	1.52	0.88	0.14	1.12
CLO	1.61	0.97	0.16	1.09
BUP	1.42	0.58	0.20	0.88
IDB	0.17	0.53	0.27	0.37
CAF	0.19	0.40	0.13	0.68

Scheme 5



studied. It should be noted that sorbent **P6** the synthesis of which involved no functional monomers exhibits smaller k values. This confirms the important role of functional groups in molecular recognition. Sorption of compounds containing a secondary nitrogen atom (PRO, DES, MAP) on polymers **P4**, **P5** and **P7** was less efficient than that of nortriptyline but more efficient as compared with compounds containing a tertiary nitrogen atom (AMI, IMI, CLO, TRI). This can be explained by the fact that alkyl substituents at the nitrogen atom hinder the formation of the hydrogen bond $N \cdots HO-P$. Despite being secondary amines, BUP and IDM exhibit smaller retention factors as compared with NOR, which suggests that the shape and size of a molecular imprint affect the molecular recognition.

Usually, polymeric sorbents prepared by non-covalent molecular imprinting are less efficient in the chromatographic isolation of the analyte that has been used as the molecular template in comparison with sorbents obtained by covalent imprinting. This is manifested in pronounced broadening of the elution peak of the substance in question.^{27,28} The shape of the chromatographic peak of NOR on polymer **P4** prepared by covalent molecular imprinting could be substantially improved (Fig. 3 *a*) as compared with the NOR peaks on sorbents **P5** and **P7** synthesised by non-covalent imprinting (Fig. 3 *b,c*).²⁶

Covalent imprinting was also employed for the preparation of a sorbent that selectively adsorbs cholesterol²⁹ based on cholesterol 4-vinylphenyl carbonate and ethylene glycol dimethacrylate as the cross-linking agent. The sorption properties of this sorbent were compared with those of sorbents obtained by non-covalent imprinting with cholesterol as the template and methacrylic acid or 4-vinylpyridine as functional monomers. Chromatographic

separation of a mixture of cholesterol with β -estradiol was carried out.

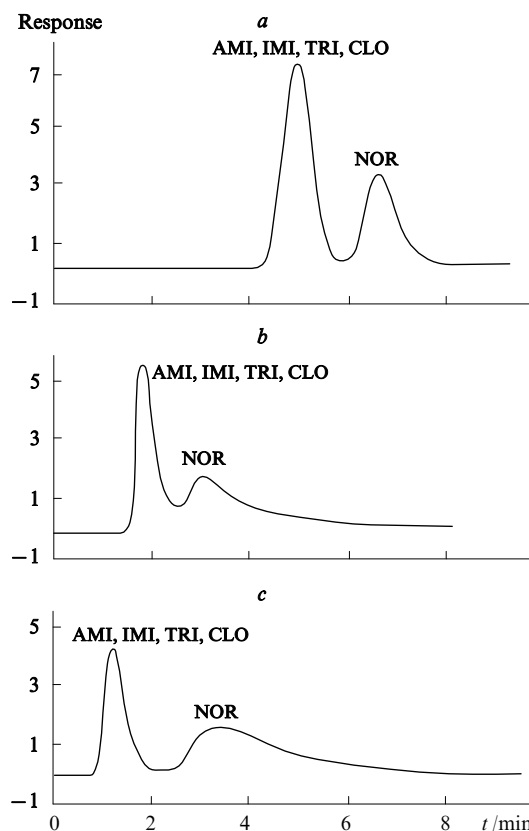
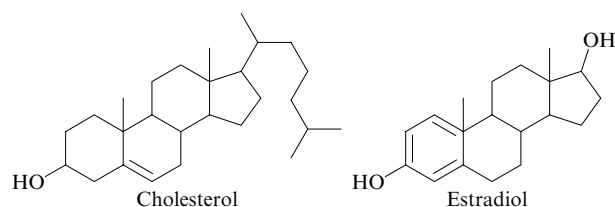
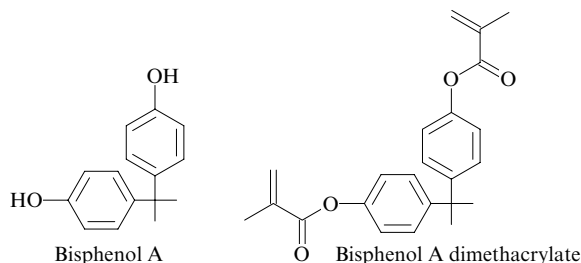


Figure 3. Chromatograms illustrating the efficiency of sorbents **P4** (*a*), **P5** (*b*) and **P7** (*c*) in the separation of a mixture of tricyclic antidepressants.

The separation was observed on all sorbents; however, the polymer prepared by covalent imprinting had a higher adsorption capacity with respect to cholesterol and exhibited five-fold higher chromatographic efficiency as compared with polymers prepared by non-covalent imprinting.

A polymer that selectively adsorbs bisphenol A [2,2-bis(4-hydroxyphenyl)propane] was prepared³⁰ by co-polymerisation of bisphenol A dimethacrylate with triethylene glycol dimethacrylate or trimethylolpropane trimethacrylate.[‡]



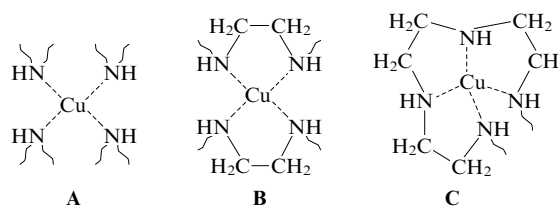
The retention of bisphenol A, its analogues and certain hormones on the polymeric sorbent prepared was studied. It was shown that the sorbents retain best the compounds that contain two 4,4'-hydroxyl groups and have rigid structures and molecular sizes close to that of bisphenol A.

In the 1970s, Kabanov *et al.*^{31–33} developed an original method of synthesis of polymeric materials with three-dimensional networks 'tuned' to the sorption of definite ions. The complementarity of the 3D-regions of polymeric networks and a given type of metal ions was achieved by the preliminary conformational tuning[§] of macromolecules of non-cross-linked polymers with respect to these ions, which was followed by the fixation of such a conformation by intermolecular cross-linking and removal of metal ions (templates) from the system. It should be emphasised that complementarity does not exist on its own but arises in the process of adsorption of a given ion and manifests itself in the decrease in the energy and entropy consumed in the conformational rearrangement of segments of macromolecules during the formation of their complexes with the metal.

In general features, the procedure of preparation of such 'tuned' sorbents is as follows:³⁴ an aqueous-ethanolic solution of a transition metal salt (*e.g.*, 0.2 M CuCl₂) is added to a dilute solution of a non-cross-linked polymer in an organic solvent [*e.g.*, 5% solution of partly quaternised poly(4-vinylpyridine) in ethanol] together with aqueous ammonia for precipitation of the metal–polymer complex. Following drying, the metal–polymer complex is cross-linked by a cross-linking agent. The resulting cross-linked polymer is washed with dilute HCl to remove the metal ions. Naturally, upon desorption of the metal ions the conformation of chain segments of the polymeric network that incorporated these ions changes; however, due to cross-linking, the polymeric matrix retains by and large its topological characteristics, which favours the resorption of the same metal ions.

The relationship between the structure of complexes 'polymeric matrix–metal ion' and the recognition efficiency was studied systematically³⁵ using oligomers of poly(ethyleneimine) (PEI) cross-linked with a reaction product of epichlorohydrin with ammonia. Before cross-linking, PEI was treated with a solution of copper(II) and nickel(II) salts (the concentration of ions varied from 1 to 3 mmol g^{−1} PEI). A preliminary EPR study has shown that the PEI solution contained several complexes of Cu²⁺ with PEI, which differed in the degree of deformation of the

square-planar coordination of the Cu²⁺ ion and in the number of ethylenediamine fragments.



Complex A is formed as a result of interaction of a Cu²⁺ ion with amino groups that belong to four different chains, whereas complex B involves its interaction with ethylenediamine fragments that belong to two chains. The existence of complex C all amino groups in which belong to the same PEI chain is also possible. Obviously, complexes with the same composition can exist in the sorbent as well. At low degrees of protonation of amino groups, the sorbents preferentially contained complexes of the B and C types, whereas at high degrees of protonation, they contained complexes A. Sorbents non-tuned with respect to Cu²⁺ ions produced complexes A and even triamine complexes. In contrast, tuned sorbents preferentially produced complexes of the type C. EPR spectroscopic studies proved that for protonated sorbents, the increase in the content of copper leads to the rearrangement of interchain complexes into intrachain complexes. Thus, the introduction of a great amount of copper favours the fixation of such molecular conformations that are best suited for the formation of complexes and that are observed in solutions where the molecules exhibit the highest mobility. Indeed, studies of the adsorption properties of a sorbent prepared in the presence of a great amount of copper demonstrated that this sorbent exhibited the maximum sorption capacity and sorption rate. This favours the formation of uniform active sites, which is essential for the synthesis of selective catalysts.

Synthesis of catalysts tuned with respect to ethylbenzene, namely, cobalt complexes with a co-polymer of diethyl vinylphosphonate and acrylic acid, is described.³⁶ Kinetic studies of liquid-phase oxidation of ethylbenzene with molecular oxygen have shown that the oxidation rate on a catalyst the structure of which was formed in the presence of ethylbenzene substantially exceeds that on the same catalyst prepared by conventional procedures without tuning of its structure.

III. Physicochemical fundamentals of molecular imprinting

Despite the seeming transparency and relative simplicity of the scheme of synthesis of polymeric sorbents capable of molecular recognition and the clarity of the model of the recognition process, many unsolved problems still exist. Particularly, the physical nature of non-covalent interactions responsible for the formation of template–monomer complexes is unclear; there is no versatile model that would allow one to describe the distribution of recognition sites according to the energy.

Relatively few studies are devoted to the physicochemical properties of molecular imprinting. The factors that govern the formation of polymeric systems by the molecular imprinting method are considered in a review.³⁷ The first stage in the formation of polymeric systems capable of molecular recognition is the formation of a pre-polymerisation complex of the template molecule with functional monomers due to non-covalent intermolecular interactions. The stability of this complex (which ultimately determines the ability of the synthesised material to recognise molecules) depends on many factors, particularly, thermodynamic. The change in the Gibbs free energy (ΔG_{bind}) due to the formation of a template–monomer pre-polymerisation complex is described by equation

[‡] Certain complications were associated with the chemical removal of bisphenol A from the polymer under the action of a sodium hydroxide solution.

[§] By changing the polymeric chain conformation due to the formation of complexes with metal ions.

$$\Delta G_{\text{bind}} = \Delta G_{\text{t+r}} + \Delta G_{\text{r}} + \Delta G_{\text{h}} + \Delta G_{\text{vib}} + \Sigma \Delta G_{\text{p}} + \Delta G_{\text{conf}} + \Delta G_{\text{vdw}}.$$

Here, the terms G_i reflect the changes in the Gibbs free energy due to translation and rotation ($\Delta G_{\text{t+r}}$), restriction of rotors as a result of the formation of complexes (ΔG_{r}), hydrophobic interactions (ΔG_{h}), residual vibrational modes (ΔG_{vib}), the sum of contributions of polar interactions template–monomer ($\Sigma \Delta G_{\text{p}}$), adverse conformational changes (ΔG_{conf}) and unfavourable van der Waals interactions (ΔG_{vdw}).

Ultimately, the value of ΔG_{bind} determines the number of molecular recognition sites and their distribution according to the energy (the degree of heterogeneity). Obviously, the more stable the pre-polymerisation complex the higher its concentration in the equilibrium pre-polymerisation mixture and, hence, the larger the number of recognition sites in the polymer formed and the more efficient the recognition of the original template molecules. The probability of the formation of template–monomer complexes and their stability depend on the nature of all components (template, monomers, solvent, *etc.*) present in the pre-polymerisation mixture and also on the external conditions (pressure, temperature, *etc.*). The strength of interactions such as monomer–monomer, template–template, solvent–monomer and solvent–template affects the equilibrium of the formation of a complex of the template molecule with the functional monomer and, hence, the number and ‘quality’ of the resulting molecular recognition sites.

The second stage is the polymerisation (polycondensation) of the template–monomer complex in the presence of the cross-linking agent and other components of the mixture. It is evident that the optimum conditions of polymerisation can differ from the conditions that favour the formation of a pre-polymerisation complex. For example, the polymerisation process often requires elevated temperatures to be maintained; however, bearing in mind that the functional monomer–template complex is formed only due to electrostatic interactions, the increase in the temperature is undesirable due to weakening of these interactions.

In the third stage, the template is removed, which is accompanied by the liberation of molecular recognition sites. It should be noted that it is sometimes difficult to remove the template from highly cross-linked polymers; hence, a certain amount of template molecules remain incorporated into the polymeric matrix. This reduces the analyte detection limit. When such a polymer is used in analytical studies, the template is gradually eluted from it, which decreases the accuracy of analyte detection.

Different procedures for the efficient removal of template molecules from the polymeric matrix are described.³⁸ These include, for example, sonication or microwave irradiation during the extraction, extraction with supercritical CO₂ containing an organic solvent as an additive, the use of anhydrous formic, acetic or trifluoroacetic acids for washing the polymer. It was found that, in the general case, the extraction should preferably be carried out with the solvent that has been used in the synthesis of this polymer.

Yet another problem, which one inevitably faces in the synthesis of polymers capable of molecular recognition (especially when preparing sorbents by non-covalent molecular imprinting), is the energy heterogeneity[¶] of the adsorption sites formed. The synthesised polymeric sorbent usually contains a certain number of recognition sites with high affinity to the original template molecules [according to some data, the fraction of highly specific sites of molecular recognition may vary from 0% to 35% (Refs 39 and 40)], a certain number of adsorption sites with a low degree of affinity and also a fraction of adsorption sites with intermediate energy characteristics. Thus, there is always a certain distribution of recognition sites according to the energy.

It is known that the efficiency and selectivity of chromatographic separation on polymers prepared by molecular imprinting strongly depend on the load of the mixture to be separated, the separation being highly efficient and selective for low load and *vice versa*.⁴¹

There are several general experimental approaches to prove that the materials prepared by molecular imprinting recognise better the template molecules than other components in the mixture. In any case, a correct comparison requires a sorbent prepared under identical conditions and with the same reagents but in the absence of template molecules. To prove the existence of the molecular imprinting effect, it is necessary to compare the adsorption of template molecules on the material prepared in its presence (the so-called molecularly imprinted sample) and a material synthesised in the absence of template molecules (the so-called control sample). The comparison is carried out under either dynamic or static conditions. In the dynamic mode (chromatographic conditions), the synthesised polymers (including the control sample) play the role of a stationary phase, and the imprinting effect is judged from chromatographic parameters (retention time and retention factors, separation factors and indices) measured for different components in a mixture that also contains the molecular template. The static mode includes, as a rule, measurements of either the equilibrium adsorption of template molecules on the molecularly imprinted and control samples or the adsorption of different substances and, separately, the adsorption of template molecules on the imprinted sample.

As was noted above, the synthesis of polymeric sorbents using the molecular imprinting method is virtually always characterised by the distribution of recognition sites according to the energy. To assess the fraction of sites highly specific with respect to template molecules, one has to study the energy distribution of adsorption sites.

The simplest model that assumes the presence of only two (less often, three) types of recognition sites corresponds to the bi-Langmuir (or tri-Langmuir) isotherm

$$a = \frac{a_{01}K_1C}{1 + K_1C} + \frac{a_{02}K_2C}{1 + K_2C}$$

$$\left(\text{or } a = \frac{a_{01}K_1C}{1 + K_1C} + \frac{a_{02}K_2C}{1 + K_2C} + \frac{a_{03}K_3C}{1 + K_3C} \right),$$

where a is the equilibrium adsorption /mol g⁻¹; C is the equilibrium concentration of adsorbate in solution /mol litre⁻¹; a_{01} , a_{02} (a_{03}) are the numbers of recognition sites of the first and second (third) types, respectively /mol g⁻¹; K_1 , K_2 (K_3) are the adsorption constants on these sites /litre mol⁻¹.

This model was used for the approximation of experimentally obtained^{41–43} adsorption isotherms. The adsorption isotherm was plotted in coordinates a/C – a and the resulting curve was approximated with two crossed lines to find the parameters a_{01} , a_{02} , K_1 , K_2 . Based on the slopes of these lines and the segments they intercept on the ordinate, the values of a_{01} , K_1 and a_{02} , K_2 were found for the recognition sites of the first and second types, respectively. However, it should be admitted that the model that assumes the presence of only two types of recognition sites is rather limited; hence, it was proposed to use other models.

In one of such models, the Freundlich isotherm was used in the approximation of a set of experimental points⁴⁴

$$a = KC^m,$$

where m is a constant ($0 < m < 1$). The applicability of the Freundlich equation to the description of experimental adsorption isotherms was checked for 12 different sorbents prepared by non-covalent molecular imprinting. It was found that 11 of 12 isotherms are well ($R > 0.95$) fitted by the Freundlich equation. The main drawback of this equation is that this is inapplicable in the region of high concentrations, because, according to the

¶ Heterogeneity of adsorption sites limits the application of these polymers as the stationary phases for HPLC.

Freundlich equation, adsorption cannot infinitely increase with the increase in the concentration.

A more versatile model⁴⁵ employs the Langmuir–Freundlich equation

$$a = \frac{a_{\max} KC^m}{1 + KC^m},$$

where $a_{\max}$ is the maximum adsorption/mol g⁻¹; K is the constant related with the average adsorption constant (K_0) by the equation $K_0 = K^{1/m}$; m is the heterogeneity index ($0 < m < 1$). The Langmuir–Freundlich isotherm is transformed into the Langmuir isotherm for $m = 1$ and into the Freundlich isotherm for $C \rightarrow 0$ or $K \rightarrow 0$.

It was shown⁴⁵ that the Langmuir–Freundlich isotherm can be used for the approximation of a set of experimental points for materials synthesised by both non-covalent and covalent imprinting methods. The main advantage of this model is that it allows one to obtain the data on the energy distribution of recognition sites, provided the parameters a_0 , K and m are known. A method was proposed⁴⁵ that makes it possible to obtain the required distribution. Plotting the distribution of adsorption sites according to the energy makes it possible to compare the efficiency of molecular recognition by diverse materials, irrespective of their nature and the type of template molecules. It is noteworthy that the distribution can be calculated only for a concentration range in which the experimental isotherm was plotted. The limitation of this model is that a large body of experimental data is required to obtain reasonable values of a_0 , K and m .

IV. Molecular imprinting on mineral supports

Two approaches to the preparation of molecular imprints on mineral supports were developed, namely, imprinting in the bulk (3D imprinting) and on the surface of a mineral support (2D imprinting).

1. Imprinting in the bulk of a mineral support

Generation of molecular imprints in the bulk of a mineral support assumes that the mineral support structure is formed in the presence of template molecules. An attempt was undertaken⁴⁶ to reveal the factors that determine the template recognition. For this purpose, the following six pairs of compounds were chosen: Methyl Red–*p*-Methyl Red, Methyl Orange–Ethyl Orange, histidyl-alanine–histidyl-leucine, Methyl Red–Ethyl Red, 2,7-diamino-9-fluorenone–3,3'-diaminodiphenylmethane, D,L-histidine–L-histidine.

The effect of imprinting was studied by comparing the adsorption of a molecular template (one compound from a pair chosen) with the adsorption of a structurally related compound (the second in the pair) on a sorbent prepared by molecular imprinting.

According to the results obtained, the imprinting effect was much more pronounced when *p*-Methyl Red was used as the template as compared with Methyl Red. On the whole, the studies of the relative adsorption of the pairs listed above have shown that the effect manifests itself only for the first three pairs of compounds. Based on the results obtained, the following conclusions were drawn:

- recognition of template molecules requires the presence of three or more sites of interaction between the molecule to be recognised and the imprint;

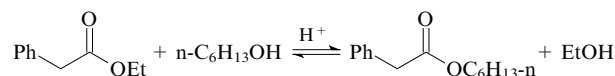
- for molecular recognition, the position of a functional group in the template molecule is more important than the size of the latter;

- recognition of chiral molecules requires stronger interactions or larger numbers of interaction sites.

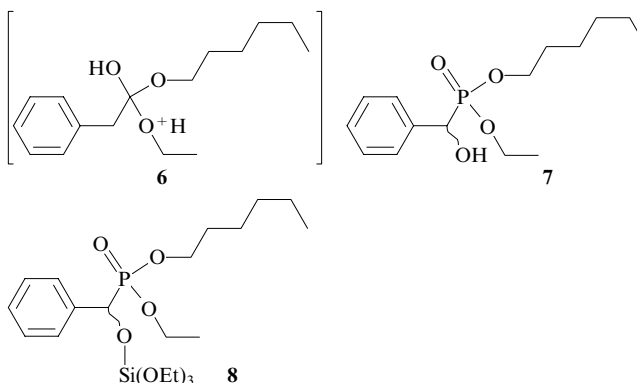
Unfortunately, no data on the diameters of pores and the specific surface areas of the samples prepared were reported in

Ref. 46. It cannot be ruled out that these factors can be responsible for the effect observed.

Synthesis of silica gel that specifically catalyses transesterification of ethyl phenylacetate was described.⁴⁷

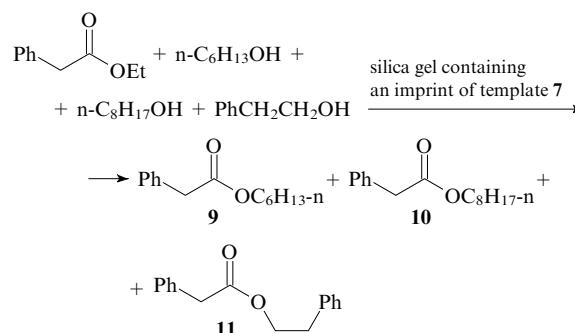


Structure **6** represents the transition state of this reaction; this is why compound **7** was chosen as the template. Derivative **8** was synthesised to incorporate the template into the resulting silica gel. Co-polycondensation with tetraethoxysilane followed by calcination was expected to 'leave behind' the recognition sites matching the transition state of the transesterification reaction.



For comparison, a control silica gel sample was synthesised (in the absence of the template). Silica gel samples prepared both in the presence and in the absence of the template had equal surface areas and the same size distributions of pores.

To check this hypothesis, transesterification of ethyl phenylacetate was carried out using an equimolar mixture of octan-1-ol, hexan-1-ol and 2-phenylethanol on silica gel prepared by covalent imprinting.



The results obtained pointed to the preferential formation of *n*-hexyl and *n*-octyl phenylacetates (the ratio **9**:**10**:**11** was 7:8:1), which, at first glance, might indicate the presence of cavities complementary to the analogue of the transition state of this reaction. The transesterification reaction with these three alcohols proceeded at approximately the same rates both in the homogeneous phase and on the control sample.

However, as was found later,^{48,49} the results obtained cannot serve as a proof of the imprinting effect on the transesterification reaction. First, comprehensive studies of synthesised materials, which involved solid-state ³¹P NMR spectroscopy and thermogravimetric analysis, have shown that the template molecule is merely adsorbed by the sorbent rather than covalently bound. Hence, the formation of specific cavities is questionable, *i.e.*, the observed selectivity in the transesterification reaction cannot be unambiguously explained as the manifestation of the molecular imprinting effect. Second, for general reasons, it follows that the

presence of a transition state analogue in the reaction mixture should inhibit the transesterification reaction; however, no such inhibition was observed.⁴⁷ Moreover, in their later study,⁴⁹ the authors failed to reproduce their own results on the selective transesterification. Apparently, the selectivity observed earlier⁴⁷ is explained better as a result of different diffusion rates of alcohols and esters in micropores. Similar results, namely, the dependence of selectivity on the diffusion rate rather than on the presence of specific recognition sites, were obtained^{50, 51} for materials synthesised by the sol–gel method. These examples revealed the following drawbacks of using the sol–gel synthesis in the technology of molecular imprinting, *viz.*, poor reproducibility due to the impossibility of strict control over the pore size during the synthesis and a probability that the observations of diffusion phenomena in micropores would be wrongly interpreted as the imprinting effect. One can avoid some of these drawbacks by employing imprints prepared on the surfaces of mineral supports.

2. Surface modification of mineral supports

As was mentioned above, the presence of a template in the stage of synthesis of sorbents affects the chromatographic properties of the latter^{52, 53} and also the activity and selectivity of stereospecific catalysts.^{54–56} This method is also used in the preparation of materials with definite spatial structures.^{57–59}

It is very significant that most of published procedures of the preparation of organised surfaces, which involve the use of template molecules, have a common drawback, namely, the low stability of imprints formed on the surface. For example, operation with modified silica in aqueous media can be accompanied by the surface restructuring, which leads to the blurring and disappearance of imprints formed. This is why attention is focused on the materials with fixed molecular imprints, which represent covalently fixed structures. Such structures can be obtained by chemical modification of the surface.^{60, 61}

The possibility of construction of ordered structures on the surfaces of inorganic supports, particularly silica, is determined by the fact that its surface is uniformly covered with hydroxyl groups.

The methods of surface modification of oxide supports aimed at the formation of recognising materials can be divided into the following four groups:

- (1) preliminary adsorption of template molecules followed by chemical modification of unoccupied surface areas;
- (2) multipoint fixation of complex molecules on the surface followed by the removal of the central fixing fragment;
- (3) fixation of silanes on the support surface (polycondensation in pores) in the presence of template molecules;
- (4) fixation of a polymeric layer capable of molecular recognition on the particles of mineral oxides or in their pores.

A sufficiently comprehensive survey⁶² is devoted to the preparation of chemically modified oxide surfaces capable of molecular recognition.

a. Method involving preliminary adsorption of template

This method includes the stages of preliminary adsorption of the template, chemical modification of the remaining unoccupied surface and removal of the template (Fig. 4). As a result of such a modification of the support surface, the latter retains areas that resemble the template in the shape and exhibit chemical properties different from those of the modified areas.

To form ultrathin silica layers, Japanese scientists employed chemical vapour deposition (CVD). For this purpose, tetramethoxysilane (TMOS) was deposited from the gas phase onto oxide supports such as zeolite,⁶³ alumina,^{64–66} titania and zirconia,^{66, 67} tin oxide⁶⁸ or silicalite.⁶⁹ The pretreatment of the support surface with an aldehyde (*e.g.*, benzaldehyde) results in the formation of surface areas with chemisorbed stable benzoate anions.⁷⁰ Further modification of such a surface with TMOS involves only free surface areas. Thus this method was applied for

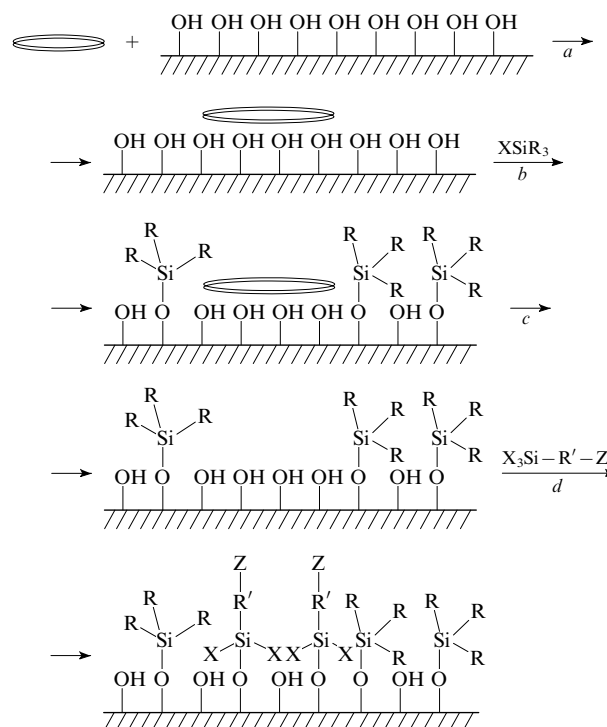


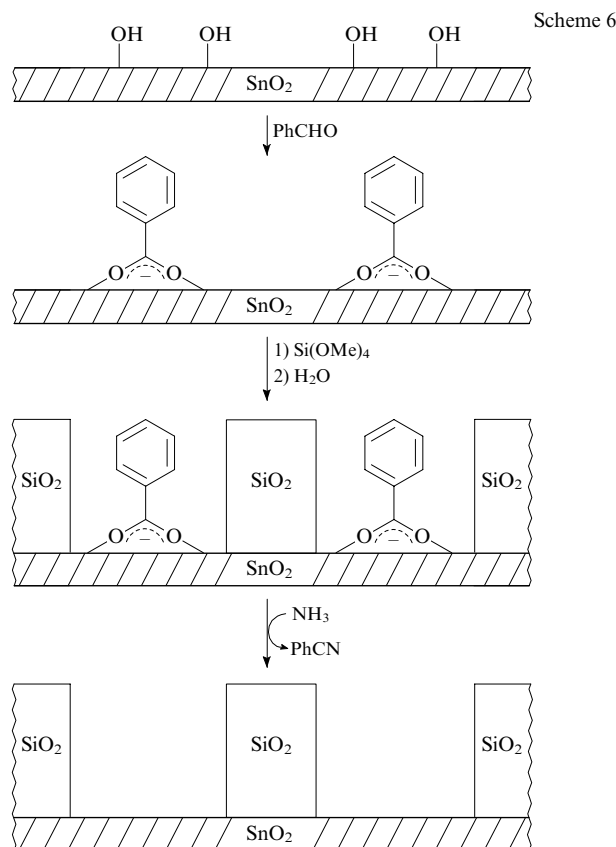
Figure 4. Preparation of molecular imprints in a graft layer. (a) template adsorption, (b) modification of the unoccupied surface, (c) template desorption, (d) modification of 'imprints'.

modification of the surface of γ -alumina.⁷¹ Studies of benzaldehyde adsorption on the sorbent samples have shown that they behave as molecular sieves with respect to benzaldehyde. It was found that the formation of a siloxane network in the adsorption of tetramethoxysilane on the surface of benzaldehyde-treated γ - Al_2O_3 is prevented due to the presence of template molecules, namely, benzaldehyde, on the surface.

Systems based on tin oxide were also studied.^{72, 73} Upon adsorption of benzaldehyde (graft density 1.49 nm^{-2}) or α -naphthaldehyde (0.77 nm^{-2}) on the tin oxide surface, the latter was treated with TMOS, which was followed by the hydrolysis. The cycle 'treatment with TMOS–hydrolysis' was repeated several times. As a result, the surface concentration of silicon atoms was 6.2 or 2.9 atoms per nm^2 , respectively, which exceeds the monolayer coverage of the free surface. The template was removed with ammonia (Scheme 6).

Studies of the adsorption of these aldehydes and of 2-chloro- and 2,6-dichlorobenzaldehydes have shown that all of them are sorbed better on the unmodified surface of tin oxide. For silica-modified samples studied, the best results were achieved when α -naphthaldehyde was used as the template. However, the samples behaved as molecular sieves only at high silicon contents (4.5 and 6.2 atoms per nm^2).

Electroconductivity and catalytic activity of pure tin oxide (sample 1) and tin oxide samples with SiO_2 layers deposited by a similar procedure with α -naphthaldehyde (sample 2), benzaldehyde (sample 3) and butyraldehyde (sample 4) as the templates were studied.⁷⁴ It was found that the adsorption of C_8 hydrocarbons with different structures first causes a sharp decrease in the resistance of samples and then its increase; this is why the comparison was carried out in the point of a minimum. The ratio between the resistances of the starting sample (R_a) and a sample with adsorbed hydrocarbons (R_g) was used as the criterion of conductivity (Fig. 5).



The catalytic activity of samples 1–4 was assessed based on the conversion of linear, branched and cyclic hydrocarbons C₆ in the course of their oxidative destruction to CO₂ (Fig. 6). An attempt was undertaken to relate the activity of samples 1–4 in the oxidative cracking of hydrocarbons C₆ to the molecular imprint size and check the correspondence of the latter to the size of the adsorbed hydrocarbon (Table 3).

The idea of using molecular imprints in the preparation of covalently grafted islet structures was put forward by Fadeev⁷⁵ in 1986. He noted that chemical modification of a surface that contains pre-adsorbed template molecules allows one to ‘fix’ the imprints and thus increase their stability. Further modification of the ‘imprints’ obtained can be carried out by conventional methods of surface chemistry.

‘Sharp’ imprints can be obtained, if the template is adsorbed unambiguously and sufficiently strongly on the surface, which prevents its washing out during the modification. At the same time, the template adsorption should be reversible to allow its removal from the surface after the chemical modification. It was

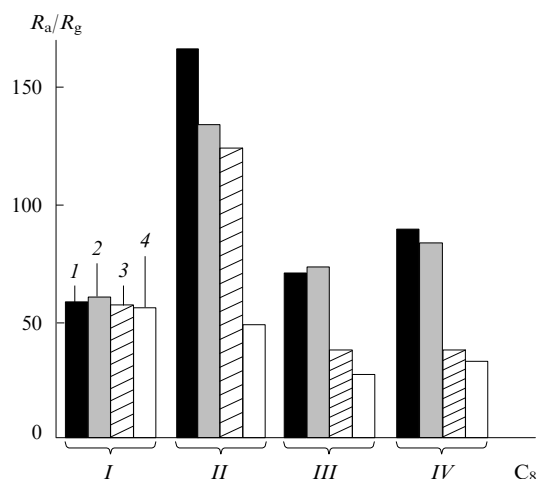


Figure 5. Changes in the conductivity of samples of (I) SnO₂ and (2–4) SiO₂/SnO₂ as a result of adsorption of different hydrocarbons C₈ (I–IV) at 643 K.⁷⁴

(I) n-octane, (II) 2-methylheptane, (III) 2,3-dimethylhexane, (IV) cyclo-octane. The preparation of samples 2–4 involved preliminary adsorption of the following templates: (2) α-naphthaldehyde, (3) benzaldehyde and (4) butyraldehyde.

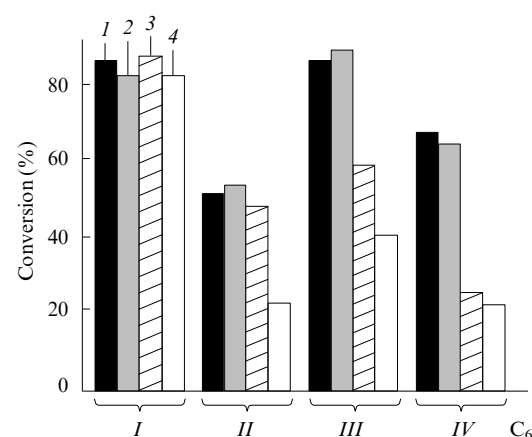


Figure 6. Oxidation of alkanes C₆ at 643 K on (I) SnO₂ and (2–4) SiO₂/SnO₂ samples.⁷⁴

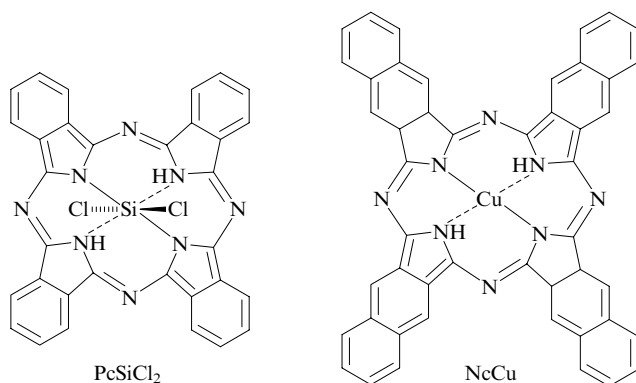
(I) n-hexane, (II) 2-methylpentane, (III) 2,3-dimethylbutane, (IV) cyclohexane. For the description of samples 1–4, see the caption to Fig. 5.

proposed that metal phthalocyanines, particularly silicon dichloride phthalocyanine (PcSiCl₂) and copper naphthalocyanine (NcCu) should be used as the templates.⁷⁵

Table 3. The size of template molecules used for the modification of the tin oxide surface and the sensitivity of prepared sorbents with respect to C₆ alkanes.

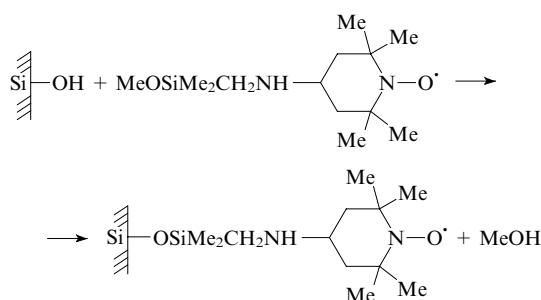
Template	Sensitivity with respect to				
	template molecule size /nm	n-hexane (0.36 × 0.48)	2-methylpentane (0.37 × 0.60)	2,3-dimethylbutane (0.57 × 0.62)	cyclohexane (0.43 × 0.61)
None	—	h	h	h	h
α-Naphthaldehyde	0.37 × 0.92	h	h	h	h
Benzaldehyde	0.37 × 0.67	h	h	l	l
Butyraldehyde	0.36 × 0.48	h	l	l	l

Notes. The following abbreviations are used: h corresponds to high sensitivity, l corresponds to low sensitivity. Sizes of C₆ molecules are given in nm.



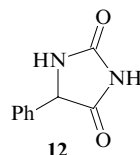
Phthalocyanines are adsorbed sufficiently strongly (but reversibly) on silica, occupy large landing areas per molecule and are easily modified. Moreover, they are excellent chromophores, which makes easier their detection in the adsorbed state. Table 4 shows the conditions of adsorption of copper naphthalocyanine on the surface of silochrome 120 (entry I) and of silicon dichloride phthalocyanine on silochrome 120 modified with 3-(aminopropyl)triethoxysilane (entry II), and also the conditions of surface modification and template removal.

The completeness of the phthalocyanine adsorption and desorption was monitored by spectrophotometric techniques. The formation of imprints in the graft layer upon removal of adsorbed templates was proved using the method of paramagnetic labels, which involved treatment of the sorbent sample with an excess of iminoxyl radicals.^{76–78}

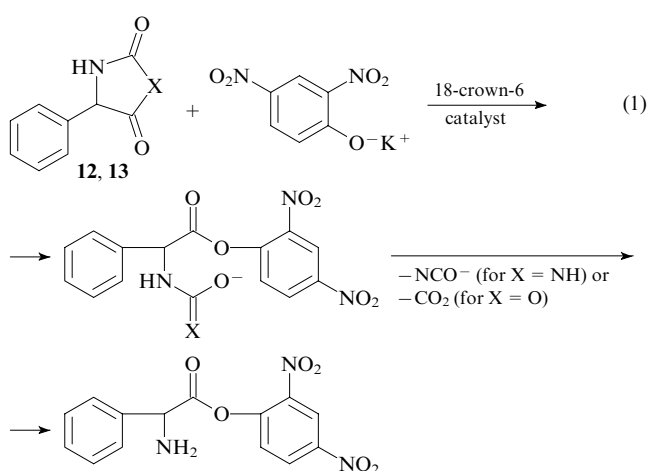


A comparison of EPR spectra of molecularly imprinted sorbent samples, which were prepared in the presence of templates, and the control samples, which had the known uniform distribution of the paramagnetic label, has shown that the label molecules in the former samples are located more closely to one another. The EPR data on the distances between the neighbouring labels and the number of labels correspond to the results of calculations based on the silica surface area and the size and number of imprints. The comparison of adsorption properties of molecularly imprinted and the control sorbent samples have shown that the adsorption capacity of the former with respect to the corresponding template molecules increases. These results point to the formation of the corresponding islet nanostructures on the silica surface.

A large series of publications described the development of methods for the synthesis of catalysts capable of molecular recognition. The idea that underlies these methods is that compounds with structures close to that of a catalytic reaction transition state could serve as the templates in the synthesis of catalysts. It was proposed^{79–87} to synthesise enantioselective catalysts based on silica gels with *R* or *S* enantiomers imprinted, in particular, (*R*)- or (*S*)-5-phenylimidazolidine-2,4-dione [5-phenylhydantoin (**12**)].⁸⁷



For this purpose, the surface of pure SiO₂ was treated with concentrated HCl to produce silanol groups, washed and then doped with Al³⁺ ions (by adding aluminium chloride and heating to 80 °C for 3 h) to obtain aluminium-substituted active centres (Lewis acid sites). After this treatment, a solution of the template (5-phenylhydantoin) was added to silica gel and the samples were stored for a week at pH 4. Then the template was extracted in the Soxhlet apparatus until its complete removal from the surface. The catalysts obtained were assayed in reactions of *R* and *S* isomers of 5-phenylhydantoin (**12**) and 4-phenyl-1,3-oxazolidine-2,5-dione (**13**) with potassium 2,4-dinitrophenoxide. Table 5 shows the kinetic parameters of reaction (1) for X = O.



X = NH (**12**), O (**13**); catalyst is silica gel with an imprint of (*R*)- or (*S*)-5-phenylhydantoin.

It follows from Table 5 that the reaction rate constants substantially differ depending on the catalyst type used. The highest rate is achieved for a catalyst with the configuration identical to that of the corresponding substrate. The results obtained can be explained by the formation of chiral cavities on the silica gel surface (Fig. 7). It is these cavities that determine the catalyst stereoselectivity. From the temperature dependence of the catalytic reaction rate it was possible to calculate the activation parameters for each catalyst type. The energy of activation of the *S*-substrate on the *S*-catalyst is lower than the energy of activation of the *R*-substrate on the *S*-catalyst. The possibility of the preparation of stereospecific catalysts by the molecular imprinting method was confirmed by the example of other catalytic reactions (see Refs 88 and 89).

b. Multipoint fixation of complex molecules

In essence, the method of multipoint fixation of complex molecules [*e.g.*, (X₃Si–R'–Z)_mA] on the surface of oxides consists of the preparation of sorbents in which the functional groups Z are fixed at a certain distance from the sorbent surface that favours subsequent selective binding of fragment A of these molecules.

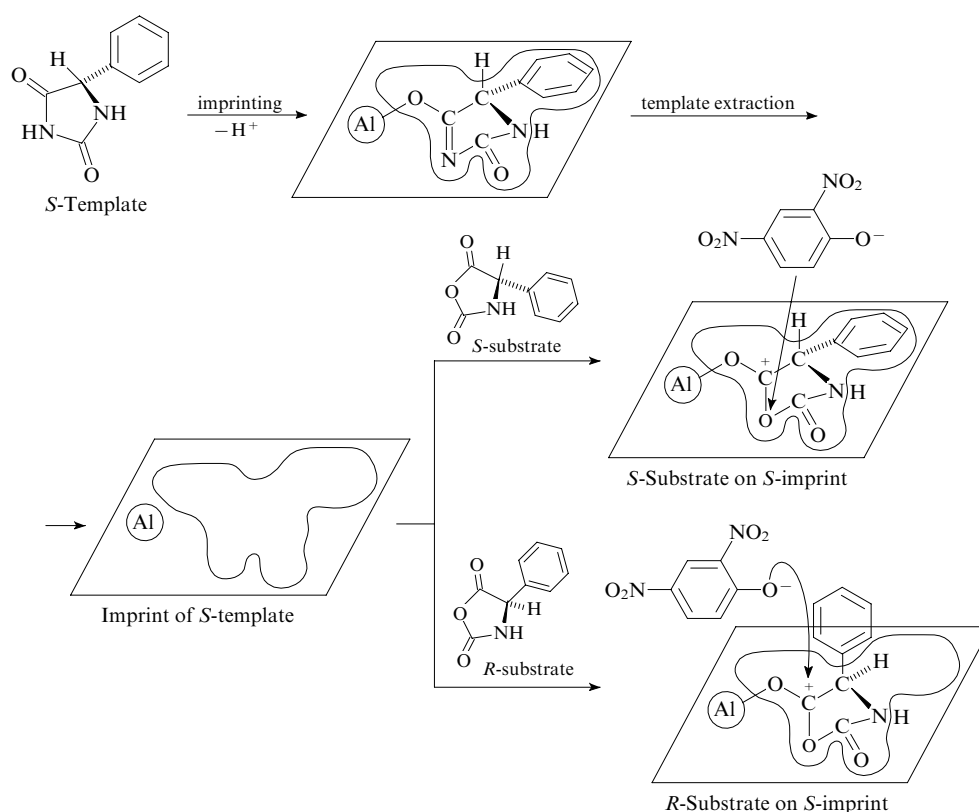
Table 4. Conditions of template adsorption on the silica surface, subsequent surface modification and removal of template molecules.

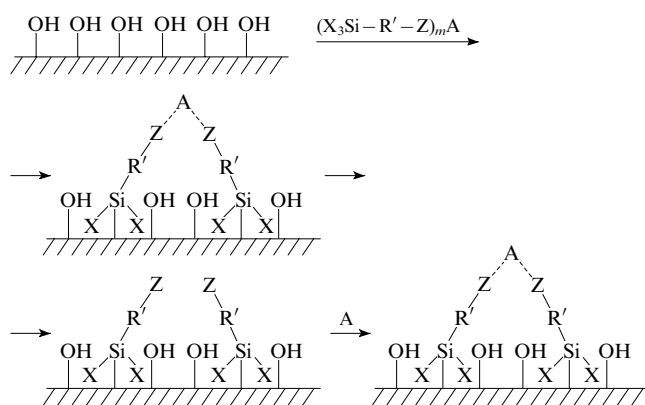
Entry	Original surface	Template molecule	Conditions of template adsorption	Amount of adsorbed template / $\mu\text{mol m}^{-2}$	Conditions of modification of a surface containing adsorbed template	Conditions of removal the template from the surface	'Resulting' surface
I	Silochrome 120	NcCu	Solution in toluene ($\sim 10^{-6}$ M)	0.0017	Treatment with trimethylchlorosilane in gas phase at 60 °C	Treatment with a mixture of trimethylacetyl chloride and morpholine in hexane	'Islets' of original silica on the 'background' of a trimethylsilane monolayer
II	Silochrome 120 modified with aminopropyl groups	PcSiCl ₂	Solution in toluene ($\sim 10^{-6}$ M)	0.0057	Treatment with ethyl acrylate in propan-2-ol at 60 °C	Extraction with toluene with addition of acetic acid in the Soxhlet apparatus	'Islets' of amino-propyl groups on the 'background' of ethyl acrylamide

Table 5. Kinetic parameters of reaction (1) mediated by a catalyst prepared by the matrix imprinting method.⁸⁷

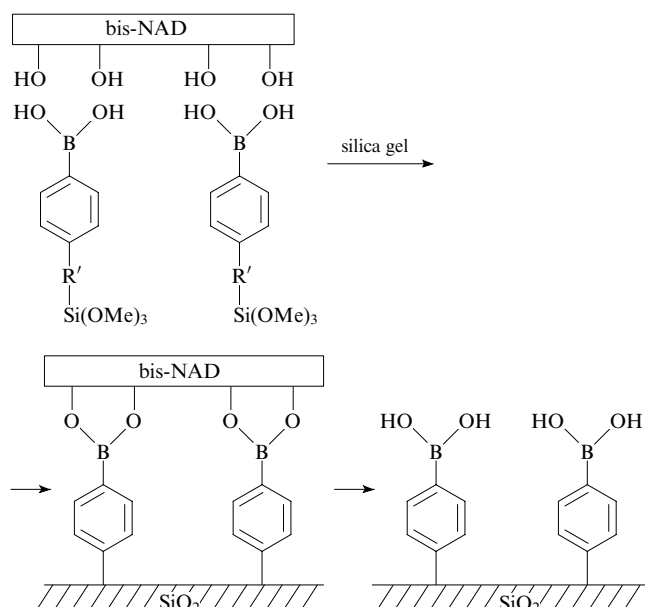
Configuration of 5-phenylhydantoin imprint on the catalyst surface	Substrate 13 configuration	$10^{-4} K_M$ /mol litre ⁻¹	$10^{-4} k_{\text{max}}$ /s ⁻¹	$10^2 k_{\text{cat}}$ /s ⁻¹	$10^5 k_{\text{cat}}/K_M$ /mol ⁻¹ s ⁻¹ litre	Enantio-selectivity ^a
<i>R</i>	<i>R</i>	1.93	5.64	4.29	22.2	1.34
	<i>S</i>	2.14	4.68	3.56	16.6	
<i>S</i>	<i>S</i>	5.26	7.13	4.87	9.25	2.01
	<i>R</i>	7.16	4.82	3.29	4.60	
<i>RS</i> (see ^b)	<i>R</i>	5.02	5.45	4.76	9.48	1.0
	<i>S</i>	5.02	5.45	4.76	9.48	

Notes. Designations: K_M is the Michaelis–Menten constant; k_{max} is the maximum rate constant calculated for the first-order reaction mechanism; k_{cat} is the average value of k_{max} normalised with respect to the number of catalytic sites in 50 mg of catalyst. ^a Determined based on the ratio k_{cat}/K_M for (*R*)- and (*S*)-4-phenyl-1,3-oxazolidine-2,5-diones. ^b Catalyst was prepared with the use of a racemate as the template.

**Figure 7.** A scheme of enantioselective catalysis on an imprint obtained with the use of *S*-template.⁸⁷



This method was used for the synthesis of a sorbent selective with respect to nicotinamide adenine dinucleotide (NAD) and containing boronate groups at a fixed distance from one another.^{90,91} The synthesis is based on the known reaction of phenylboronic acid with the sugar fragments of bis(nicotinamide adenine dinucleotide) (bis-NAD).



The reaction product of 4-[(MeO)₃SiR']C₆H₄B(OPr)₂ with two types of bis-NAD, which contained spacers of different length (7 and 17 Å) between NAD fragments, was used as the modifier of the silica gel surface.

Following fixation of the modifier, the silica gel surface was additionally silanised with dodecyltriethoxysilane, phenyltriethoxysilane, *N*-(2-aminoethyl)-3-aminopropyltriethoxysilane and bis(2-hydroxyethyl)aminopropyltriethoxysilane to improve the sorbent properties. The sorbents obtained were used in the chromatographic determination of bis-NAD by HPLC. It was found that the retention of each of bis-NAD types on the sorbent modified with this particular NAD type was twice stronger as compared with sorbents modified with the other NAD types.

A method of modification of the silica gel surface that involved the use of the Ru[bipy-CH=N(CH₂)₃Si(OEt)₃]₃ complex was described.⁹² After hydrolytic cleavage of the CH=N bond of this complex, three amino groups fixed at a definite distance from one another remained on the silica gel surface. Such sorbents can be used for selective sorption of ruthenium or as piezoelectric sensors. These amino groups can be modified further with the aim of preparation of sorbents for HPLC.⁹³

c. Method of fixation of silanes in the presence of template molecules

The simplest method of preparation of sorbents with molecular imprints is based on the polycondensation of alkoxy-silanes in the pores (or on the surface) of silica gel, which is carried out in the presence of a template (Fig. 8).

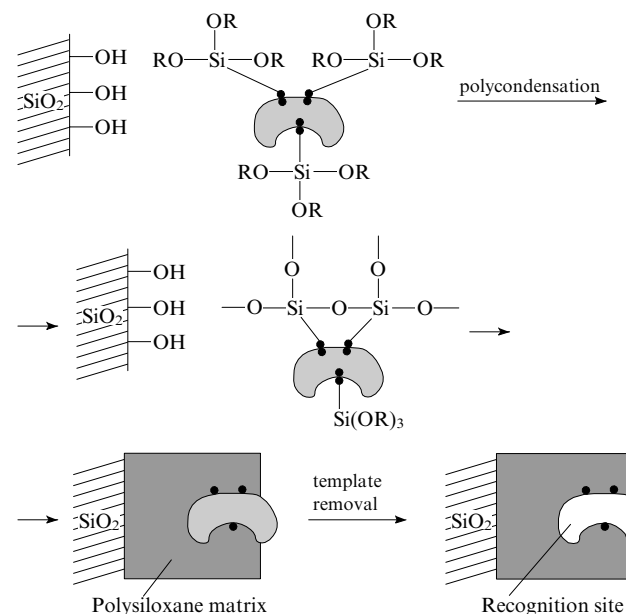


Figure 8. A scheme of hydrolytic polycondensation of alkoxy-silanes on the silica gel surface in the presence of a molecular template.

Synthesis of silica gel-based sorbents selective to a given dye was described.⁹¹ A mixture of phenyltriethoxysilane, *N*-(2-aminoethyl)-3-aminopropyltriethoxysilane and bis(2-hydroxyethyl)-aminopropyltriethoxysilane was added to a porous silica gel impregnated with a dye (Rhodanine Blue or Saffranine O) and their polycondensation was carried out.

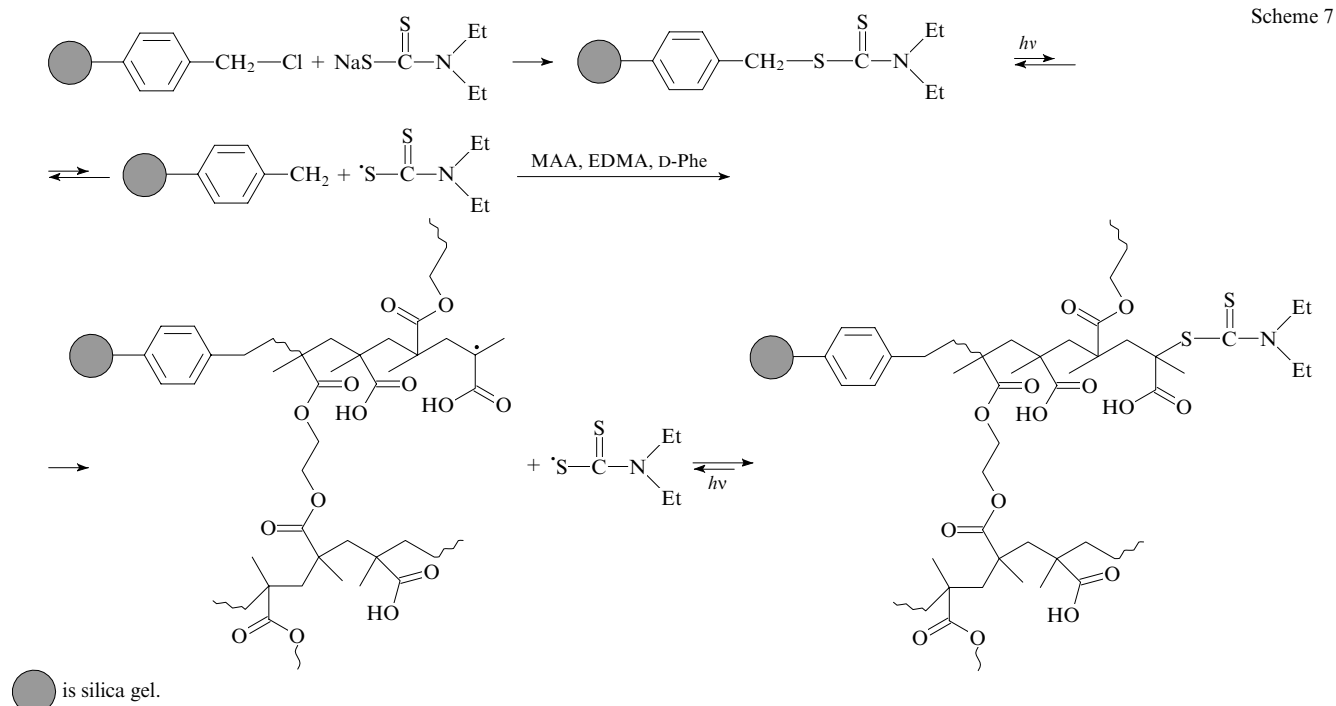
Based on the same silane mixture and a silane with a fragment of 3-aminophenylboronic acid, sorbents containing transferrin and bovine serum albumin imprints were prepared.⁹¹ Of the sorbents obtained, only that synthesised in the presence of transferrin exhibited selectivity.

Silica gels with imprints of ricin and its A and B chains were prepared in the pores of silica gels impregnated with these compounds by polymerisation of a mixture of tetraethoxysilane and bis(2-hydroxyethyl)aminopropyltriethoxysilane.⁹⁴ Each of three silica gels bound almost exclusively the object that served as the molecular template. Later, a similar method was used in the preparation of silica gels containing imprints of *N*-decyl-D-phenylalanine-2-aminopyridine.⁹⁵

d. Synthesis of polymers capable of molecular recognition

The methods of synthesis of polymers for molecular recognition are sufficiently well developed. However, swelling, lability and insufficient permeability limit their application. Most of these limitations can be overcome by fixing a thin polymeric layer on the surface of particles of a porous silica gel or in its pores. Strong binding is achieved by preliminary chemical attachment to the silica gel surface of functional groups that can be involved in subsequent polymerisation.

This method was used in the synthesis of sorbents for chromatographic determination of imidazole.⁴⁰ First, 3-(triethoxysilyl)propyl methacrylate was fixed to the silica gel surface. Then, ethylene glycol dimethacrylate, copper *N*-(4-vinylphenyl)-



iminodiacetate and a molecular template of the imidazole series [1,4- and 1,3-bis(imidazol-1-ylmethyl)benzene or 4,4'-bis(imidazol-1-ylmethyl)biphenyl] were added and polymerisation was induced by azobis(isobutyronitrile). The synthesised material was packed into HPLC columns, copper ions were exchanged for zinc ions, and the sorbent was used in the chromatographic determination of imidazole or template molecules. The preferential binding of molecules that served as the templates during the sample preparation was observed.

Complexes of copper *N*-(4-vinylphenyl)iminodiacetate with L-, D- and L,D-phenylalanine and other amino acids can be used as molecular templates.^{96,97} Selectivity of chromatographic resolution of L,D-phenylalanine on a sorbent prepared with a copper–D-phenylalanine complex as the molecular template was 1.65, while the selectivity of separation of L,D-thyrosine on the same sorbent was 1.56. The same column was used for the resolution of racemic α -methylphenylethylamine (selectivity 1.32); however, attempts to resolve a racemate of α -methylcinnamic acid failed.

Treatment of silica gel with surface-bound active chlorobenzyl groups with sodium *N,N'*-diethyldithiocarbamate afforded an UV-sensitive initiator of radical polymerisation.⁹⁸ This was used in the radical polymerisation of methacrylic acid and ethylene glycol dimethacrylate in the presence of L- or D-phenylalanine (L- or D-Phe) anilides as the templates (Scheme 7). The same materials were prepared in the absence of the template. The separation factors ($\alpha = k'_L/k'_D$, where k'_L and k'_D are the retention factors for L- and D-Phe) of enantiomeric template molecules on HPLC columns packed with sorbents prepared in the presence of L-Phe and D-Phe were 2.4 and 0.35, respectively, and 1 in the absence of amino acid.

Other sorbents intended for the separation of L- and D-phenylalanine anilides were prepared analogously. For this purpose, a radical azo-initiator was fixed on the surface of porous silicas Si-1000, Si-300 and Si-100 and non-porous silica gel; then, MAA and EDMA were polymerised in the presence of L-phenylalanine anilide.⁹⁹ The optimum chromatographic separation of L- and D-phenylalanine anilides with the separation factor of up to 7 was achieved for a polymeric film of a thickness of 6–7 nm.

Silica gel with fixed vinyl groups was used in the co-polymerisation of acryloylcyclodextrin and *N,N'*-methylene di(acryl-

Table 6. Retention times of amino acids, peptides and *m*-nitrophenol on chromatographic columns with different sorbents.¹⁰¹

Compound	Retention time (min) on sorbents ^a		
	A	B	C
L-Phe-L-Phe	9.61	10.20	10.62
D-Phe-D-Phe	9.68	9.73	11.73
L-Phe	4.21	4.27	4.34
D-Phe	4.17	4.25	4.32
<i>m</i> -Nitrophenol	24.65	21.47	23.65

^a Sorbents that contain no molecular imprints (A) and contain L-Phe-L-Phe (B) and D-Phe-L-Phe imprints (C).

amide) in the presence of molecular templates, namely, L-Phe-L-Phe or D-Phe-D-Phe.¹⁰⁰ Table 6 shows some results obtained on chromatographic columns packed with these sorbents.¹⁰¹

The surface of capillaries for capillary electrophoresis was modified analogously.¹⁰² First, the capillary surface was treated with (methacryloyloxypropyl)trimethoxysilane. Then, the pre-polymerisation mixture that contained monomers, a cross-linking agent (TRIM), a radical initiator [2,2'-azobis(isobutyronitrile)] and template molecules [(*S*)-propranolol, (*S*)-metoprolol or (*S*)-atenolol], was introduced into the capillary columns. After completion of polymerisation, template molecules were removed by extraction with acetonitrile, methanol or a methanol–acetic acid mixture. The columns thus modified were used in the separation of certain organic substances.

V. The applications of materials capable of molecular recognition

Polymers with molecular imprints attract keen attention of scientists and engineers. First of all, this is associated with the active quest for selective sorbents (including sorbents for HPLC), the materials for membranes and sensors and artificial antibodies (Fig. 9).

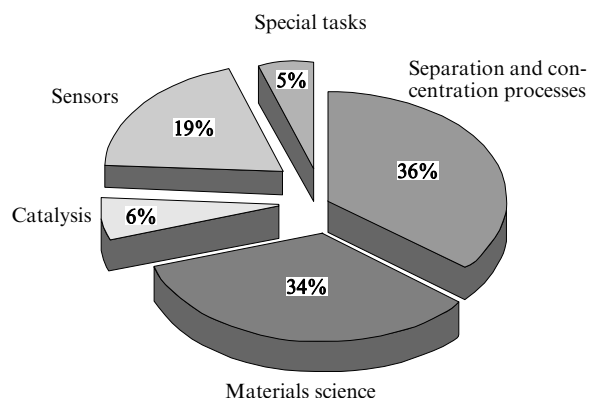


Figure 9. Distribution of application fields of polymers with molecular imprints (according to the data from Ref. 101).

Sorbents based on polymers with molecular imprints exhibit several obvious advantages as compared with conventional sorbents. They are characterised by high chemical affinity and selectivity with respect to target molecules (which in certain cases is comparable with the selectivity of biomolecules), high stability, which exceeds that of biomolecules, relatively easy adaptability to various practical applications and relatively low cost.¹⁰¹

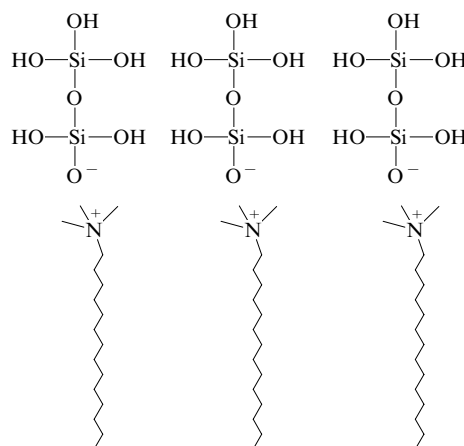
Polymers with molecular imprints are employed most often in the separation and concentration (*e.g.*, see a survey¹⁰³). The search for effective sorbents for the exhaustive cleaning of water[†] and the processing of industrial and domestic wastes is in progress. The USA alone spend more than \$ 500 million for the manufacture of sorbents for chromatographic columns, the percentage of polymers with molecular imprints being 1%–3%.¹⁰¹ In the pharmaceutical industry, the biopharmaceutic branch (production and purification of recombinant proteins and monoclonal antibodies) is most dynamic. The use of sorbents with molecular imprints in the separation of proteins is described in Ref. 104.

Chemical sensors based on polymers with molecular imprints are being actively developed. They are considered as an alternative to biosensors, which exhibit low stability and are very expensive. To date, sensors based on polymers with molecular imprints have already been developed for the detection of certain herbicides,¹⁰⁵ sugars,¹⁰⁶ medical drugs,¹⁰⁷ nucleic acids,¹⁰⁸ toxins,¹⁰⁹ *etc.*

Porous materials with the template-determined pore sizes closely relate to the subjects considered in the present review. In this case, it is surfactants that serve as templates; however, their sizes exceed those of molecules and are determined by the geometry of surfactant globules. In 1992, synthesis of the first structured mesoporous material, MCM-41 (Mobil Composition of Matter), which is remarkable for its regular pores with a narrow size distribution (a result of hexagonal packing of linear cylindrical pores), was reported.¹¹⁰

To explain why mesoporous materials form ordered structures, Beck *et al.*¹¹¹ have proposed the so-called LCT (Liquid Crystal Templating) mechanism. They assumed that the formation of an ordered structure is associated with micelles that are formed in surfactant solutions (with a concentration exceeding the critical micelle concentration) and serve as the templates in the synthesis of MCM-41 and related materials. First, spherical micelles are formed and, next, cylindrical. The latter are transformed into the so-called micellar rods upon the reaction with silicate.

In the second stage, the micellar rods are ordered hexagonally to afford a sort of a composite, which contains the bound organic and inorganic layers. Calcination of the obtained composite and removal of organic component produce an inorganic structure with hexagonally ordered cylindrical pores of identical diameters.



A recently published review¹¹² is devoted to the synthesis and physicochemical and catalytic properties of mesoporous titanium silicate materials.

VI. Conclusion

The analysis of data discussed in the present review points to the substantial interest of scientists in the synthesis of materials capable of molecular recognition. The most remarkable results are achieved in the field of synthesis of organic polymeric materials, which is explained by the wide possibilities of varying the chemical nature of monomers and cross-linking agents and also the flexibility of the polymeric structure.

To date, only few studies are devoted to designing mineral matrices with imprints. The approach based on functionalisation of the surface by multipoint fixation of complex molecules can be applied to the solution of only very specific problems. Sorbents prepared by the modification of areas left unoccupied after the template adsorption also find limited application, because the imprints formed on the surface are complementary to the templates only as regards their geometry.

Being versatile, the materials obtained by polycondensation of siloxanes or polymerisation of organic monomers in the support pores in the presence of template molecules show more promise. It is hoped that mineral supports with imprints, first of all, silica will find application in HPLC.

Both the published data and our own experience allow us to suggest that the clarity of the idea of molecular imprinting is rather illusory. The possibility of achieving the desired result is often limited by the ambiguous mechanism of the process under study and, as a consequence, a considerable non-uniformity of generated adsorption sites. Hence, it is not surprising that one can rarely enhance the specificity of a recognising material by more than 30%, whereas biological evolution has developed absolutely specific materials implemented in 'antigene–antibody' interactions. It cannot be ruled out that the use of methods of molecular biology, particularly, the use of aptamers, in the synthesis of recognising materials will prove to be more promising than the attempts to develop chemical models of biological processes. Nonetheless, the synthesis and application of artificial materials with molecular imprints are being progressively developed in scientific studies and occupy the increasingly strong position in many applied fields.

We are grateful to S Z Bernadyuk and A V Buryak for helpful discussions of this review.

[†] For example, see D M Han, G Z Fang, X P Yan. *J. Chromatogr., A* **1100** 131 (2005).

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^a — *Russ. J. Phys. Chem. (Engl. Transl.)*

^b — *Dokl. Chem. (Engl. Transl.)*

^c — *Polim. Sci. (Engl. Transl.)*

^d — *Kinet. Catal. (Engl. Transl.)*

^e — *Colloid. J. (Engl. Transl.)*

^f — *Biophysics (Engl. Transl.)*

^g — *Russ. J. Anal. Chem. (Engl. Transl.)*

Topological structure and relaxation properties of branched polymers

V I Irzhak

Contents

I. Introduction	919
II. Architecture of branched macromolecules	919
III. Rheological properties	922
IV. Relaxation modulus	926
V. Relaxation spectra	929
VI. Conclusion	930

Abstract. Topological structures of branched polymers, including weakly and highly branched chains, star-shaped, H and pom–pom polymers, dendrimers and comb-like, hyperbranched and critically branched polymers, are characterised. Experimental data on their rheological and relaxation properties are analysed. Theoretical approaches to the description of relaxation spectra of branched polymers are outlined. The bibliography includes 272 references.

I. Introduction

The relaxation properties of polymers are to a large extent determined by their architecture.¹ Nevertheless, such factor as branching that influences large-scale relaxation has received much less attention than the molecular mass distribution (MMD). However, the branching factor has attracted considerable interest in recent years² due to the fact that the scope of synthesis of branched-chain polymers with desired topological structures has been widened.^{3–5}

In recent years, the line of investigation associated with the synthesis of hyperbranched (superbranched) polymers (HBP) has been extensively developed in polymer chemistry and technology.^{5–13} This interest is due to the fact that hyperbranched polymers have unique properties. Nanosized HBP particles are soluble in virtually all media and have a high sorption capacity.¹⁴ Due to this fact, HBP have found wide use in technology (polymeric and construction materials, paint and varnish production, organic glasses, nanocomposites, *etc.*), electronics and microelectronics (polyelectrolytes, semiconductors, polymeric plasmons, *etc.*), chemistry (nanosized reactors), medicine (pharmacological nanocontainers) and ecology (sensitive environmental sensors).^{11, 13, 15} In the early stage of the development of science and technology of branched polymers, dendrimers, *i.e.*, polymers having highly regular topological structures (regular Cayley trees, RCT), have been considered as HBP. In scientific literature, emphasis has been given to the development of procedures for the synthesis of dendrimers^{5, 6, 9} and investigation of the rheolog-

ical and sorption properties^{6, 10} associated primarily with the use of dendrimers as transporting agents (for example, to deliver drugs to targeted sites). Evidently, the synthesis of dendrimers is a very complex problem because a stepwise increase in the number of generations is required to meet the condition of regularity of the structure.

In recent years, studies on the synthesis of HBP by conventional methods of polymer chemistry, *i.e.*, by polycondensation and polymerisation, have been extensively carried out.^{11, 12} The resulting topological structures are less regular than those of dendrimers (irregular Cayley trees, ICT). Macromolecules formed by these methods are characterised by a broad molecular mass distribution and a broad distribution over the number of peripheral branches. Nevertheless, the desired properties of these macromolecules are only slightly worse than those of dendrimers and such macromolecules are relatively cheap due to a low cost of the starting materials and the simple synthesis technology.

The relaxation properties of dendrimers were studied in sufficient detail both experimentally^{6, 16–24} and theoretically.^{25–34} However, studies on the relaxation properties of HBP with an irregular topological structure are scarce. A knowledge of these properties can apparently be obtained by analysing the published data on the influence of branching of polymer chains on their relaxation behaviour. In other words, the relaxation properties of weakly and randomly branched polymers, star-like, comb-like, H and pom–pom polymers and critically branched polymers formed in the vicinity of the gel point are of considerable interest. This problem is dealt with in the present review.

II. Architecture of branched macromolecules

The following topological types of branched polymers were described in the literature.

1. **Randomly branched polymers.** The branching number can vary so that macromolecules can be both weakly and highly branched. This type of polymers is characterised by the branching number per chain or per a particular chain length and the average molecular mass of branches. In essence, the topological structure of branched macromolecules is ICT. Each numbered branch (starting from one end of the main chain) belongs to a particular generation. The structures of these chains are determined by the kinetics of the process of their formation, in particular, by the kinetics of the chain transfer reaction through the polymer (as in the case of radical polymerisation of ethylene or vinyl acetate).

2. **Comb-like polymers** are formed if side chains (which can be rather long) are attached to the main chain more or less regularly.

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

Received 22 May 2006

Uspekhi Khimii 75 (10) 1018–1034 (2006); translated by T N Safonova

Generally, the functionality of the branching points (f) is three. However, comb-like macromolecules with $f = 4$ ('centipedes') and $f = 6$ ('barbed wire') are also known. Polymeric molecules with densely attached side branches are considered as one-dimensional polymers (cylindrical brushes).

3. Star-shaped polymers are characterised by the number of branches (arms) coming from a single centre, the functionality and the molecular mass of branches (M_a). It is generally assumed that all branches have the same length. Asymmetric three-arm stars are sometimes called T polymers (two short arms and one long arm) and Y polymers (one short and two long arms).

4. H polymers. By H polymers are meant chains carrying two branches of equal length at each end. These polymers can be characterised by the following two parameters: the molecular masses of the chain and branches.

5. Pom–pom polymers are structurally analogous to H polymers with the difference that the number of branches at both ends is larger than two. Hence, these polymers are characterised by an additional structural parameter, *viz.*, the number of branches at each chain end.

6. Dendrimers are star-shaped (in some publications (see, for example, Refs 25, 27 and 34) these polymers are called 'starbursts'). However, branches coming from the centre belong to the first generation. The arms are branched at the ends to form the second generation of branches, which, in turn, are branched at ends to form the third generation, *etc.* If the first generation consists of f_0 branches and each branch point generates f branches in the next generation, the total number of branches in the k th generation is

$$p_k = f_0 f^{k-1}.$$

The total number of branches in a macromolecule consisting of G generations is

$$P_G = \sum_{k=1}^G p_k = f_0 \frac{f^G - 1}{f - 1}. \quad (1)$$

7. Hyperbranched polymers. The above-described polymer structures are, in essence, HBP. However, since these structures are commonly called dendrimers, the term HBP will be used in reference to tree-like macromolecules with irregular structures (ICT topological structures), which are prepared by conventional polymerisation or polycondensation methods.

The structures of HBP, unlike those of dendrimers, were not unambiguously determined. Hence, *a priori* conclusions about the structures of such polymers can be drawn based on the characteristic features of the mechanism of their formation. Polycondensation of AB_f -type oligomers, for which f is generally equal to 2, is the simplest (from the kinetic point of view) industrial synthesis of HBP.¹³ This process was theoretically studied by the Flory method of combinatorial analysis.³⁵ More recently, various statistical^{36–51} and kinetic methods, including computer simulation,^{49, 52–63} have been used to calculate the MMD function.

In the absence of cyclisation, HBP macromolecules prepared by the above-mentioned method contain one unreacted functional group of type A and $(fn - n + 1)$ functional groups of type B (n is the number of monomeric units in the molecule). Hence, the degrees of conversion at these groups (α_A or α_B , respectively) are related to each other by the following equation

$$\alpha_A = f\alpha_B.$$

The distribution function over groups B is determined by the equations

$$\langle b \rangle_n = (f - 1) \bar{P}_n + 1,$$

$$\langle b \rangle_w = \frac{(f - 1)^2 \bar{P}_w \bar{P}_n + 2(f - 1) \bar{P}_n + 1}{1 + (f - 1) \bar{P}_n},$$

$$\frac{\langle b \rangle_w}{\langle b \rangle_n} \approx \frac{\bar{P}_w}{\bar{P}_n},$$

where the average degrees of polymerisation (in the absence of the substitution effect, *i.e.*, calculated statistically) are as follows:

$$\bar{P}_n = (1 - \alpha_A)^{-1},$$

$$\bar{P}_w = \frac{f - \alpha_A^2}{f(1 - \alpha_A)^2},$$

$$\frac{\bar{P}_w}{\bar{P}_n} = \frac{f - \alpha_A^2}{f} \bar{P}_n = \frac{1}{f} (1 + \alpha_A) + \frac{f - 1}{f} \bar{P}_n.$$

It is evident that both the average degrees of polymerisation and their ratio characterising the width of the molecular mass distribution and, correspondingly, the distribution over functional groups B increase indefinitely with increasing degree of conversion.

An alternative method of calculation of MMD for hyperbranched polymers based on the principles of percolation theory⁶⁴ was developed in Ref. 59. If an HBP macromolecule is represented as a critical cluster, the distribution function (*i.e.*, the fraction of molecules containing n monomeric units) is described by the equation

$$p_n \cong n^{-\tau} f\left(\frac{n}{n_{\max}}\right),$$

where, according to the percolation theory,⁶⁵ $\tau = 3/2$, $f \sim \exp(-n/n_{\max})$, $n_{\max} \sim (1 - \alpha_A)^{-1/\sigma}$, $\sigma = 1/2$. For HBP, the distribution function takes the following form:

$$p_n = \begin{cases} \frac{n^{\tau-2}}{\Gamma(\tau-2, \beta)} \exp\left(-\frac{n}{n_{\max}}\right) & \text{at } n_{\min} < n < n_{\max}; \\ 0 & \text{at } n_{\min} > n > n_{\max}, \end{cases}$$

Γ is the incomplete gamma function, and $\beta = n_{\min}/n_{\max}$.

The so-called Frey parameter⁶⁵ or the degree of branching (DB), which is equal to zero[†] for linear polymers and equal to unity for ideal dendrimers, is used for topological characterisation of more complex systems (for example, of those prepared by polycondensation $AB_f + B_g$ or polymerisation). For systems consisting of AB_2 -type oligomers, this parameter is equal to the ratio of twice the number of branching units (d) to the sum of twice the number of branching and linear units (l)

$$DB = \frac{2d}{2d + l}.$$

For oligomers AB_f ,

$$DB = \frac{fd}{fd + l}.$$

Finally, in the general case, including various polymerisation methods of synthesis (and not only of HBP),

$$DB = \frac{d + t}{d + t + l},$$

where t is the number of end units. As an example, let us mention the results of the study,⁶⁶ where the structure of commercial HBP 'Boltorn', which was prepared by polycondensation of 2,2-bis-(hydroxymethyl)propionic acid with pentaerythritol as the central core, was examined. Due to the statistical character of the process, the macromolecules contained all three types of fragments (Table 1).

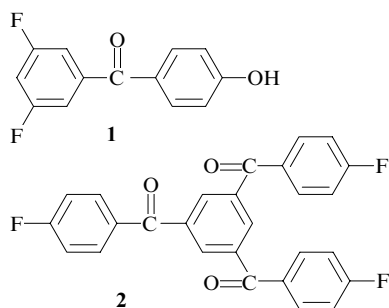
[†] To be more precise, $2/P_n \approx 0$.

Table 1. Characteristics of HBP 'Boltorn'.⁶⁶

$\langle P \rangle_n$	d (%)	t (%)	l (%)	DB
16.68	13.5	28.5	58.0	0.42
21.37	16.5	26.5	57.0	0.43
61.36	17.5	23.5	59.0	0.41

Evidently, variations in either the structure⁶⁷ or concentration in the central core⁶⁸ will lead to changes in the degree of branching.

For example, it was demonstrated⁶⁸ that DB for the polycondensation product of compound **1** is 0.49, whereas DB are 0.62 and 0.67 for copolycondensation of compounds **1** and **2** in 2 : 1 molar ratios of 1 : 57 and 1 : 28, respectively.



The topological structure of HBP is determined by the kinetic parameters of the processes of their formation. In a number of studies,^{54,56} the degree of branching was demonstrated to be dependent on the ratio of the kinetic constants of the first (k_1) and second (k_2) addition, *i.e.*, on the substitution effect, even in the simplest case of polycondensation of AB₂-type oligomers. In the case of $k_1 = k_2$, *i.e.*, in the limit, at $\alpha_B = 1$, DB is 0.5. The degree of branching increases and approaches unity as the $k_2:k_1$ ratio increases; and DB decreases as this ratio decreases. In other words, the positive substitution effect results in that HBP are similar in the branching parameter to dendrimers, although the topological structure of HBP corresponds to ICT due to the statistical character of the process. In the case of the negative substitution effect, HBP have an architecture of linear polymers. The results of kinetic analysis of the structure of a model polymer (a computer model) performed in the study⁴⁹ are given in Table 2. The structure of the macromolecule was expressed in terms of the relative concentrations of the diads of the monomeric units of different types: branching units containing both reacted groups B, end units containing both unreacted groups and middle units containing one reacted group B.

Table 2. Influence of the ratio of the kinetic constants of the first and second addition on the characteristics of the structure of a model polymer.⁴⁹

Parameter ^a	$k_1:k_2 = 1:1$	$k_1:k_2 = 1:0.1$	$k_1:k_2 = 1:10$
$l-t$	0.125	0.065	0.047
$l-l$	0.250	0.715	0.012
$l-d$	0.125	0.065	0.047
$d-t$	0.125	0.012	0.399
$d-l$	0.250	0.131	0.096
$d-d$	0.125	0.012	0.399
T	0.250	0.078	0.447
L	0.500	0.844	0.106
D	0.250	0.078	0.47
DB	0.50	0.156	0.894

^a T , L and D are the fractions of the monomeric units t , l and d , respectively.

Polycondensation of monomers, such as *p*-chloromethylstyrene (inimers),⁶⁹ in the presence of a polyfunctional initiator is a prominent example of the influence of the kinetics of the formation of HBP on their structure. It was demonstrated^{70,71} that the polydispersity and the degree of branching of the product can be changed by varying the rate of addition of the monomer into a reactor.

The cyclisation reaction has a substantial effect on the topological structure of HBP.^{53,54,72,73} For example, polycondensation of 2,2-bis(hydroxymethyl)propionic acid was demonstrated⁵³ to afford macromolecules containing rings that are formed as a result of the intramolecular reaction of the acidic and hydroxy groups (Table 3).

Table 3. Mole fractions of poly[2,2-bis(hydroxymethyl)propionic acid] macromolecules containing rings at different degrees of conversion (α_A) and degrees of polymerisation (n).⁵³

n	$\alpha_A = 0.840$	$\alpha_A = 0.947$	$\alpha_A = 0.981$
4	0.15	0.30	0.48
5	0.30	0.47	0.60
6	0.39	0.46	0.83
7	0.28	0.47	0.75
8	0.29	0.42	0.75
9	0.34	0.66	0.77
10	0.27	0.61	0.74
11	0.24	0.48	0.68
12	0.29	0.63	0.87
13	—	0.64	0.92

As can be seen from Table 3, the molar fraction of macromolecules containing rings is virtually independent of the degree of polymerisation (the exception is the tetramer) but noticeably increases with increasing degree of conversion. It should be noted that cyclisation substantially limits the average degree of polymerisation so that $\bar{P}_w$ is finite even at $\alpha_A = 1$. This fact was confirmed experimentally⁷³ in the study of siloxysilane-based HBP of types AB₂, AB₄ and AB₆ and theoretically by the results of kinetic calculations and computer simulation.^{53,54,74} The in-depth study of polycondensation of oligomers AB₂ and AB₄ by the Monte Carlo method demonstrated⁷⁴ that, in the limit, all macromolecules contain rings of which more than 80% are the simplest rings, so that the average ring size for these oligomers is 1.65 and 1.39, respectively. In this case, the maximum average degrees of polymerisation are 10.7 and 7.5, respectively.

The fact that the structural characteristics (DB, $\bar{M}_n$ and $\bar{M}_w$) of commercial HBP 'Boltorn H40' differ substantially from the corresponding values calculated by probability methods is attributed⁷⁵ to the influence of various kinetic factors. Evidently, these factors have a more pronounced effect in the polymerisation method of synthesis of HBP. For example, the width of MMD in the case of radical copolymerisation of methyl methacrylate with ethylene glycol diacrylate (the molar ratio is 100:15) in the presence of dodecylmercaptan as a chain-transfer agent substantially depends on the concentration of the latter (Fig. 1). Both the ratio $\langle \bar{M} \rangle_w / \langle \bar{M} \rangle_n$ and $\langle \bar{M} \rangle_w$ exponentially decrease with increasing concentration.⁷⁶

When considering the properties of branched polymers, the following fact should be taken into account. Weakly branched macromolecules, such as polymers with rarely attached side branches, H polymers and stars with a small number of arms, are characterised by the absence of intramolecular steric hindrance so that all branches adopt a Gaussian conformation. Comb-like polymers, stars with a large number of arms, dendrimers and HBP are characterised by intramolecular steric hindrance and only peripheral fragments of their chains can adopt a Gaussian conformation. These macromolecules consist of a core with an extended conformation of the chains and low-mobility monomeric units and the peripheral shell with the

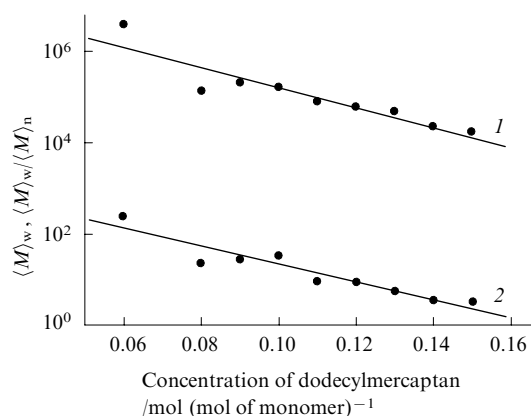


Figure 1. Plot of the parameters of the topological structures of HBP prepared by radical copolymerisation of methyl methacrylate with ethylene glycol diacrylate in the presence of dodecylmercaptan as the chain-transfer agent vs. the concentration of the latter.⁷⁶
(1) $\langle M \rangle_w$, (2) $\langle M \rangle_w / \langle M \rangle_n$.

Gaussian conformation of the chains and flexible monomeric units.^{25, 77, 78} According to theoretical⁷⁹ and experimental⁸⁰ data, peripheral chains are somewhat extended.

The presence of this heterogeneous structure is reflected in the ratio of the hydrodynamic radius of the macromolecule (R_h) to the radius of gyration (R_g)

$$\rho = \frac{R_h}{R_g}.$$

This parameter quantitatively characterises the average density of monomeric units in the globule formed by the polymer.⁸¹ For example, $\rho = 1.291$ for a dense sphere, $\rho = 0.73$ – 0.78 for linear polystyrene, and ρ is 1.043 and 0.971 for ~ 50 -arm stars containing branches with a molecular mass of 10^4 and 2×10^4 , respectively. A decrease in the average density with increasing length of branches is evidently associated with the change in the ratio of the volume of the core to the volume of the shell.

Study by pulsed NMR spectroscopy demonstrated⁷⁸ that hyperbranched poly(ether ketones) have a heterogeneous structure. Two correlation times are indicative of the presence of a solid core and a loose shell.

The solid-like structure of the core of 3-ethyl-3-(hydroxymethyl)oxetane-based HBP is evidenced by the results of the study of the value and structure of the free volume by the positron annihilation method.⁸² The free volume increases with increasing DB, whereas the glass transition temperature decreases. At the same time, the presence of a solid-like structure (paracrystalline structure according to the classification proposed in the study⁸²) with a certain distribution of the free volume over holes is detected even at temperatures higher than T_g .

Due to interactions between branches, the rigidity of comb-like macromolecules increases,^{83, 84} so that such polymers adopt an extended conformation even in θ conditions.⁸⁵

8. Critically branched macromolecules (critical clusters). The formation of cross-linked polymers by all methods (polycondensation, polymerisation or cross-linking) is accompanied by a substantial increase in the molecular mass and broadening of MMD as the conversion approaches the critical value α_c (the gelation point).^{35, 86–88} For example, experiments demonstrated⁸⁹ that polycondensation leads to an exponential increase in the molecular mass in the vicinity of α_c

$$\bar{M}_w \propto |\alpha_c - \alpha|^{-\gamma},$$

where $\gamma = 1.8 \pm 0.3$. According to the mean-field theory,³⁵ $\gamma = 2$, whereas $\gamma = 1.74$ according to the percolation theory.⁶⁴ Once the gel point is achieved, an infinite cluster is formed,^{90, 91} and then this cluster is transformed into a gel fraction. After gel point is

attained, the width of MMD of the components of the finite-size sol fraction decreases.^{86, 88} Therefore, polymers have a specific topological structure at the gel point, and this structure is characterised in terms of the formalism of fractal geometry.^{64, 92} The fractal dimensionality of the cluster (D_f) determines the relation between the volume and the mass

$$R \propto M^{1/D_f},$$

where R is the radius and M is the mass of the cluster. It is known^{93, 94} that $D_f = 2$ for linear ‘bodyless’ chains, and $D_f = 5/3$ if the excluded volume effect is taken into account. According to the percolation theory,^{64, 92} $D_f = 2.53$ in the critical conversion region. Consequently, branched macromolecules have smaller volume in this region compared to linear chains.

III. Rheological properties

The viscosity (η) of melts of linear polymers is related to their molecular masses in a complex way. Low-molecular-weight compounds are characterised by a linear dependence, whereas macromolecules whose molecular masses are larger than the critical value (M_c) are characterised by an exponential dependence, the exponent being generally taken equal to 3.4 ± 0.2 (see Refs 94–96) (in the studies,^{97–99} this exponent was found to be 4). The change in the type of the dependence is attributed to the formation of an entangled network accompanied by a change in the type of motion of macromolecules (from free to reptation).^{94–96} The average molecular mass of entangled networks is expressed by the equation

$$M_e = \frac{M_c}{2}.$$

According to the classical reptation theory,^{95, 96}

$$\eta \propto M^3,$$

but this relation is true only for very large molecular masses ($M \gg M_c$). In particular,⁹⁹ for 1,4-polyisoprene $M > 2 \times 10^5$, whereas $M_c = 1.35 \times 10^4$.

It is known^{86, 100–102} that the viscosity of polymers is described by the dependence

$$\eta \propto [\eta]^v \text{ or } \eta \propto R^v,$$

where $[\eta]$ is the characteristic viscosity, the exponent $v \approx 6$ – 7 , and R is the rms radius of the globule. The validity of this relation was experimentally established for different types of polymers, such as linear polymers with different degrees of rigidity, cyclic polymers, star-shaped polymers with different branch numbers, H polymers, comb-like polymers, randomly branched polymers and cross-linked polymer globules.^{103–107}

Therefore, if the viscosity is considered as a function of the globule size (an argument), it is independent of the topology of the polymer. However, the globule size is very sensitive to the chain structure.^{94, 108–116} For macromolecules with equal molecular masses, the larger the branching in the macromolecule, the smaller the rms radius of the globule. The shrinkage factors g for multifunctional stars, *i.e.*, the ratios of the characteristic viscosities of star-shaped and linear polymers with equal molecular masses under θ conditions, are given as an example in Table 4.

There is evidence that the ratio of the radius of gyration of a macromolecular star to the radius of gyration of a branch increases depending on the functionality only to $f \approx 6$ and remains unchanged upon a further increase in f .¹¹⁷ This is also true for stars with a polydisperse length distribution of branches.

In the study,¹¹⁸ branched polyethylene macromolecules were synthesised and their topological structures were determined. These macromolecules were demonstrated to be A_2B -type three-arm stars (T polymers), pom–pom and comb-like polymers. The following equations were demonstrated to be fulfilled with high accuracy.

Table 4. Dependence of the size of a globule formed by stars on their functionality (the number of arms).

Polymer	Solvent	$T/^{\circ}\text{C}$	f	g	Ref.
Polystyrene	Cyclohexane	35	3	0.78	111
			4	0.63	111
			6	0.46	111
			12	0.275	112
Polybutadiene	Dioxane	26.5	32	0.151	113
			64	0.092	114
			270	0.06	115
Polyisoprene	Dioxane	34	4	0.65	111
			6	0.46	111
Polytetrahydrofuran	THF	25	3	0.81	116
			6	0.64	116

For stars,

$$g = 1 - \frac{6s}{(s+2)^3} = 1 - \frac{3}{2}\mu(1-\mu)^2,$$

where s is the ratio M_A/M_B , $\mu = M_A/M$, and M is the molecular mass of the polymer.

The plot $g(\mu)$ is a curve with a minimum, the minimum value $g = 7/9$ corresponding to a star with equal arms. At $\mu = 0$ and 1, g is equal to unity, because a linear chain is formed in both cases.

For pom–pom polymers,

$$g = \mu^3 + 3\mu^2(1-\mu) + \frac{3}{2}\left(\frac{f+1}{f}\right)\mu(1-\mu)^2 + \frac{3f-1}{2f^2}(1-\mu)^3,$$

where $\mu = M_0/M$, M_0 is the molecular mass of the main chain, and f is the functionality of the branching point.

For comb-like polymers,

$$g = \mu^3 + \frac{2p+1}{p+1}\mu^2(1-\mu) + \frac{p+2}{p}\mu(1-\mu)^2 + \frac{3p-2}{p^2}(1-\mu)^3,$$

where $\mu = M_0/M$ and p is the number of side branches.

In the last-mentioned two cases, the plots $g(\mu)$ are monotonic curves. As $\mu \rightarrow 1$, the functions $g(\mu)$ tend to unity. When $\mu \rightarrow 0$, i.e., when most of the polymer mass is in branches, these functions tend, respectively, to

$$g = \frac{3f-1}{2f^2} \quad \text{and} \quad g = \frac{3p-2}{p^2}.$$

It should be noted that the latter equation is not fulfilled for comb-like polymers based on polystyrene^{119,120} and poly(α -methylstyrene).¹²¹

An ellipsoid shape typical of linear macromolecules is transformed into a spherical shape in the case of symmetric star-shaped polymers, the asphericity decreases with increasing number of arms.¹²²

In the presence of branches, the characteristic viscosity depends more weakly on the molecular mass [the Mark–Kuhn–Houwink (MKH) equation]. For example, the $[\eta]$ functions (tetrahydrofuran, 30 °C) of the molecular mass of polystyrene with different topological structures take the following form:⁸¹ for linear polymers,

$$[\eta] = 9.6 \times 10^{-5} \bar{M}_w^{0.73},$$

for 8-arm stars,

$$[\eta] = 1.42 \times 10^{-4} \bar{M}_w^{0.68},$$

for polymers with the number of arms > 20 ,

$$[\eta] = 6.45 \times 10^{-4} \bar{M}_w^{0.39}.$$

Dendrimers are characterised by an even weaker dependence. For example, the exponent in the MKH equation for a propyleneimine-based polymer containing the diaminobutane core and for a polyamidoamine-based polymer is 0.235¹²³ and 0.05,¹²⁴ respectively.

Theoretical analysis of the dynamics in dendrimers demonstrated²⁷ that the characteristic viscosity linearly depends on the number of generations (calculations were performed up to the seventh generation). A linear dependence was found also for HBP prepared by polycondensation of 2,2-bis(hydroxymethyl)propionic acid with tetrafunctional ethoxylated pentaerythritol as the central core.¹²⁵ It should be taken into account that the notion of generation for HBP is arbitrary and implies not the macromolecular structure but the composition of the reaction mixture. The first generation is formed when the reactants are used in a molar ratio of 1:4; the second generation, in a molar ratio of 1:12; the third generation, in a molar ratio of 1:28, etc. [see Eqn (1)]. As opposed to dendrimers, the width of MMD for HBP increases with increasing number of the generation (Fig. 2). Figure 2 shows also the dependences of the characteristic viscosity and the exponent (a) in the MKH equation vs. the number of generations. Evidently, it is the increase in the polydispersity of HBP that leads to an increase in the two last-mentioned characteristics.

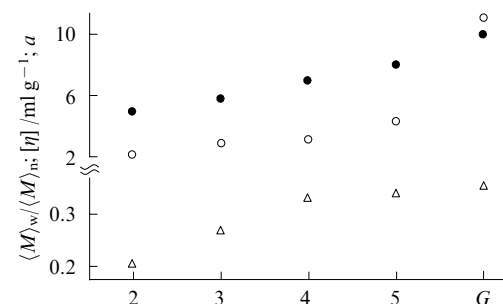


Figure 2. Dependence of the parameters of the topological structure of HBP prepared by polycondensation of 2,2-bis(hydroxymethyl)propionic acid on the number of generation.¹²³ (1) $\langle \bar{M} \rangle_w / \langle \bar{M} \rangle_n$, (2) $[\eta]$, (3) the exponent in the MKH equation.

Study of the structures of dendrimers³³ by Monte Carlo computer simulation using the bond fluctuation model^{126,127} demonstrated that the hydrodynamic radius of the macromolecule almost linearly increases with increasing number of the generation G , whereas the analogous plot of the characteristic viscosity is a curve with a maximum (Fig. 3). These results are in agreement with experimental data¹²⁸ for dendrimers based on 3,5-dihydroxybenzyl alcohol with 1,1,1-tris(4-hydroxyphenyl)ethane as the central core. The non-monotonic character of the curve $[\eta] = f(G)$ was found also in the studies.^{32,129–132}

However, there is experimental evidence for the absence of the maximum in the plots of $[\eta]$ vs. the number of the generation.^{133–135} Data for a polybutylcarbosilane dendrimer¹³⁵ presented in Fig. 3 (straight line 3) serve as an example.

The non-monotonic character of the dependence under consideration is due to a change in the fractal dimension of the macromolecule as the number of generations of the dendrimer increases. The authors believe¹³² that the behaviour changes from being of polymer type to colloidal type. Actually, as can be seen from the results of the study³³ presented in Fig. 4, the density distribution of monomers in the bulk of the globule becomes more uniform (excluding the central core) with increasing G . Analogous results were obtained in the study³² by molecular dynamics. Analysis of the ratio of the radius of gyration of the globule R_g

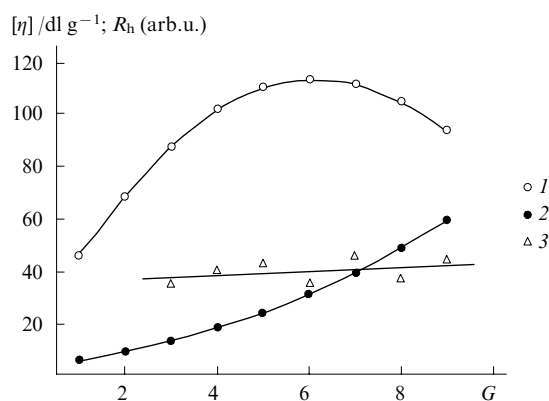


Figure 3. Plots of the characteristics of a dendrimer globule on the number of generation.
(1) $[\eta]$, (2) the hydrodynamic radius R_h (computer simulation data³³), (3) $[\eta] \times 10^3$ (results of the study¹³⁵).

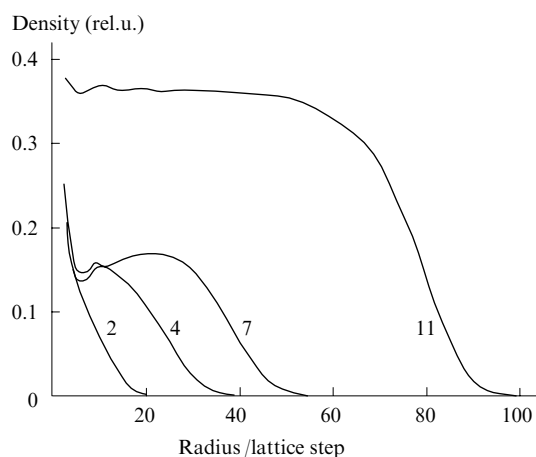


Figure 4. Density distribution of monomeric units in the bulk of a dendrimer globule based on computer simulation data.³³
The numbers of generations are given above the curves.

formed by different dendrimers to the hydrodynamic radius R_h depending on the number of generations G demonstrated²⁴ that this ratio varies from 1.17 (typical of Gaussian chains) to 0.77 (characteristic of a solid sphere). In other words, the average density of monomeric units in macromolecules increases with increasing globule size.

However, the character of the density distribution depends to a large extent on the following factors: the degree of intermolecular interactions between branches,¹³³ the exclusion volume¹³⁶ and the flexibility of branches.¹³⁷ In the absence of an extreme dependence, polymers are characterised by high density, which is the same for different generations (this fact was demonstrated in the study¹³⁵). In other words, in these cases dendrimers of all studied generations exhibit properties of colloidal rather than polymeric particles.

As for HBP, an analogous dependence for the characteristic viscosity was found by computer simulation.¹³⁸ To our knowledge, direct experimental evidence is lacking.

Branched chains are characterised by a complicated thermorheological behaviour^{107, 139–149} due to the fact that the effective energy of viscous flow of branched polymers (unlike that of linear polymers) depends on the molecular mass, MMD and the degree of branching. It is even proposed to use these dependences for the determination of weak long-chain branching, which cannot be revealed by other methods.¹⁴⁸ For example, the temperature dependence of the viscosity of a low-density polyethylene melt

characterised by long-chain branching was demonstrated¹⁵⁰ to be a function of MMD. The effective activation energy (E_a) of flow increases from 25.5 to 36.8 kJ mol^{−1} as the polydispersity index $\langle M \rangle_w / \langle M \rangle_n$ changes from 3.3 to 12.7.

Analogous results were obtained for polycarbonate.¹⁵¹ The temperature dependence of flow of linear polycarbonate is determined by $E_a = 109$ kJ mol^{−1}, whereas $E_a = 121$ kJ mol^{−1} for a branched polymer (~ 0.7 branchings per chain) with approximately the same molecular mass and the polydispersity index.

The relationship between E_a and the degree of branching L ($L < 1$ per 10^4 carbon atoms of the polyethylene chain) is represented by the relation:¹⁴⁷

$$E_a \propto \bar{M}_w^2 L.$$

It was demonstrated¹⁵² that

$$E_a \propto \log \bar{M}_w,$$

if the polyethylene chain adopts a configuration of three- or four-arm symmetric and asymmetric stars as well as of H- and comb-like (up to 30 branches) polymers.

The prevailing opinion is that the thermorheological effect is associated with the globule size. It is suggested that the influence of the temperature on the viscosity is determined not only by the temperature dependence of the friction coefficient but also by the temperature coefficient of the globule size¹⁵³

$$\kappa = \frac{d \ln \langle r^2 \rangle}{dT},$$

where $\langle r^2 \rangle$ is the rms radius of gyration of the macromolecule. The coefficient κ increases with increasing degree of branching.^{107, 142, 143} As a consequence, the effective activation energy of viscosity also increases.

Graessley hypothesised¹³⁹ that the part of the activation energy associated with the branching effect is related to the branch length by the equation

$$E_b = A \frac{M_a}{M_e},$$

where A is the coefficient dependent on the chemical structure of macromolecules and the coefficient κ .

However, it appeared that the relationship between A and κ is rather complex and even non-correlated.^{1, 154} Apparently, the nature of the thermorheological effect is not associated with the topological properties of the macromolecular globule. Actually, globules formed by macromolecules, including those formed by branched molecules,¹⁵⁵ in blocks have a θ size and the temperature has no effect on this parameter, as opposed to the state in dilute solutions.⁹⁴ The concentration of entanglements is also temperature independent because the entanglements are not energetic in nature.⁹⁴ However, the temperature exerts a strong effect on the concentration and the lifetime of branching points of the physical network,¹⁵⁶ such as nematic clusters.¹⁵⁷ This hypothesis is supported, for example, by the fact that the thermorheological properties are typical of polyethylene,^{147, 158} which is prone to crystallisation and, consequently, to the formation of nematic clusters, but is not typical of an essentially amorphous polystyrene.¹⁵⁴ Therefore, the phenomenon under consideration is most likely associated with the physical network rather than with entanglements. The fact that it is necessary to take into account energy interactions was also noted in the study,¹⁵⁹ where a hairpin model, *viz.*, intrachain folded structures, was considered.

The characteristic viscosity of weakly branched polyethylene chains (the number of branches per 10^4 carbon atoms of the main chain < 1) is similar to that of linear chains with the same molecular mass,^{160–163} but the viscosity of the former is higher.^{147, 158, 161–164} For example, the region of the degrees of branching L up to 0.5 per 10^4 carbon atoms is characterised¹⁶⁴ by

$$\eta \propto \exp(5.6 L).$$

An increase in the viscosity with increasing degree of branching was observed for polypropylene as well.¹⁶⁵

The viscosity of polyethylene was demonstrated¹⁵² to depend approximately exponentially on the molecular mass if the chain adopts a configuration of three- or four-arm symmetric stars, asymmetric stars or H polymers. For symmetric stars, the following relation is fulfilled:

$$\eta \propto M_a^{6.5}.$$

For asymmetric stars, no analogous relations were found.

In the study of 1,4-polyisoprene, the viscosity of three-arm stars, including asymmetric stars, was demonstrated¹⁶⁶ to depend on the molecular mass of the largest branch as $M^{5.9}$ (M_a/M_e was varied from 7 to 43).

For moderately and highly branched polyethylene macromolecules (the number of branches per 10^4 carbon atoms of the main chain is much larger than unity), $g < 1$. As a consequence, their viscosity is lower than that of linear macromolecules with the same molecular mass.¹⁶⁷ Analogous results were obtained for polypropylene (the number of branches varies from 0.8 to 7.8 per 10^4 carbon atoms)¹⁶⁸ and poly(methyl methacrylate) (185 branches per 10^4 carbon atoms).¹⁶⁹ In the former case, the viscosity decreases by a factor of ~ 50 , and it decreases by more than two orders of magnitude in the latter case.

In the reptation theory of star-shaped chains,^{96, 154, 170} the following equation was derived:

$$\eta \propto \left(\frac{M_a}{M_e}\right)^b \exp\left(\nu \frac{M_a}{M_e}\right), \quad (2)$$

where b and ν are model parameters.

Relation (2) reflects the fact that the ratio of the radius of a globule formed by star macromolecules to the radius of the branch is independent of the number of branches at $f > 6$, this relation being true for both monodisperse and random length distributions of branches.¹⁷¹ Actually, it was experimentally demonstrated¹⁷² that the viscosity of star-shaped polymers is independent of the branch number if the latter is larger than three, but the viscosity depends almost exponentially on M_a .^{96, 173} The corresponding data for monodisperse star polyisoprene are shown in Fig. 5. It can be seen that the number of branches is of no significance. Polymers with small M_a (see Fig. 5a) obey the power law with the exponent of 2, and polymers with large M_a (see Fig. 5b) are governed by the exponential law according to Eqn (2).

The rheological properties of dendrimers with a small number of generations ($G < 4$) are similar to those of star-shaped polymers.^{21, 130, 174} Due to a spherical shape and a rather close packing of dendrimers with a large number of generations, the properties of solutions and melts of such polymers are analogous to those of colloidal compounds.^{19, 21, 23, 32, 130, 174, 175} The dependence of the viscosity on the molecular mass of amidoamine-based dendrimers was demonstrated¹⁷⁵ to be quadratic for low G and linear for high G (G varies from 1 to 7, and the molecular masses vary from 5×10^2 to 1.17×10^5). The same dependences were found for propyleneimine-based dendrimers.¹⁹ This was confirmed by data from computer simulation by molecular dynamics.³²

Since the topological structure of HBP can vary over a wide range, the rheological characteristics of these polymers are ambiguous. The plots of the viscosity of HBP prepared by copolycondensation of AB₂-type monomers $\{N\text{-}[3,5\text{-di}(\text{tert-butyl} \text{dimethylsilyloxy})\text{phenyl}]\text{-4-fluorophthalimide}\}$ with AB-type monomers $\{N\text{-}[3\text{-}(\text{tert-butyl} \text{dimethylsilyloxy})\text{phenyl}]\text{-4-fluorophthalimide}\}$ ¹⁷⁶ vs. the degree of branching and $[\eta] = f(\text{DB})$ (see Ref. 177) are presented in Fig. 6. A decrease in the degree of branching due to an increase in the fraction of linear fragments in the structure of a copolymer leads to an exponential increase in the volume of a globule formed by the macromolecules and, consequently, in the viscosity of HBP melts.

The viscosity of highly branched polymers is also described by the relation (2).^{19, 173, 178, 179} It was experimentally

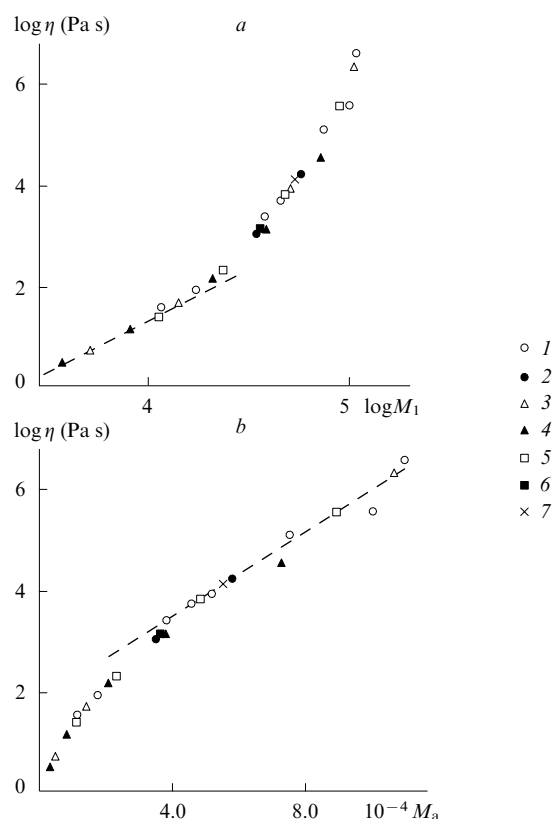


Figure 5. Plots of the viscosity of the polyisoprene melt vs. the molecular mass of the arm in logarithmic (a) and semilogarithmic (b) coordinates.¹⁷³ The functionality: (1) 4, (2) 5, (3) 8, (4) 12, (5) 18, (6) 27, (7) 33.

found^{96, 107, 154, 180–182} that in this case $0.5 \leq b \leq 2$, $\nu < 1$ (according to the reptation theory,⁹⁶ $b = 2$, $\nu = 15/8$).

As in the case of linear polymers, the dependence of the viscosity of solutions and melts of branched polymers on the conditions of their deformation, *i.e.*, non-Newtonian flow is observed only for rather large molecules. At the same time, the degree of branching plays an important role. It was demonstrated¹⁶⁷ that the critical shear rate $\dot{\gamma}_c$, which determines the region where the viscosity begins to decrease with increasing shear rate, increases with increasing degree of branching of weakly branched low-density polyethylene. These results were confirmed by the data from computer simulation by molecular dynamics.¹⁸³ Analogous results were obtained for polycarbonate.¹⁵¹ For the same degree of polymerisation, star-shaped (from 3 to 6 arms),

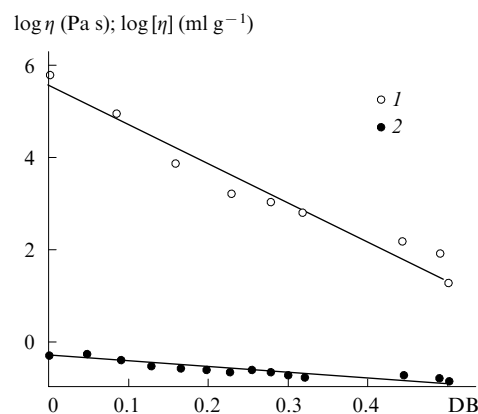


Figure 6. Plots of the viscosity of the melt (1) and the characteristic viscosity (2) of HBP vs. the degree of branching.^{176, 177}

comb-like (from 4 to 8 branches) and H polymers are characterised by higher viscosity at high shear rates compared to linear polymers. At the same time, linear polymers are characterised by a larger difference between normal stresses. Branched polymers have a high longitudinal viscosity^{184,185} and are characterised by an increase in the viscosity with time in the course of uniaxial deformation.^{168,186–193} The higher the degree of branching the larger the increase in viscosity. Highly branched polyethylene, which was prepared with the use of the complex (Pd + diimine) catalyst, shows Newtonian flow behaviour.¹⁹⁴

In studies of polyamidoamine,^{21,174} it was demonstrated that dendrimers exhibit the same properties; the smaller the number of the generation G , the larger γ_c . At $G = 1$, no decrease in the viscosity in the region of shear rates under study (approximately up to $3 \times 10^2 \text{ s}^{-1}$) was observed. The effect of a decrease in the viscosity with increasing molecular mass of propyleneimine-based dendrimers and HBP having a chemical structure of ester and ester amide was found in the study.¹⁹ The viscosity of low-molecular-weight compounds ($\bar{M}_n < 4.3 \times 10^2$) is independent of the shear rate (Newtonian flow). Melts of a dendrimer based on 2-dimethylpropionic acid up to the fifth generation inclusive¹⁷⁹ and a dendrimer based on polyamidoamine at low temperatures up to the sixth generation behave analogously. At higher temperatures, the viscosity depends on the shear rate, the temperature range of Newtonian flow decreasing with increasing number of the generation. For $G = 2$, Newtonian flow is retained up to 85°C ; for $G = 4$, up to 70°C , whereas the dependence of the viscosity on the shear rate for $G = 6$ is observed already at 40°C .²¹

The characteristic rheological features of HBP depend on their structure. Study of poly(ester amide)¹⁹⁵ demonstrated that the higher DB the smaller γ_c .

Hyperbranched polymers based on esters and ester imides¹⁷⁶ have the same properties, γ_c decreasing with increasing DB due to an increase in the fraction of an AB-type copolymer. An analogous effect was documented in the study by molecular dynamics of HBP with a variable length of linear fragments.¹⁹⁶

The chemical structure of terminal groups responsible for the character of intra- and intermolecular interactions is an important factor that has an effect not only on the rheological properties of hyperbranched polymers but also on the glass transition temperature.¹³ For example, the viscosities of dendrimers based on propyleneimine with terminal nitrile groups differ by an order of magnitude from those of dendrimers with terminal amino groups.¹⁹ In the latter case, the structure of macromolecules is more compact and, consequently, the viscosity is lower due apparently to intramolecular hydrogen bonding. An HBP melt based on polyester with terminal hydroxy groups shows Newtonian flow behaviour, whereas the flow of concentrated solutions of ester imide HBP is non-Newtonian (the viscosity depends on the shear rate). The replacement of 60% of terminal hydroxy groups in HBP prepared from 2,2-bis(hydroxymethyl)propionic acid by the ester groups $\text{O}_2\text{C}(\text{CH}_2)_{10}\text{Me}$ leads to a decrease in the viscosity by more than two orders of magnitude.¹²⁵ It was demonstrated³⁰ that the flow of polyamidoamine dendrimers is temperature dependent. The higher the temperature, the more substantial the non-Newtonian character of flow. This phenomenon is apparently associated with a decrease in the concentration of intramolecular hydrogen bonds and formation of a labile network due to chain–chain intermolecular interactions. The possible mechanism of this process was proposed in the study.¹⁹⁷ It was hypothesised¹⁹⁸ that a substantial difference in the character of intermolecular interactions is responsible for a sharp decrease in the viscosity of melts of three-arm star polybutadienes upon the replacement of terminal dimethylamino groups by polar zwitterionic groups.

IV. Relaxation modulus

Main theories of the relaxation mechanism of branched polymers^{2,154,199–201} are based, first, on the tube model,[‡] and, second, on the hierarchy of relaxation processes.^{166,202–206} De Gennes considered diffusion of star-shaped chains in the presence of fixed obstacles and demonstrated¹⁷⁰ that the branching point is fixed in space and, consequently, the reptation motion is forbidden until the relaxation process to this point is not completed. In the presence of several branches, the term ‘hierarchy’ of relaxation is introduced,^{207–209} which is determined by the relaxation time dependent on the branch length. The scheme of relaxation of branched macromolecules is shown in Fig. 7. It is suggested that the shortest branch is the first to relax, resulting in an increase in the effective friction coefficient of the main-chain unit linked to the branching point. Then the same occurs with longer branches, the longer being the branch the larger being the corresponding friction coefficients. Only once relaxation of the longest branch is completed, the reptation motion of the whole macromolecule becomes possible. When estimating the relaxation times of branches of the second and succeeding hierarchical levels, it is customary to take into account dynamic expansion of a tube due to relaxation of branches,¹⁹⁹ i.e., the influence of the number of branches is analogous to the solvent effect. It should be noted that there is a reason^{210,211} to doubt the necessity of taking into account this effect.

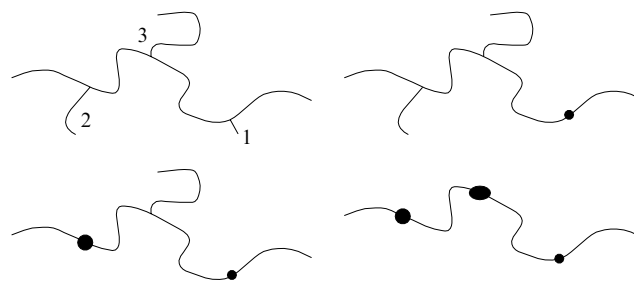


Figure 7. Scheme of relaxation of branched macromolecules, in which the branch length is larger than M_e .

The numbers at branches correspond to the hierarchical level. The size of branching points reflects the effective friction coefficient.

The concentration of fragments belonging to this hierarchical level is determined by the equation

$$c_i = N_i \frac{M_{bi}}{M_w},$$

where N_i and M_{bi} are the number of branches of the i th level and their molecular mass, respectively.

From the aforesaid, according to the publication,²¹² the following hierarchy of the relaxation times of ICT can be proposed. The time required for reaching the coordinate s by the end of the chain belonging to the first hierarchical level is determined by the equation¹⁷²

$$t_1(s) = t_0 \left[\frac{6v}{M_e M_{b1}} \left(\frac{s^2}{2} - \frac{s^3}{3 M_{b1}} \right) \right],$$

‡ A tube is a region that limits the lateral motion of macromolecules, where reptation motion is possible.^{94–96}

and the maximum time corresponds to the coordinate $s = M_{b1}$. Hence, for this level we have

$$\tau_1^{\max} = t_0 \exp\left(\frac{\nu M_{b1}}{M_e}\right);$$

for succeeding levels

$$\tau_i^{\max} = \tau_{i-1}^{\max} \left(\frac{M_{bi}}{M_e}\right)^{1/2} \exp\left(\frac{\nu M_{bi}}{M_e}\right).$$

In these equations, t_0 , according to the theory,¹⁷² is the characteristic time for three-arm stars

$$t_0 = \frac{4}{3} \tau_0 \frac{M_{b1}^2}{m_0^2} \left(\frac{\pi M_e}{\nu M_{b1}}\right)^{1/2},$$

where ν is the constant, which is equal to 0.56 for the first level and slightly changes with the hierarchical level, m_0 is the molecular mass of the monomeric unit, and τ_0 is the elementary relaxation time characterising diffusion of the monomeric unit.

For macromolecules with a functionality of branching points larger than three (star-shaped, H and pom–pom polymers), the same scheme is used for calculations of the relaxation times corrected for the fact that the branches coming from a single point are ‘separated’ by a zero-length main chain fragment.²⁰⁸

The relaxation modulus is determined as a sum of the contributions of all levels

$$G(t) = G_N^0 \sum_i c_i F_i(t),$$

$$F_i(t) = 2 \int_0^{M_{bi}} \left[\left(\bar{c}_i - c_i \frac{s}{M_{bi}} \right) \exp\left(-\frac{t}{t_i(s)}\right) \right] ds, \quad (3)$$

where G_N^0 is the modulus corresponding to a high-elasticity plateau, $\bar{c}_i$ is the ‘dynamic’ concentration of branches of the i th level,

$$\bar{c}_i = \sum_{k=i}^N c_k;$$

N is the total number of levels.

In experiments, Eqn (3) is manifested, in particular, in that the dependence of the length of a high-elasticity plateau $\Delta \log \omega$ (ω is the deformation frequency) on the molecular mass for branched polymers is stronger than that for linear polymers. As can be seen from the data presented in Fig. 8, the coefficient ν for linear monodisperse polystyrene²¹³ in the relation

$$\Delta \log \omega \propto \nu \log M$$

is 3.5, whereas $\nu = 4.8$ for four-arm star polyisoprene.²¹⁴ For molecular mass ($\bar{M}_w \approx 6 \times 10^4$), the frequency dependences of the real (G') and imaginary (G'') parts of the complex relaxation modulus of linear polymers are virtually equal to those of three-arm star-shaped polymers. At the same time, the terminal region for eight-arm polymers is substantially shifted to higher frequencies, although the character of the dependences $G'(\omega)$ and $G''(\omega)$ remains the same:¹⁷⁸

$$G' \propto \omega^2 \text{ and } G'' \propto \omega.$$

A complication of the topological structure of macromolecules leads to a shortening of the high-elasticity plateau. This can be seen, for example, in Fig. 9, which presents the curves of the frequency dependences of the relaxation modulus for a six-arm pom–pom polymer (three arms are attached to each end of the main chain) and an analogous polymer, which contains two branches at the midpoint of the chain, resulting in the formation of an eight-arm polymer. The molecular masses of the polymers are 2.15×10^5 . The high-elasticity plateau for highly branched

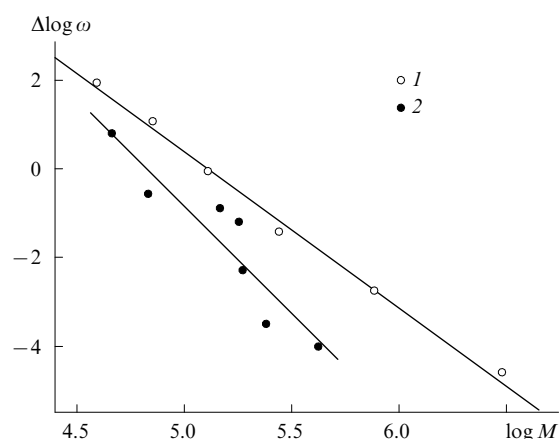


Figure 8. Plots of the length of a high-elasticity plateau vs. the molecular masses of linear (1) and four-arm star-shaped (2) polymers.^{213, 214}

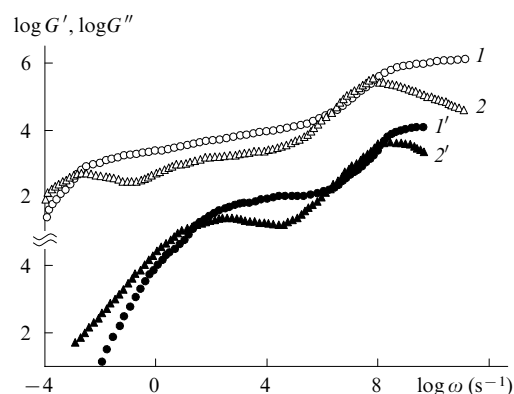


Figure 9. Frequency dependences of G' (1, 2) and G'' (1', 2') for 6-arm (1, 1') and 8-arm (2, 2') polymers.²¹⁵

stars¹⁷⁸ (the branch number is ~ 50) virtually disappears, and in the terminal zone $G' \propto \omega^{1.12}$ and $G'' \propto \omega^{0.91}$ ($\bar{M}_w \approx 2.5 \times 10^5$); $G' \propto \omega^{1.1}$ and $G'' \propto \omega^{0.85}$ ($\bar{M}_w \approx 5.75 \times 10^5$).

It was suggested⁷⁷ that star-shaped polymers can be arbitrarily classified into two groups depending on the relaxation properties. One class includes polymers, which contain a relatively small number of long branches (or a large number of branches, but the branches are very long). These macromolecules are characterised by typical polymer dynamics. In particular, the highly elastic state is typical of such polymers. The topological structures of macromolecules belonging to another class are characterised by the presence of a large number of relatively short branches, and such polymers exhibit properties, which are more typical of colloidal systems.

An analogous behaviour is typical of macromolecules with more complex topological structures, for example, of comb-like²¹⁶ and pom–pom polymers.²¹⁷ The frequency dependence of the relaxation modulus of polymers with long branches ($M_a \geq 10 M_e$) can be approximately described in terms of a theory, which is based on the above-mentioned postulates and was developed in the studies,^{2, 201, 218} meanwhile this theory is inapplicable to polymers with shorter branches [$M_a \sim (2-3) M_e$]. In the region of moderate frequencies (a high-elasticity plateau), both G' and G'' change as $\sim \omega^{0.5}$. In the terminal region, G' is proportional to $\sim \omega^{1.5}$, and $G'' \propto \omega$. As can be seen, the above relations are not adequately described by Rouse dynamics.

An approach based on the Rouse chain model is applicable to relaxation of dendrimers.¹⁹ The minimum number of modes

required for an adequate description of experimental data depends on the macromolecule size as follows:²¹

Number of generations of branches	<3	4	5	6
Number of modes	1	2	9	15

However, this gives rise to a 'non-Rouse' dependence of the relaxation modulus on the frequency in the terminal zone

$$G' \propto \omega^{1.49}, G'' \propto \omega^{0.92}.$$

A deviation from Rouse dynamics was found in the study²¹⁹ for dendrimers based on branched polystyrene. Although in this case the topological structure of macromolecules is RCT, the authors suggested that the structures of these macromolecules are analogous to those of critical clusters and, consequently, the relaxation modulus depends on the time according to a power law (see below).

In the case of HBP based on 2,2-bis(hydroxymethyl)propionic acid ($M_w = 2.6 \times 10^4$), a high-elasticity plateau is absent at all.¹⁷² Relaxation of hyperbranched poly(ester amide) occurs according to Rouse dynamics^{176, 220} if DB > 0.2 (DB was varied by changing the ratio of the comonomers AB and AB₂). For DB < 2, there is a tendency to form a high-elasticity plateau. The same relaxation mechanism was established for 5-(hydroxyalkoxy)isophthalate-⁵⁹ and ether ketone-based^{68, 221} HBP. However, in these cases the Rouse law is also approximately fulfilled in the moderate frequency region, whereas it is fulfilled only for G'' but not for G' in the terminal region. It should be noted that the above relaxation characteristics should correspond to the Kargin–Slonimskii–Rouse model, *i.e.*, to linear rather than to branched chains.

Rouse dynamics and the absence of a high-elasticity plateau in the moderate and low frequency region in the case of relaxation of highly branched polymers^{19, 21, 59, 68, 77, 169, 176, 219, 220} and weakly branched polyethylene^{158, 161, 222} suggest that the topological structures of these compounds are similar to those of critical clusters. The fact that the structure of HBP has fractal properties (self-similarity) was demonstrated by computer simulation.⁷⁴

The relaxation properties of a polymer system at the gel point are described by a power law^{223–227}

$$G(t) \propto t^{-n}, \quad (4)$$

where G is the relaxation modulus and t is the running time.

The exponent n is related to the fractal dimensionality by the equation²²⁸

$$n = \frac{D}{D_f + 2},$$

where D is the space dimensionality; $n = 0.66$ for a three-dimensional space and the fractal dimensionality of the critical cluster $D_f = 2.53$.

The exponent n in Eqn (4) varies depending on the system (Table 5).

If the conversion α is expressed in the form

$$\varepsilon = \left| \frac{\alpha - \alpha_c}{\alpha} \right|,$$

where ε is the relative conversion and α_c is the critical conversion, then at $\alpha < \alpha_c$ the dependence of the viscosity on ε takes the form

$$\eta \propto \varepsilon^{-s},$$

at $\alpha > \alpha_c$ the dependence of the shear modulus on ε is as follows:^{229–234}

$$G \propto \varepsilon^r.$$

The exponents s and r are related to n by the equation

$$n = \frac{r}{s + r}.$$

As a consequence of Eqn (4), the frequency dependences obey a power law

$$G' \sim \omega^n \cos\left(\frac{\pi n}{2}\right), G'' \sim \omega^n \sin\left(\frac{\pi n}{2}\right),$$

where $\delta = \pi n/2$. Consequently, $\tan \delta$ is frequency independent.

These relations were confirmed by numerous experiments, in particular, for three-dimensional polymerisation of methacrylate-based oligomers²³⁵ and in the case of end-linking of polydimethylsiloxane.²³⁶ Analogous dependences are typical of biopolymers.^{237, 238} In the latter case, physical conditions, for example, the temperature, pH or concentrations of the components, are responsible for the formation of an equilibrium network. In xanthane solutions, the exponent ρ in the formula

$$\tan \delta \propto \omega^\rho$$

Table 5. Exponents n in formula (4) for various systems.

System	n	Ref.
Theoretical estimates	0.706	232
	0.79	241
	0.66	242
Polyethylene, number of branches per 10^5 carbon atoms		
2.6	0.711	221
3.7	0.622	221
4.2	0.589	221
8.0	0.511	221
Branched polypropylene	0.46	193
	0.53	193
Branched poly(methyl methacrylate)	0.54	167
22-Arm comb-like polybutadiene	0.55	243
Comb-like copolymer of styrene and butadiene (~30 branches)	~0.5	206
32-Arm pom–pom copolymer of styrene and butadiene	0.55	244
Hyperbranched poly(ether imide)	2/3	19
Chemical gel formation		
Cross-linking of polydimethylsiloxane	0.5	224
	0.69 ± 0.005	234
Curing of epoxy resin	0.7	245
	0.70 ± 0.02	246
	0.71	247
	0.70 ± 0.05	248
	0.5–0.8	249
Polymerisation of methacrylate oligomers (increases with increasing functionality)	from 0.4 ± 0.2 to 0.6 ± 0.1	235
Cross-linking of bifunctional oligodimethylsiloxane containing terminal vinyl groups by a polyfunctional reagent ($f = 4$ and 11) containing the reactive $\equiv \text{SiH}$ groups	from 0.69 to 0.76	236
Polycondensation of tetraethoxysilane	0.72 ± 0.03	250
Pectin + Ca^{2+}	0.71	251
Cross-linking of L-guluronic and D-mannuronic acids	0.55	252
Diisocyanate + triol + alcohol	0.73	233
Triisocyanate + diol	0.5	253
Poly(oxypropylene)triol + diisocyanate	0.69	216
Physical gel formation		
Thermoreversible triblock copolymer	0.70 ± 0.02	217
Thermoreversible microgel	0.02	254
Gelatin	$0.46 - 0.70^a$	255
Multiarm polyacrylic acid (concentration transition)	0.21	256
Crystallisation of polypropylene	0.13	257

^a Depending on the concentration and temperature.

for complexation with Al^{3+} ions varies from -0.1 to 0.08 depending on the temperature and is equal to zero at $32\text{ }^{\circ}C$.²³⁹ The exponent ρ varies approximately in the same range depending on pH, the critical pH being 2.9.

Lowering of the temperature in an aqueous-methanolic solution of spherical microgel particles of *N*-isopropylacrylamide leads to the gel–sol transformation (the lower critical temperature is $32\text{ }^{\circ}C$).²⁴⁰ In this case, the above phenomenon is also observed, the temperature of $\sim 29\text{ }^{\circ}C$ corresponding to the zero value of the exponent ρ .

It should be noted that identification of the topological structures of hyperbranched polymers with those of critical clusters is arbitrary. Actually, although the dependence $G'(\omega)$ is virtually identical to $G''(\omega)$ in a moderate frequency region, their ratio, *i.e.*, $\tan \delta$, does change with frequency,^{19, 59, 206} which is not typical of true fractal structures of critical clusters. If hyperbranched polymers are prepared by three-dimensional copolymerisation or chain cross-linking, macromolecules formed in the vicinity of the gelation point have structural characteristics of critical clusters, which was demonstrated by direct structural studies using gel permeation chromatography and static and dynamic light scattering.^{234, 257–259}

V. Relaxation spectra

The relaxation spectrum (RS) is a universal characteristic of the relaxation properties of polymers.^{1, 93, 96, 181, 260} On the one hand, analysis of theoretical models of the dynamics of polymer chains provides knowledge about RS. On the other hand, in spite of difficulties in reproducing such spectra from the results of relaxation experiments,^{261–263} a comparison of RS is considered as the most adequate procedure for estimation of the validity of a theoretical approach. Since the relaxation spectrum is sensitive to the topological structure of the polymer chain,¹ branching would be expected to be reflected in the spectral pattern. However, data demonstrating the influence of branching on RS are scarce.

One of approaches is based on the use of an empirical BSW spectrum,[§] which satisfactorily describes the frequency dependence of the relaxation modulus of linear polymers as the following three branches: a descending branch at $\lambda \leq \lambda_1$, an ascending branch at $\lambda_1 \leq \lambda \leq \lambda_{\max}$ and a sharply descending branch at $\lambda > \lambda_{\max}$ (see Refs 225, 264 and 265)

$$H(\lambda) = \left[H_g \left(\frac{\lambda}{\lambda_c} \right)^{-n_g} + n_e G_N^0 \left(\frac{\lambda}{\lambda_{\max}} \right)^{n_e} \right] \exp \left[- \left(\frac{\lambda}{\lambda_{\max}} \right)^{\beta} \right], \quad (5)$$

where

$$H_g = n_e G_N^0 \left(\frac{\lambda_1}{\lambda_{\max}} \right)^{n_e} \left(\frac{\lambda_1}{\lambda_c} \right)^{n_g}.$$

Here, λ is the relaxation time, λ_1 is the time at which two first branches coincide (intersect), λ_c characterises the segment mobility, and $\lambda_{\max}$ is the maximum Rouse or Doi–Edwards relaxation time depending on the conditions of realisation of the chain dynamics. As a rule, $n_g \approx 0.67$, $n_e \approx 0.30$, and $\beta = 2$.

Investigation of star-shaped polymers²⁶⁶ led to a substantial complication of BSW spectra. It appeared that Eqn (5) should be supplemented with the term

$$n_0 G_0 \left(\frac{\lambda}{\lambda_0} \right)^{n_0} \exp \left(\frac{\lambda}{\lambda_0} \right),$$

where n_0 and G_0 are constants.

Hatzikiriakos *et al.*²⁶⁶ analysed the parameters of the expression for BSW spectra thus modified for a series of star polybutadienes with a regular structure with $f = 4–125$. The parameters

§ BSW are the first letters of the last names of the authors of the study.²⁶⁴

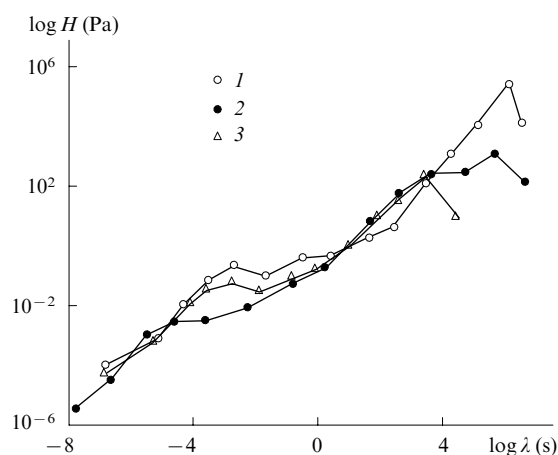


Figure 10. Relaxation BSW spectra of linear (1), 125-arm star-shaped (2) and 4-arm star-shaped (3) polymers.²⁶⁶

G_N^0 , H_g and λ_c can be considered independent, within experimental error, of the molecular mass and the number of branches. The parameters G_0 , $\lambda_{\max}$ and λ_1 depend more on the molecular mass of branches than on their number. The parameter λ_0 is influenced by both structural characteristics. It was suggested²⁶⁶ that these results do not qualitatively contradict the theoretical concepts. The relaxation time distribution functions (BSW spectra) shown in Fig. 10 illustrate that the relaxation properties of star-shaped polymers are in fact independent of the number of branches.

At the same time, a substantial broadening of the spectrum was observed (calculations were carried out according to a procedure published in the study²⁶⁷) with increasing number of branches L in polyethylene^{147, 163} in the region $L \leq 1$ per 10^4 carbon atoms, *i.e.*, where branching leads to an increase in the viscosity (see above).

The general approach to the solution of the problem of dynamics of chains with a complex topological structure, which generalises the Rouse model (theoretical calculation of RS) was described by Müller.²⁴¹ A macromolecule adopting an arbitrary configuration is represented as a set of N points in a d -dimensional space ($d \geq 2$), each point occupying the position $R_i(t)$, $i = 1, 2, \dots, N$. The movement of these points is limited by elastic harmonic bonds, which link point units in pairs thus providing the desired architecture. The potential energy of this macromolecule is

$$U \propto \sum_{i,j} (R_i - R_j)^2.$$

In the simplest case, the relaxation dynamics is described by the equation

$$\frac{\partial U(t)}{\partial R_i} = -\zeta_i \left[\frac{dR_i(t)}{dt} - v_{\text{ext}}(R_i(t), t) \right] + \xi_i(t), \quad (6)$$

where ζ_i is the friction coefficient, v_{ext} is the external shear stress, and ξ_i is the randomly fluctuating force (thermal noise).

A somewhat different approach providing an efficient solution of Eqn (6) based on matrix factorisation and giving rise to a total RS was developed in the study.²⁶⁸ The motion of elastically linked particles is described by an analogous equation system.

$$\zeta_i \mathbf{x}_i = \sum_j p_{ij} (\mathbf{x}_j - \mathbf{x}_i), \quad i = 1, \dots, n, \quad (6a)$$

where $\mathbf{x}_i$ is the vector of coordinates of the i th particle, and $p_{ij} = p_{ji} \geq 0$, $\zeta_i > 0$ for all i and j . The equation system (6a) is associated with a link graph of particles. The vertices i and j are linked to each other if $p_{ij} > 0$. It is reasonable to consider the

linkage components into which (in the general case) this graph is split as model macromolecules (monomeric units of the latter are essentially the graph vertices). Infinite values $\zeta_i = \infty$ can be ascribed to the friction coefficients of individual branching points in model (6a). For such branching points, $x_i = 0$, i.e., branching points with infinitely large friction are fixed. Since system (6a) is split into independent differential equation subsystems corresponding to linked subgraphs of bonds, it is sufficient to study motion of an isolated macromolecule.

To take into account interchain interactions, Eqn (6) for stars and analogous structures is solved based on the reptation model.^{2, 154, 200, 201, 269} For dendrimers, interchain interactions are generally ignored, and relaxation processes are attributed to intrachain conformational rearrangements.^{27–31} The same is true for HBP and other polymers with topological structures of highly branched and hyperbranched ICT, which can be considered as critical clusters.^{60, 256}

The parameters of RS characterising the relaxation properties of branched polymers are given in Table 6. Of the total spectrum, two relaxation times are generally distinguished: segmental and normal.²⁷⁰

Table 6. Parameters of RS characterising the relaxation properties of branched polymers.

Parameter of RS	Polymer structure	Relationship between the parameter of RS and structure parameters	Ref.
Largest Rouse relaxation time, λ_{rep}	linear chain in a tube	$\frac{3\zeta N^3}{\pi^2 k}$	97
Relaxation time of the branch, λ_a	branched chain, stars	$\frac{\zeta}{\pi^2 k} \exp\left(\frac{vN_a}{3}\right)$	97
Diffusion time of the centre of gravity, λ_D	dendrimer	$\frac{6g2^G \zeta}{k}$	27
Relaxation time of the centre of gravity relative to the central atom, λ_s	"	$\frac{5\zeta}{k}$	27
Relaxation time of rotational and internal elastic motion of monomeric units, $\lambda_r = \lambda_e$	"	$\frac{2^{g+1} \zeta}{k}$	27

Note. ζ is the friction coefficient of a segment; N is the number of segments in the chain; $k = 3k_B T/a^2$, where k_B is the Boltzmann constant, T is the absolute temperature, a is the segment size; v is the numerical coefficient the value of which depends on the model used;¹⁵⁴ N_a is the number of monomeric units in the branch.

As far as is known, only Gotlib and co-workers^{28–30} have brought the theory to calculations of RS. In these studies, the dynamic model of dendrimers with an arbitrary functionality of branching points was considered, both external friction of branching points against environmental (ζ) and internal friction of points against each other (ζ_{int}) being taken into account. Two types of RS, internal and external, are distinguished. The internal relaxation spectrum corresponds to oscillating motion of branching points and takes the form

$$H_{\text{int}}(\lambda) = H_{\text{int}0} \left[4(f-1) - \left(\frac{1}{\lambda/\lambda_0 - p} - f \right)^2 \right]^{-1/2} \frac{\lambda/\lambda_0}{(\lambda/\lambda_0 - p)^2},$$

where the relaxation time is expressed by the equation

$$\lambda = \zeta \left[Kf \left(1 - 2 \frac{\sqrt{f-1}}{f} \cos \varphi \right) \right]^{-1} + \frac{\zeta_{\text{int}}}{K}$$

and is in the range between λ_{min} and λ_{max} :

$$\lambda_{\text{min}} = \zeta \left[Kf \left(1 + 2 \frac{\sqrt{f-1}}{f} \right) \right]^{-1} + \frac{\zeta_{\text{int}}}{K},$$

$$\lambda_{\text{max}} = \zeta \left[Kf \left(1 - 2 \frac{\sqrt{f-1}}{f} \right) \right]^{-1} + \frac{\zeta_{\text{int}}}{K}.$$

In these equations, f is the functionality of the branching point, $\lambda_0 = \zeta/K$, K is the modulus of elasticity of a coil spring that connects the branching points of the macromolecule; $p = \zeta_{\text{int}}/\zeta$; φ is the phase shift of vibration of the branching point, $\pi/g \leq \varphi \leq \pi(G-1)/G$.

The external spectrum reflects the pulsation motion of dendrimers or its parts relative to the centre and takes the form

$$H_{\text{ext}}(\lambda) = H_{\text{ext}0}(\lambda) \frac{\lambda/\lambda_0}{(\lambda/\lambda_0 - p)^2},$$

$$\lambda_j = \frac{\zeta(f-1)^{j+1}}{K(f-2)^2} + \frac{\zeta_{\text{int}}}{K},$$

$$\lambda_{\text{min}} = \frac{\zeta(f-1)^3}{K(f-2)^2} + \frac{\zeta_{\text{int}}}{K},$$

$$\lambda_{\text{max}} = \frac{\zeta(f-1)^{G+1}}{K(f-2)^2} + \frac{\zeta_{\text{int}}}{K},$$

j is the number of generation, $j = 2, \dots, G$.

The exponential character of the time dependence of the relaxation modulus [see Eqn (4)] signifies that, as expected, RS of critical clusters is described by a power law (CW distribution),[¶]

$$H(\lambda) = H_0 \left(\frac{\lambda}{\lambda_0} \right)^{-n}$$

for $\lambda_0 < \lambda < \lambda_{\text{max}}$, $0 < n < 1$, $\lambda_{\text{max}} \propto |\alpha_c - \alpha|^{-7}$.

The time λ_0 determines the glass transition conditions and depends, like the front factor H_0 , on the chemical structure of the polymer.

VI. Conclusion

From the aforesaid, unambiguous conclusions on the topological structures of HBP cannot be drawn. Actually, calculations with the use of data on the kinetics of formation^{89, 271} provide evidence for MMD of polymers at nearly critical conversions but without consideration of the effects of cyclisation and exclusion volume. An approach based on the percolation model^{59, 64} is suitable only for the critical conversion region and it is not quite clear whether it can be adequately applied to real systems and different degrees of conversion. Computer simulation accounts for the effects of cyclisation and exclusion volume,^{53–55, 72, 74, 272} but it is difficult to relate these results to the real mechanism of formation of macromolecules. Apparently, this is why it is necessary to use the MMD model functions, for example, the Flory–Schultz distribution.²³¹

The relaxation mechanisms of HBP are not associated with the presence of entanglements^{59, 74} but are conditioned, like those of dendrimers, by intramolecular rearrangements. High elasticity is apparently attributed to interchain interactions between peripheral branches of highest-molecular-weight fractions.²⁰ However, it is apparently impossible to apply the theory of RS developed for dendrimers to HBP because it is necessary to take into account

¶CW are the first letters of the last names of the authors of the studies.^{222, 223}

irregularity of the architecture of HBP. To use CW spectra, one should first make sure that the topological structures of HBP are actually identical to those of critical clusters. Therefore, to get an insight into the relaxation mechanism of HBP, it is necessary, first, to refine understanding of their architecture and, second, develop a theory of relaxation spectra of HBP with a desired topological structure.

This review has been written with the financial support of the Russian Foundation for Basic Research and the Government of the Moscow Region (Project r2004naukograd No. 04-01-97 202).

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Oleg Matveevich Nefedov
(on his 75th birthday)

On November 25, 2006, Academician Oleg Matveevich Nefedov celebrated his 75th birthday.

O M Nefedov is an outstanding scientist who has won general recognition owing to his contribution to organic and physical organic chemistry. The scope of his research activities at the Institute of Organic Chemistry of the RAS includes chemistry of carbenes, their analogues and other unstable molecules and small rings; design of novel methods and techniques for the synthesis of fluoroaromatic compounds from available raw stuff; development and introduction into routine chemical practice of advanced technologies for preparation of pesticides, medicinal drugs, *etc.* In the last five years alone, the results of these studies were published in more than 40 articles and were covered by five RF patents.

The scientific achievements of O M Nefedov were rewarded by three State Prizes for Science and Technology (1983, 1990 and 2002); by several academic prizes, such as N D Zelinsky Prize (1987), N N Semenov Prize (1991) and A M Butlerov Prize (2003); by A P Karpinsky International Prize (1993); by D I Mendeleev Gold Medal (1998) and by National Prize 'Man of the Year-2002' for Science. O M Nefedov is an honorary member of several international and foreign academies and scientific societies.

Oleg Matveevich is actively engaged in scientific, organizational and educational work. He was elected Editor-in-Chief of the Journals 'Uspekhi Khimii' ('Russian Chemical Reviews'), 'Izvestiya Akademii Nauk, Seriya Khimicheskaya' ('Russian Chemical Bulletin, International Edition'), 'Mendeleev Communications', and is a member of editorial boards of several international journals. Fifty-eight candidates and seven doctors of sciences prepared and successfully defended their theses under his guidance. In 1990, a Higher Chemical College of the RAS was established on his initiative and under his permanent chairmanship on the basis of the D I Mendeleev Russian University for Chemical Technology. In 2006, O M Nefedov was awarded a Prize of the Government of the Russian Federation for Education for his research-and-educational work entitled 'Some Innovative Trends in the Development of Higher Education and Their Integration Into Fundamental Science' and the introduction of a continuous educational cycle 'Chemical Lyceum — Higher Chemical College — Post-Graduate Courses' into the routine practice of some leading chemical institutes within the RAS.

Oleg Matveevich Nefedov is widely known for his great erudition, breadth of mind, versatility of scientific interests and unique working capacity. He is Chairmain of the Commission for Scientific and Technical Policy at the Moscow City Government, Chairman of the National Committee of Russian Chemists, member of the Bureau and Executive Committee of the International Union of Pure and Applied Chemistry (IUPAC) and President of the last four Mendeleev Congresses for General and Applied Chemistry (1989–2007).

The Editorial Board and the Editorial Staff of the Journal 'Uspekhi Khimii' ('Russian Chemical Reviews') heartily congratulate Oleg Matveevich on the occasion of his 75th birthday and wish him good health and much success in all his deeds.

Theoretical studies on [3 + 2]-cycloaddition reactions

M L Kuznetsov

Contents

I. Introduction	935
II. The cycloaddition reactions: a theoretical background	935
III. Computational methods used in studies of [3 + 2]-cycloaddition reactions	938
IV. Reactions of allyl type dipoles	939
V. Reactions of propargyl–allenyl type dipoles	946
VI. Reactions of heterocumulenes	953
VII. Other reactions	953
VIII. Intramolecular cycloaddition reactions	954
IX. Conclusion	955

Abstract. The results of theoretical studies on [3 + 2]-cycloaddition reactions carried out during the last decade are summarised. The reaction mechanisms are discussed. The catalyst, solvent, and substituent effects on the reactivities of compounds and on the mechanisms, regioselectivity and stereoselectivity of reactions are considered. The results of theoretical studies are compared with corresponding experimental data. The bibliography includes 328 references.

I. Introduction

Research on [3 + 2]-cycloaddition reactions began more than 100 years ago with a pioneering study by Buchner¹ who reported the reactions of ethyl diazoacetate with α,β -unsaturated esters. At present, the [3 + 2]-cycloaddition reactions are widely used in synthetic organic chemistry, in particular, for the synthesis of various five-membered heterocyclic systems that are used in industry and medicine and as synthons for fine organic synthesis.^{2,3}

In the 1950s–1960s, the number of publications concerned with the [3 + 2]-cycloaddition reactions increased dramatically. This predetermined the need of summarising the results obtained and gave an impetus to studies, including theoretical ones, on the mechanisms of the processes in question. Systematic investigations of theoretical aspects of cycloaddition were initiated by Woodward and Hoffmann^{4,5} who developed a theory of pericyclic processes and by Huisgen^{6–10} and Firestone^{11–14} who reported a series of studies on the mechanisms of dipolar [3 + 2]-cycloaddition reactions.

However, wide use of theoretical methods became possible only in the 1980–1990s. This is due to progress in hardware and software (computational algorithms) development. Quantum-chemical methods are a powerful tool of studying chemical

reactions including cycloaddition ones. Indeed, in addition to help in interpreting experimental data, which is of great value *per se*, theoretical calculations allow one to predict many properties of compounds and chemical reactions, sometimes providing a unique possibility of studying unstable compounds and intermediates. Additionally, they are successfully used for analysing the effects of various factors on the reactivities of compounds and on the rates, regioselectivity and stereoselectivity of reactions, *etc.* At present, cycloaddition processes are intensively studied by quantum-chemical methods.

In the last decade a number of monographs (*e.g.*, Refs 2 and 15–18) and reviews (*e.g.*, Refs 3, 19–22) summarising the results of experimental studies of cycloaddition reactions including [3 + 2]-cycloaddition were reported. However, most part of reviews of theoretical studies on the subject were published before 1995.^{6,23–26} Chronologically, the last available reviews of studies in this field were reported by Garcia *et al.*,²⁷ who analysed the effects of the secondary orbital interaction mainly in the Diels–Alder reactions and by Leach and Houk,²⁸ who considered theory of the Diels–Alder reactions involving oxygen molecules, nitroso compounds and hydrogenated triazolinones.

The aim of this review was to summarise the results of theoretical studies on one of the most important types of cycloaddition reactions, namely, [3 + 2]-cycloaddition, carried out in the last decade (from 1994 up to 2005).

II. The cycloaddition reactions: a theoretical background

1. Classification of [3 + 2]-cycloaddition reactions with respect to the type of the interaction of frontier molecular orbitals

According to the frontier molecular orbital (FMO) theory²⁹ that underlies modern theory of chemical bonding, the course of chemical reactions is governed by the interaction between the highest occupied and lowest unoccupied MOs (HOMO and LUMO, respectively) of the reactant molecules. One of the first models that treated the cycloaddition reactions from the standpoint of the FMO theory was proposed by Woodward and Hoffmann (Woodward–Hoffmann rule).⁵ This is the concept of the conservation of orbital symmetry, which became part of all textbooks of modern organic chemistry, being up to date a

M L Kuznetsov Department of Chemistry, Moscow State Pedagogical University, Nesvizhskii per. 3, 119021 Moscow, Russian Federation.
Fax (7-495) 246 77 66, tel. (7-495) 246 83 54,
e-mail: inorgchem@comail.ru

Received 19 January 2006

Uspekhi Khimii 75 (11) 1045–1073 (2006); translated by A M Raevskiy

powerful tool of qualitative description of cycloaddition processes.

Sustmann proposed a classification of dipolar [3 + 2]-cycloaddition reactions with respect to the character of the HOMO–LUMO interaction in the initial compounds.^{30,31} According to his classification, which is widely used at present, the [3 + 2]-cycloaddition reactions can be divided into three groups. Group I comprises the reactions controlled by the HOMO_{dipole}–LUMO_{dipolarophile} interaction, or the so-called normal-electron-demand (NED) reactions. Processes governed by the HOMO_{dipolarophile}–LUMO_{dipole} interaction, or the so-called inverse-electron-demand (IED) reactions, form Group III. If the energies of the valence MOs of two reactants are similar, the reaction is controlled by both types of the HOMO–LUMO interaction. These processes belong to group II (Fig. 1).

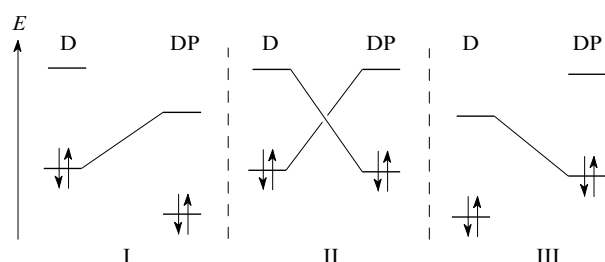


Figure 1. Classification of cycloaddition reactions according to Sustmann.

Hereinafter, 'D' stands for dipole and 'DP' stands for dipolarophile.

2. Main types of cycloaddition reaction mechanisms

There are two main mechanisms of cycloaddition reactions, namely, a concerted mechanism and a stepwise one. A concerted cycloaddition reaction occurs in a single step involving the formation of one transition state (TS) (Fig. 2a).[†] The stepwise mechanism involves a number of stages. It begins with the formation of acyclic transition state and corresponding intermediate and completes with the ring closure and formation of final product (Fig. 2b). The transition states and intermediates can be dipolar (zwitter-ionic), singlet or triplet biradical structures.

The concerted mechanism can be synchronous or asynchronous. In the former case the reactant molecules approach one another synchronously with the formation of new bonds in the transition state. In the latter case new bonds in the transition state are formed in turn. Different authors use different criteria for assessment of the synchronicity of processes. Often, the relative lengths of the contacts a...c and b...d in the transition state (see Fig. 2a) are used as a measure of the synchronicity of the reaction mechanism. However, in practice this criterion can be applied only to the reactions with the same type of the interacting atoms. If new chemical bonds are formed between atoms of different elements, the lengths of these contacts can be appreciably different from each other even for the synchronous cycloaddition.

A more reliable criterion is provided by the bond populations (e.g., the relative Wiberg indices³²) for the contacts a...c and b...d, which depend on the nature of the interacting atoms. The smaller the difference between the Wiberg indices, the higher the synchronicity of the mechanism. However, in this case information on the synchronicity of the process is also incomplete because the analysis is restricted to only two bonds that are formed during

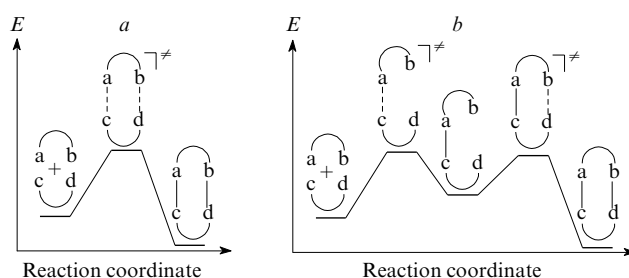


Figure 2. Energy profiles of concerted (a) and stepwise (b) cycloaddition reactions.

the reaction. A more correct quantitative measure of the degree of synchronicity was introduced by Moyano *et al.*,³³ who proposed to allow for all bonds involved in the cycloaddition process. According to Moyano *et al.*,³³ the degree of synchronicity, S_y , of a reaction is given by

$$S_y = 1 - \frac{\sum_{i=1}^n |\delta B_i - \delta B_{av}| / \delta B_{av}}{2n - 2}. \quad (1)$$

Here n is the number of bonds involved in the reaction (for the [3 + 2]-cycloaddition, $n = 5$) and δB_i is the relative variation of the Wiberg indices for the i th bond, which is calculated from the following relationship

$$\delta B_i = \frac{B_i^{ts} - B_i^r}{B_i^p - B_i^r},$$

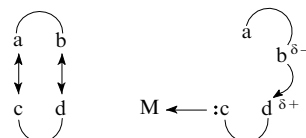
where the superscripts 'p', 'r' and 'ts' correspond to the product, reactants and transition state, respectively, and the average value of the δB_{av} is determined from

$$\delta B_{av} = n^{-1} \sum_{i=1}^n \delta B_i.$$

For true synchronous processes, $S_y = 1$, whereas for asynchronous ones $S_y = 0$.

Among various factors affecting the cycloaddition reaction mechanisms, the Lewis acid coordination to one of the reactants plays the key role. Usually, complexation is accompanied by an abrupt increase in the asynchronicity of the reaction or even by a change from concerted to stepwise reaction mechanism (see below). This change in the mechanism can be explained from the standpoint of charge control. The interaction of the Lewis acid with the reactant causes transfer of the electron density from the ligand to the catalyst (Scheme 1).

Scheme 1



As a result, the ligand becomes more electrophilic, which facilitates the attack of the second reactant by the negatively charged end.

3. Substituent effects on the energy characteristics of cycloaddition reactions

Obviously, replacement of substituents in the reactant molecules should affect their reactivities in some way. This can be qualitatively interpreted in terms of the FMO theory. In particular, one can expect that introduction of electron-withdrawing substituents into the dipolarophile molecule and/or electron-donating substituents into the dipole molecule will facilitate the NED reactions

[†] This mechanism is also called a 'one-step' and 'two-stage' mechanism. The latter term seems to be quite inappropriate; here the formation of transition state from reactants is treated as the first stage and the formation of reaction products from the TS is treated as the second stage.

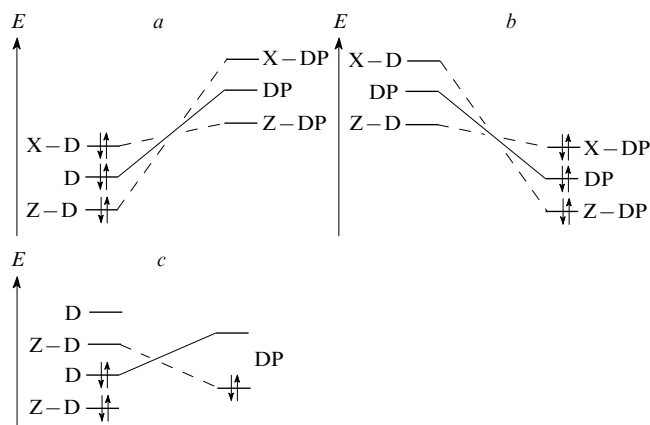


Figure 3. Substituent effects on the frontier MO energies.

Reaction type: a normal-electron-demand reaction (a), an inverse-electron-demand reaction (b), and a reaction accompanied by a change from 'weak' normal to 'weak' inverse electron demand interaction (c); X is the electron-donating substituent and Z is the electron-withdrawing substituent.

due to a decrease in the energy difference between the dipole HOMO and dipolarophile LUMO (Fig. 3 a). On the contrary, the introduction of electron-donating substituents into the dipolarophile molecule and/or electron-withdrawing groups into the dipole molecule should slow down the reactions due to an increase in the ΔE value for the FMOs. The reverse situation is characteristic of the IED reactions (Fig. 3 b). If the corresponding frontier MOs of the initial reactants have nearly equal energies, the introduction of the substituents that cause a significant redistribution of the electron density and act oppositely for different reactants should favour the occurrence of the reaction. Moreover, the type of the HOMO–LUMO interaction is often changed from, e.g., 'weak' NED to IED or *vice versa* (Fig. 3 c). Examples are given in the text below.

It should be noted that this qualitative treatment of the substituent effects on the reactivities of reactants is simplified. In particular, the model ignores steric effects. Additionally, actual changes in the energies of the frontier orbitals are not always related to the type of the substituent introduced. Finally, the activation barrier is affected not only by the relative orbital energies of the reactants but also by other factors, e.g., the nature of the transition state and the total energy effects of bond cleavage and formation in the formation of the transition state. Thus, investigations of the substituent effects on the course of a chemical reaction require detailed studies of its mechanism and estimation of the activation energy.

4. Effect of catalyst

Carrying out [3 + 2]-cycloaddition reactions often requires the presence of a catalyst, e.g., a Lewis acid, which forms complexes with the reactant molecules. To a first approximation the effect of the Lewis acid on the course of cycloaddition processes can also be analysed from the standpoint of the FMO theory. The catalytic or promoting activity of the Lewis acid is first of all determined by the fashion of its coordination to the dipole, dipolarophile or to both reactants and by the type of the HOMO–LUMO interaction, the catalyst effect in most cases being similar to that of electron-withdrawing substituent. Selective coordination of the Lewis acid to dipolarophile accelerates the NED reactions due to a decrease in the energy difference ΔE between the dipole HOMO and dipolarophile LUMO. The Lewis acid coordination to the dipole leads to inhibition of the reaction, while coordination to both reactants has little effect on the reaction rate (Fig. 4 a). The reverse occurs in the case of the IED processes (Fig. 4 b). The use of Lewis acids in type II reactions favours the occurrence of the process if the catalyst is selectively coordinated to the dipole or to

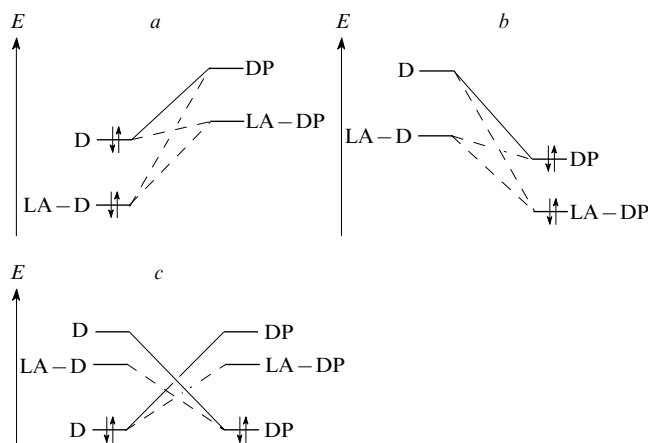


Figure 4. Lewis acid effect on the frontier MO energies.

Reaction type: a normal-electron-demand reaction (a), an inverse-electron-demand reaction (b) and an intermediate-type reaction (c); 'LA' stands for Lewis Acid.

the dipolarophile; coordination to both reactants has no effect (Fig. 4 c).

The selectivity of the metal coordination to a reactant is often related to the hardness (softness) of the donor and acceptor centres. For instance, if the donor centre in the dipolarophile is a soft base and that in the dipole is a hard base, it is more appropriate to catalyse the NED reactions with soft Lewis acids that will selectively coordinate to the dipolarophile, thus causing the processes to accelerate. The hard donor centre in the dipolarophile requires the use of a hard Lewis acid. The reverse situation is valid for the IED reactions.

The aforesaid is valid if the process occurs under orbital control. However, in order to explain the catalyst effect, in some cases the charge control should also be taken into account in addition to the orbital control (especially for dipolar [3 + 2]-cycloaddition). Indeed, in the presence of a Lewis acid the process becomes more asynchronous (see above) and thus can to some extent be treated as a nucleophilic addition reaction. Such reactions are primarily driven by the effective charges of the interacting atoms. Consider a model NED reaction. The dipolarophile c–d is activated by the metal ion M. The dipole a–b asynchronously adds to dipolarophile M–c–d (see the right side of Scheme 1). For metals in high oxidation states (*i.e.*, harder metals) the electron density is more significantly shifted from the c–d fragment to the metal and the positive charge of the atom d increases, which facilitates the addition of the dipole a–b at the negatively charged end. Thus, the activation effect of the Lewis acid in intermolecular cycloaddition reactions is due to two factors, namely, the selectivity of coordination to one of the reactants and the extent of the electron density transfer. In our example, these factors act 'in parallel' if c is the hard centre and 'antiparallel' if c is the soft centre.

5. The solvent effect

Most often quantum-chemical calculations are carried out for the gas phase (more correctly, for isolated molecules); however, real processes usually proceed in solution. The solvation effects are included using a number of models that approximate the solvent effect. These are the Kirkwood–Onsager model and the polarised continuum model (PCM) and its modifications (CPCM, IEFPCM, IPCM, SCI-PCM). To a first approximation the solvent effect on the activation barrier is determined by the relative polarity of the reactant molecules and the transition state (if the solvent is not involved in the reaction, *i.e.*, is not a part of the transition state). The higher the polarity of the structure, the greater the decrease in its energy in polar media. If

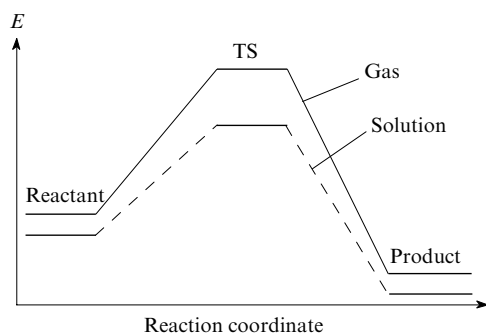
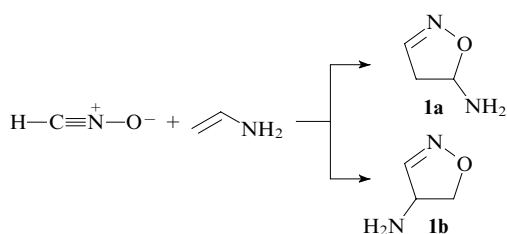


Figure 5. Influence of solvation effects on the activation energy: the case of high-polarity transition state.

the transition-state energy decreases to a greater extent compared to the reactant energies, the activation energy should decrease in a polar solvent (Fig. 5). *Vice versa*, if the overall polarity of the reactant molecules is higher than the polarity of the transition state, the reaction in high-polarity solvents will be inhibited.

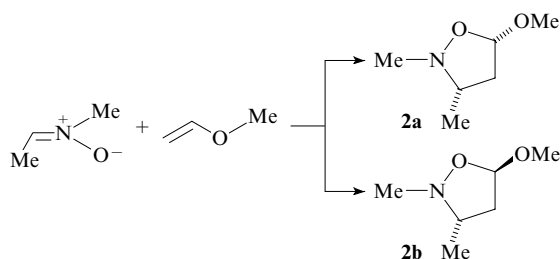
6. The chemoselectivity, the regioselectivity and the stereoselectivity

Many cycloaddition reactions are characterised by chemo-, regio- and stereoselectivity. The chemoselectivity of cycloaddition implies a selective addition of the reactant to one of several multiple bonds of the substrate. The regioselectivity of cycloaddition is associated with the addition of reactant to a given multiple bond of the substrate in a particular fashion. For instance, calculations predicted preferred formation of 5-amino-isoxazoline **1a** compared to 4-amino-substituted isomer **1b** in the reaction of formonitrile oxide $\text{HC}\equiv\text{N}^+-\text{O}^-$ (fulminic acid) with vinylamine.³⁴ In this review the 4- and 5-substituted isoxazoline will be called the *meta*- and *ortho*-isomers, respectively.



This phenomenon is often interpreted from the standpoint of the FMO theory following the rule that the reacting molecules interact through the atoms with similar (or largest) orbital coefficients.³⁵ At the same time the regioselectivity can also be governed by other factors, in particular, steric repulsion between substituents, secondary orbital interaction, formation of hydrogen bonds, *etc.*³⁶

The stereoselectivity (diastereoselectivity and enantioselectivity) is due to preferred formation of the structures with a particular stereo configuration of the environment of the chiral atoms. For instance, in the reaction of *N,C*-dimethylnitrone $\text{MeCH}=\text{N}(\text{Me})\text{O}$ with methyl vinyl ether the addition resulting in diastereomer **2a** is more favourable than the process resulting in **2b**.³⁷



7. The hard–soft acid–base principle

At present, one of the most widely used concepts in chemistry is the theory of hard and soft acids and bases,^{38–40} which is successfully employed for describing the reactivity of compounds as an alternative to the FMO theory.^{41–49} This concept is particularly widely used for interpreting the regioselectivity of various processes, *e.g.*, cycloaddition of CH_2N_2 , RN_3 , N_2O , NCO , *etc.* to the molecules with multiple bonds.^{50–54}

According to the theory of hard and soft acids and bases and the density functional theory (DFT), the total energy of intermolecular interaction can be represented by the sum

$$\Delta E_{\text{int}} = \Delta E_v + \Delta E_\mu, \quad (2)$$

where ΔE_v and ΔE_μ are the energy changes at constant external and chemical potentials, respectively.^{55–58} The first term corresponds to the processes of charge transfer between the reactant molecules. In the local–local approximation, it is expressed through the chemical potentials (μ) and ‘softnesses’ (S) of the reacting molecules A and B

$$(\Delta E_v)_{AB}^{kl} = -\frac{1}{2} \frac{(\mu_A - \mu_B)^2}{S_A f_{Ak} + S_B f_{Bl}} S_A S_B f_{Ak} f_{Bl}, \quad (3)$$

where f_{Ak} and f_{Bl} are the Fukui functions which characterise the reactivities of the atoms k and l in the molecules A and B and depend on the type of the process under study, *i.e.*, a nucleophilic (f^+), electrophilic (f^-) or radical (f^0) attack.⁵⁹ The μ and S can be calculated as follows

$$\mu \approx -\frac{I + A}{2},$$

$$S = \frac{1}{2\eta} \approx \frac{1}{I - A},$$

where I is the ionisation potential, A is the electron affinity and η is the molecular ‘hardness’.⁵⁸

The second term in Eqn (2) describes the charge reshuffling at constant chemical potential and is calculated using the expression

$$(\Delta E_\mu)_{AB}^{kl} = -\frac{1}{2} \frac{\lambda}{S_A f_{Ak} + S_B f_{Bl}},$$

where the parameter λ is proportional to the effective number of valence electrons involved in the reaction between A and B.^{46, 56, 57}

A conventional analysis of the regioselectivity of cycloaddition involves calculations of the energies, ΔE_{int} , of possible regioisomers. Clearly, the higher the total interaction energy, the more preferred the formation of the corresponding isomer.

III. Computational methods used in studies of [3 + 2]-cycloaddition reactions

At present, semiempirical quantum-chemical methods (AM1, PM3, MNDO, INDO, ZINDO, *etc.*) belong to the simplest and cheapest (from the standpoint of computational cost) techniques employed for calculations of organic molecular systems. They differ from one another in parametrisation. Although in some cases the results obtained in these approximations agree well with experimental data,^{60, 61} the properties predicted are more often significantly different from those observed experimentally.^{62–64} Therefore, the results of semiempirical calculations should be interpreted with care. At the moment, semiempirical methods are inappropriate for studying low-molecular-mass organic systems. However, they can be useful for rapid assessment of general trends and correlations⁶⁵ rather than obtaining reliable quantitative energy characteristics and investigating the mechanism of the process under study as well as in studies of large molecules (*e.g.*, macro- and biomolecules) where the use of more accurate approximations is difficult or impossible.

Until recently, the most widely used *ab initio* procedure was the Hartree–Fock (HF) method. Often, this approximation reproduces quite correctly the geometric parameters of molecules (first of all, the bonding distances between atoms of the first-to-third row elements).⁶⁶ However, the HF method ignores the electron correlation effects and therefore strongly overestimates the activation barriers and vibration frequencies. Indeed, the HF calculated activation energies for cycloaddition reactions are 1.5–2.5 times higher than experimental estimates or the activation barriers obtained from high-level approximations.^{67–73} Thus, the HF method is inappropriate for studying cycloaddition reactions.

One of the ‘simplest’ *ab initio* methods with inclusion of electron correlation effects is the Møller–Plesset perturbative method (MP2 stands for the second-order Møller–Plesset level of theory). The results obtained in this approximation agree with experimental data better than the results of HF calculations; therefore, the MP2 technique is widely used, including studies of the cycloaddition reactions.^{67,70,74–76} However, much higher computational cost of the MP2 calculations somewhat limits the field of application of the method (especially for the systems containing transition metal atoms). Additionally, in some cases the MP2 calculated geometric parameters are appreciably different from experimental data (the differences can be even larger than in the case of the HF method).⁶⁶ It is also known that the MP2 wave functions of high-spin systems are characterised by high degree of spin ‘contamination’, which can affect the results of calculations.^{77–79} Nevertheless, this approximation remains one of the most popular methods for calculation of medium-size molecular systems.

There are also other high-level approximations, which often give the results that are in excellent agreement with experimental data. These are, *e.g.*, higher-order Møller–Plesset methods [MP3, MP4DQ, MP4SDQ, MP4SDTQ; the letters ‘S’, ‘D’, ‘T’ and ‘Q’ mean that the corresponding calculations allow for single, double, triple and/or quadruple excitations], the coupled clusters method [CCD, CCSD, CCSD(T)], the quadratic configuration interaction [QCISD(T)] method, the multiconfiguration self-consistent field (MCSCF or CASSCF) method and the composite methods (G1, G2, CBS) that give the best approximation to the experimental energies (with an average deviation of 3–4 kJ mol^{−1}). It was also reported that the theoretical activation energies and energy effects of cycloaddition processes strongly depend on the level of theory at which electron correlation effects are included. For instance, the activation energies for [3 + 2]-cycloaddition reactions of (i) diazomethane, fulminic acid³⁵ and methyl azide⁸⁰ with C₂H₄ and (ii) ozone with isoprene⁷⁴ changed by 20–40 kJ mol^{−1} on going from the MP2 to the MP4, QCISD or CCSD(T) calculations. In contrast to this, the authors of other studies reported a weak dependence of the energy parameters on the computational method and basis set employed. For instance, the *E*_a value for the interaction of nitron CH₂=N(Me)O with acetonitrile varies from 48 to 59 kJ mol^{−1} when using the MP2/6-31G*, MP4SDTQ//B3LYP/6-31G*, MP4SDTQ//MP2/6-31G*, CCSD(T)//B3LYP/6-31G*, CCSD(T)//MP2/6-31G*, CBS-Q and B3LYP/6-31G* methods.⁷²

Analysis of the published data on the effect of the approximation employed on the results of calculations of cycloaddition reactions revealed the following. The relative energies obtained from the MP4SDTQ, CCSD(T) and QCISD(T) calculations with the same basis set are often similar, being in good agreement with experimental data.^{72,81} The CASSCF method often overestimates the activation energies for the concerted cycloaddition mechanism. As a consequence, the stability of biradical structures and the possibility of stepwise mechanism are overestimated even when using a large active space.^{82–84} However, the results of the CASSCF calculations with MP2 corrected energies (CASPT2//CASSCF) are similar to those of the CCSD(T), G2 and CBS calculations.^{83,85} Moreover, in some cases the open-shell systems (*e.g.*, biradical structures) and excited states can be correctly

described only in the CASSCF and CASPT2 approximations. At the same time the MP4SDTQ, CCSD(T) and QCISD(T) methods can be recommended for theoretical studies of ground-state closed-shell structures. The G2 and CBS approximations belong to the most accurate ones and give the results that are in excellent agreement with experimental data. However, these techniques are of limited use because they are only applicable to small molecular systems.

Finally, there is yet another group of computational methods with inclusion of electron correlation effects. These are the DFT methods that combine a rather high accuracy of calculations and relatively low computational cost. This predetermines high popularity of DFT methods in studies of organic and organometallic molecular systems. Most DFT studies of cycloaddition reactions were carried out with the B3LYP functional. Often, the results obtained from B3LYP calculations are in good agreement with experimental data and this approximation can be considered optimum. Nevertheless it is clear that search for the most correct method of theoretical investigation of a new cycloaddition reaction requires evaluation of various approximations, as applied to the process under study, and comparison of the results obtained with experimental data. In the lack of experimental data (this is a quite typical situation) the applicability of a particular computational method can be indirectly assessed by comparing the results obtained with those found from the highest-level approximations [G2, CBS, CCSD(T), *etc.*].

In addition to the computational methods, the choice of the basis set can also affect the results of calculations. At present, most studies of the cycloaddition reactions of medium-size organic molecules are carried out with the 6-31G* split-valence basis set of Gauss functions. In most cases a correct description of the systems under study requires the use of polarisation functions. Additionally, investigations of anion structures require augmentation of the basis sets with diffuse functions (*e.g.*, the basis sets 6-31+G**, 6-31+G** and 6-31++G**). In studies of small molecules it is possible (and desired) to employ the extended basis sets (*e.g.*, 6-311G**, 6-311+G**, cc-pVDZ, cc-pVTZ, *etc.*). If the reacting molecules contain transition-element atoms, the core electrons in these atoms are usually approximated by pseudopotentials (LanL2DZ, LanL2MB, Stuttgart pseudopotentials, *etc.*), which can also allow for relativistic effects (this is of particular importance in the case of heavy fifth- and sixth-row elements).

The energy characteristics of cycloaddition reactions are often sensitive to the change in the computational method rather than the change in the basis set.^{35,72,73,80,83} For instance, extension of the basis set from 6-31G* to 6-31+G**, 6-311+G*, 6-311++G** and 6-311++G(2df,2p) [methods MP2, CCSD(T) and MP4SDTQ, respectively] in studies of the reactions of CH₂N₂ and HCNO with C₂H₄ and C₂H₂ causes the activation energy to change only by 0.2–2.3 kJ mol^{−1} (see Refs 35 and 83). On the contrary, some authors reported strong differences between the activation barrier calculated with different basis sets.⁷¹ Thus, studies of new cycloaddition reactions require evaluation of various basis sets in order to analyse the stability of the solution to the changes in the basis set.

IV. Reactions of allyl type dipoles

Most [3 + 2]-cycloaddition reactions represent a dipolar cycloaddition (one reactant molecule is a dipole while the other reactant molecule is a dipolarophile). The dipole molecules contain highly polar bonds and fragments the atoms of which bear integer positive and negative formal charges at least in one boundary structure. The dipoles are usually divided into two main classes, namely, the allyl and propargyl-allenyl type dipoles (Fig. 6). The first type of compounds has a bent geometry of the reactive fragment due to sp²-hybridisation of the orbitals of the central atom; the second type of compounds is characterised by sp-hybridisation of AOs and linear geometry.

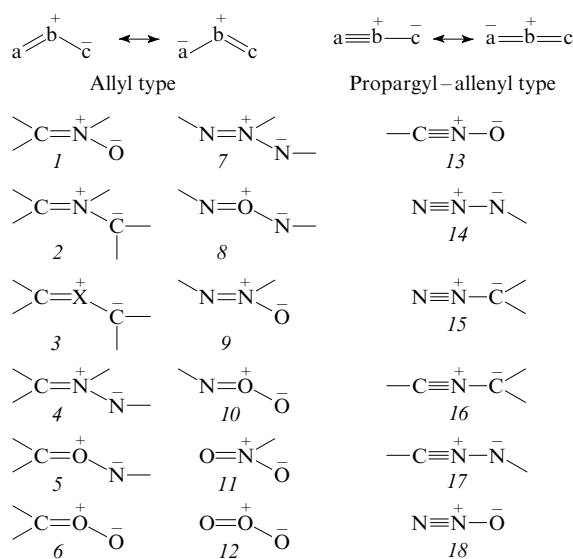


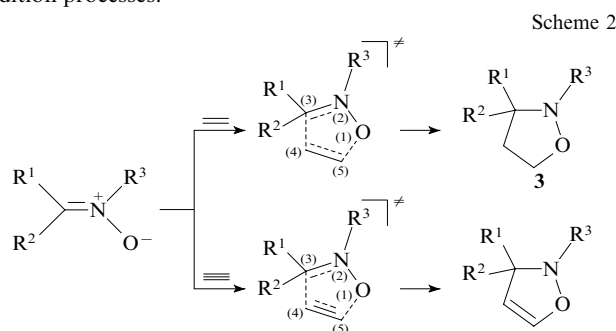
Figure 6. Main types of 1,3-dipoles.

Nitrones (1); ylides (2); carbonyl-, thio- and selenocarbonyl ylides (3); azomethine imines (4); carbonyl imines (5); carbonyl oxides (6); azoimines (7); nitrosimines (8); azoxy compounds (9); nitroso oxides (10); nitro compounds (11); ozone (12); nitrile oxides (13); azides (14); diazoalkanes (15); nitrile ylides (16); nitrile imines (17); and nitrous oxide (18).

The allyl-type dipoles comprise nitrones, ylides (including azomethine ylides, carbonyl ylides and thio- and selenocarbonyl ylides), azomethine imines, carbonyl imines, carbonyl oxides, azoimines, nitrosimines, azoxy compounds, nitroso oxides, nitro compounds and ozone. Additionally, the oxo ions and transition metal oxides can also formally be treated as dipoles.

1. Nitrones

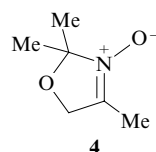
The cycloaddition of nitrones to alkenes (Scheme 2) resulting in isoxazolidine **3** is one of the best studied dipolar [3 + 2]-cycloaddition processes.



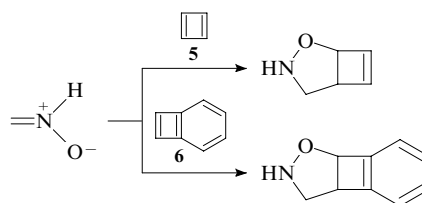
The [3 + 2]-cycloaddition processes involving nitrones are often treated as Sustmann's type II processes.^{86,87} By varying substituents in the nitrone or dipolarophile molecule one can readily change the type of the HOMO–LUMO interaction and therefore the type of the reaction, thus making it a NED or an IED process. Indeed, the cycloaddition of nitrones to such electron-deficient dipolarophiles, as acrylonitrile ($\text{CH}_2=\text{CHCN}$),⁸⁸ acrolein ($\text{CH}_2=\text{CHCHO}$),⁸⁹ methyl propiolate ($\text{CH}\equiv\text{CCO}_2\text{Me}$)^{88,90} and methyl acrylate ($\text{CH}_2=\text{CHCO}_2\text{Me}$),⁹¹ alkyne carbene chromium complex $[(\text{CO})_5\text{Cr}=\text{C}(\text{OH})\text{C}\equiv\text{CH}]$,⁹⁰ fluorinated alkenes and alkynes,^{92,93} nitroalkenes ($\text{R}^1\text{CH}=\text{CR}^2\text{NO}_2$)^{94–97} and vinylsulfonyl chloride ($\text{CH}_2=\text{CHSO}_2\text{Cl}$)⁹⁸ are controlled by the HOMO_{nitrone}–LUMO_{dipolarophile} interaction. On the other hand, the use of alkenes with electron-donating substituents, e.g., methyl vinyl ether ($\text{CH}_2=\text{CHOMe}$)³⁷ causes the reaction type to be changed to the IED process.

a. Reactions with alkenes and alkynes. The reaction mechanisms

Most authors have reported a concerted mechanism of thermally induced cycloaddition of nitrones.^{37,82,88,93,98–103} For instance, studies of the reactions of (i) *N,C*-dimethylnitrone [$\text{MeCH}=\text{N}(\text{Me})\text{O}$] with $\text{CH}_2=\text{CHOMe}$ (see Ref. 37) and (ii) cyclic nitrone **4** with methyl propiolate and acrylonitrile⁸⁸ showed that in the most stable transition states of these reactions the difference of the Wiberg bond indices for the $\text{C}(3)\cdots\text{C}(4)$ and $\text{O}(1)\cdots\text{C}(5)$ contacts (see Scheme 2) varies in the range from 0.13 to 0.27, thus indicating an asynchronous mechanism. Calculations of the S_y values for the cycloaddition of $\text{CH}_2=\text{NHO}$ to ethylene and acetylene showed that these processes are characterised by high synchronicity ($S_y=0.92$).^{99,100} Interestingly, a high synchronicity was also found for the reactions of $\text{CH}_2=\text{NHO}$ with such asymmetrical dipolarophiles, as $\text{CH}_2=\text{CHCF}_3$, $\text{F}_2\text{C}=\text{CF}_3$ and $\text{CH}\equiv\text{CCF}_3$.⁹³



The mechanisms of nitrone ($\text{CH}_2=\text{NHO}$) cycloaddition to ethylene and cyclobutadienes **5** and **6** were studied.^{82,104} The results of the B3LYP, CASSCF and QCISD calculations indicated a concerted mechanism of the nitrone interactions with $\text{CH}_2=\text{CH}_2$ and compound **6**; as to the addition to cyclobutadiene **5**, the concerted and stepwise mechanisms were found to be equiprobable due to clear antiaromatic character of compound **5**. In the case of nitrone reactions with allene ($\text{CH}_2=\text{C}=\text{CH}_2$) the stepwise cycloaddition involving the formation of biradical intermediate is energetically more favourable than concerted one.¹⁰⁵



b. Effect of Lewis acid on the reaction mechanism

The introduction of a Lewis acid catalyst into the system leads to dramatic increase in the asynchronicity of the process^{37,106,107} (for the reasons, see above). For instance, the reaction of $\text{MeCH}=\text{N}(\text{Me})\text{O}\cdots\text{BH}_3$ complex with $\text{CH}_2=\text{CHOMe}$ is accompanied by an increase in the difference between the Wiberg indices for the contacts $\text{C}(3)\cdots\text{C}(4)$ and $\text{O}(1)\cdots\text{C}(5)$ in the transition state (see Scheme 2) from 0.13 (for non-catalytic process) to 0.27.³⁷ The effect of Lewis acid (BH_3 and BF_3) on the mechanism, energy characteristics, regio- and stereoselectivity of the reaction of $\text{CH}_2=\text{NHO}$ with acrolein was also studied.¹⁰⁶ If BH_3 is coordinated to acrolein, the activation energy decreases from 105 to 53 kJ mol^{-1} and the asynchronicity of the process increases. Coordination of this Lewis acid to nitrone causes inhibition of the reaction (E_a increases by 18 kJ mol^{-1}) and some increase in its synchronicity. The theoretical activation energies reported in this study should be treated with care, because they were obtained from HF calculations ignoring the electron correlation effects [*cf.* 65.7 kJ mol^{-1} for the experimentally determined enthalpy of activation of thermally induced reaction of $\text{PhCH}=\text{N}(\text{Me})\text{O}$ with $\text{CH}_2=\text{C}(\text{Me})\text{CO}_2\text{Me}$, see Refs 7 and 108]. Nevertheless, the character of the Lewis acid effect on the reactivity (*i.e.*, acceleration of the reaction upon selective coordination of BH_3 to dipolarophile) is in qualitative agreement with the FMO theory predictions for the NED processes to which the reaction in question belongs. Interestingly, the coordination of BF_3 used instead of BH_3 to nitrone causes the reaction mechanism

to change from concerted to stepwise. Corresponding calculations revealed a Michael-type intermediate for this reaction.

Two possible mechanisms of the interaction of zinc-coordinated *N*-benzyl-*C*-(2-pyridyl)nitron with allyl alcohol were studied.⁶² However, the PM3 semiempirical method employed in that study precluded a correct description of the systems under study and the results obtained appeared to be in contradiction with experimental data.

c. Solvation effects

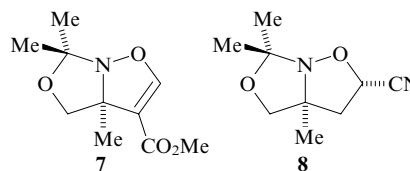
Usually, the dipolar [3 + 2]-cycloaddition reactions of nitrones occur *via* polar transition states, but the initial nitron is also a dipole. If the second reactant has a sufficiently large dipole moment, the total polarity of the reactants becomes higher than the polarity of the transition state. Therefore, when using polar solvents, one can expect an increase in the activation energy for this type of reactions. This was confirmed experimentally^{109–111} and theoretically.^{37, 94, 100} In particular, Domingo³⁷ showed that the activation barrier to the reaction of $\text{MeCH}=\text{N}(\text{Me})\text{O}\cdots\text{BH}_3$ with $\text{CH}_2=\text{CHOMe}$ increases by 7–8 kJ mol^{−1} on going from the gas phase to solution in CH_2Cl_2 . A similar effect was also obtained for the reaction of $\text{CH}_2=\text{NHO}$ with non-polar ethylene; at the same time the interaction of this nitron with acetylene is characterised by some decrease in E_a on going to solution in MeCN .¹⁰⁰ Additionally, solvation is accompanied by an increase in asynchronicity of formation of the corresponding transition state or even by a change from concerted to stepwise reaction mechanism due to, *e.g.*, stabilisation of polar acyclic intermediate in the polar solvent as in the reactions of $\text{PhR}^1\text{C}=\text{N}(\text{Ph})\text{O}$ ($\text{R}^1=\text{H}, \text{Ph}$) with nitroalkenes $\text{R}^2\text{CH}=\text{CHNO}_2$ ($\text{R}^2=\text{C}_6\text{H}_4\text{NO}_2$ -4, CN, CCl_3).^{94, 101, 112}

d. Regioselectivity and stereoselectivity

Elucidation of the nature of the regio- and stereoselectivity of the [3 + 2]-cycloaddition processes is one of the most interesting and important problems. The regioselectivity is often interpreted from the standpoint of the FMO theory as a result of preferred interaction of the dipole and dipolarophile atoms characterised by the largest orbital coefficients in the FMOs. At the same time in the case of nitrones both types of the interaction, $\text{HOMO}_{\text{nitron}}-\text{LUMO}_{\text{dipolarophile}}$, and $\text{HOMO}_{\text{dipolarophile}}-\text{LUMO}_{\text{nitron}}$, play a significant role and the orbital coefficients of all reacting atoms in the FMOs are similar. This is the reason for low regioselectivity of these reactions.^{88, 113, 114}

As mentioned above, the introduction of electron-donating or electron-withdrawing substituents into the nitron or dipolarophile molecule leads to predominance of a certain type of the HOMO–LUMO interaction and, hence, to an increase in the regioselectivity of the reaction. For instance, experimental^{115–118} and theoretical^{34, 37, 89, 93, 94, 98, 101, 118, 119} studies showed that reactions of nitrones with olefins usually result in preferred formation of *ortho*-isomers if the dipolarophile molecule contains an electron-donating substituent (*e.g.*, Alk, OAlk, NH_2) and *meta*-isomers if it contains an electron-withdrawing substituent (*e.g.*, CHO, CF_3 , NO_2 , SO_2Cl). By varying substituents in the nitron molecule one can also change the regioselectivity. For instance, the use of nitrones $\text{CH}_2=\text{N}(\text{R})\text{O}$ in the reaction with $\text{CH}_2=\text{CHNO}_2$ leads to exclusive formation of the *ortho*-isomer, whereas in the case of *C*-substituted nitrones the reaction results in the *meta*-isomer (*meta*-selectivity).^{120, 121}

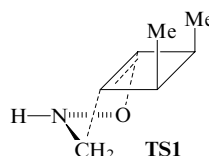
High *meta*-selectivity was predicted for the interaction of cyclic nitron **4** with methyl propiolate.⁸⁸ According to calculations, isomer **7** should be the major product [the PCM-B3LYP/6-31G* calculated activation energy difference is 11 kJ mol^{−1}, which corresponds to an isomer ratio of 85 (*meta*):1 (*ortho*)], which agrees with experimental data on selective formation of the *meta*-isomer in the reaction of compound **4** with ethyl propiolate.⁸⁸



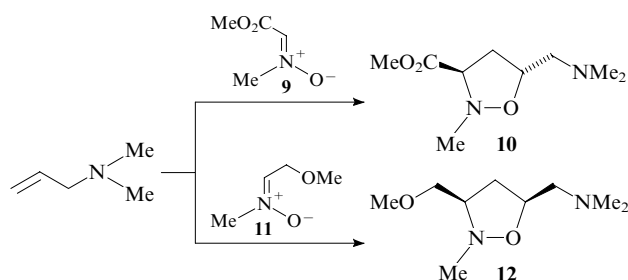
Even minor changes in the relative activation barriers to the formation of *meta*- and *ortho*-isomers lead to large variations of the relative yields of the regioisomers due to exponential dependence in the Boltzmann equation; therefore, the theoretical estimate of regioselectivity can strongly depend on the computational method and basis set employed. For the addition of nitron **4** to acrylonitrile, B3LYP/6-31G* calculations⁸⁸ showed a low *meta*-selectivity, whereas B3LYP/6-31+G* computations using the basis set augmented with diffuse functions predicted a low *ortho*-selectivity (formation of product **8**). One can expect that further extension of the basis set and use of higher-level computational methods [*e.g.*, MP4 or CCSD(T)] will provide better agreement with conclusions about exclusive formation of the *ortho*-isomer in this reaction drawn from experiment.

In some cases the regio- and stereoselectivity are governed by the nature of the solvent and the presence of the Lewis acid.^{37, 100, 122, 123} In particular, the interaction of $\text{CH}_2=\text{N}(\text{R})\text{O}$ with nitroethylene ($\text{CH}_2=\text{CHNO}_2$) shows no regioselectivity in the gas phase, but calculations with inclusion of solvent effect lead to preferred formation of the *ortho*-isomer *via* an *endo*-transition state in accordance with experimental data (see above).¹⁰⁰ Enhancement of the regio- and stereoselectivity upon the introduction of Lewis acid was observed³⁷ in calculations of the interaction of $\text{MeCH}=\text{N}(\text{Me})\text{O}$ with $\text{CH}_2=\text{CHOMe}$. The *exo:endo* isomer ratio increases from 3.8:1 (obtained from B3LYP/6-31G* calculations of thermally induced reaction) to 29:1 for the BH_3 -catalysed process. For comparison, the experimental *exo:endo* isomer ratio in the reaction of $\text{CH}_2\text{OCMe}_2\text{OCH}=\text{N}(\text{O})\text{CMe}_2\text{OCH}_2$ with $\text{CH}_2=\text{CHOEt}$ is 3:1.⁸⁸ The *exo*-stereoselectivity is due to the lack of steric hindrances to the formation of transition state in the case of *endo*-isomer.

Steric stabilisation is one of the main reasons for stereospecificity of the reactions of nitrones with *cis*-3,4-dimethylcyclobutene¹²⁴ and electron-deficient alkenes containing bulky substituents.¹²⁵ In the former case strong interaction between the nitron atoms and the methyl groups of the dipolarophile leads to almost exclusive formation of the *anti*-isomer *via* an *exo*-transition state (**TS1**). The activation energy for the formation of the corresponding *syn*-product is 8.6 kJ mol^{−1} higher (theoretical and experimental *syn:anti* product ratios are 97:3 and $\geq 99:1$, respectively), while the *endo*-addition is 33–39 kJ mol^{−1} less favourable than the *exo*-addition. The *anti*-addition is also preferable for the reactions of $\text{CH}_2=\text{NHO}$ with enol ethers, but here the stereoselectivity is mainly governed by electrostatic effects.¹²⁶



The effect of the nature of the substituent in the dipole molecule on the stereoselectivity of cycloaddition was studied.¹²⁷ The reaction of the model compounds, namely, *E*-isomer of nitron $\text{MeO}_2\text{CCH}=\text{N}(\text{Me})\text{O}$ (**9**) and *N,N*-dimethylallylamine should result in preferred formation of *trans*-product **10** through *exo*-addition, whereas in the reaction of nitron **11** should mainly afford the *cis*-isomer **12** (this process will occur under kinetic control).



The conclusions made¹²⁷ are in excellent agreement with experimental facts. Similarly, the *Si-exo*-facial stereoselectivity was calculated for the reactions of *C*-[(4,*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-*N*-methylnitrone with ethyl 2-acetoxyacrylate¹²⁸ (theoretical and experimental isomer ratios of the most stable *Si-exo*- and *Re-exo*-isomers are 7 : 1 and 2 : 1, respectively) and with vinyl acetate.¹²⁹ At the same time the cycloaddition of *C*-[(4,*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-*N*-methylnitrone to methyl acrylate,¹³⁰ *C*-(2-furyl)-*N*-methylnitrone to vinyl acetate,¹³¹ and nitrones to unsaturated arylsulfones¹³² and pyrazolon-*N,N*-dioxides to epoxynaphthalene¹³³ show *endo*-selectivity.

In some cases the stereoselectivity is governed by the effect of the secondary orbital interaction (orbital interaction between the atoms that are not involved in the cycloaddition reaction, *e.g.*, the atoms *b* and *g* or *b* and *f*, see Fig. 7). Obviously, a bonding secondary orbital interaction should stabilise a given stereoconfiguration and an antibonding interaction should destabilise it. Indeed, the *endo*-stereoselectivity theoretically predicted for the addition of nitrones to *s-cis*-acrolein ($\text{CH}_2=\text{CH}-\text{CHO}$) is governed by the bonding secondary orbital interaction between the nitrone nitrogen p-AOs and p-orbitals of the atoms in the carbonyl group of the dipolarophile.^{34, 134} However, it should be noted that the authors of some studies (see, *e.g.*, a review by Garcia *et al.*²⁷) cast some doubt on the role of the secondary orbital interaction in the stereospecific course of reactions.

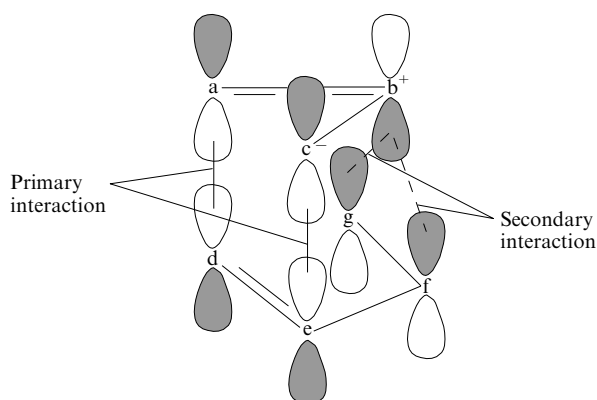
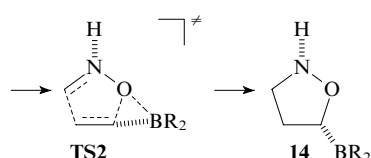
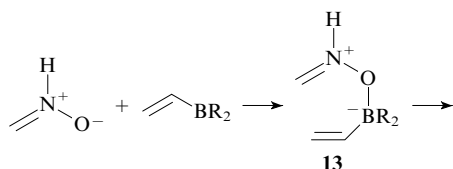


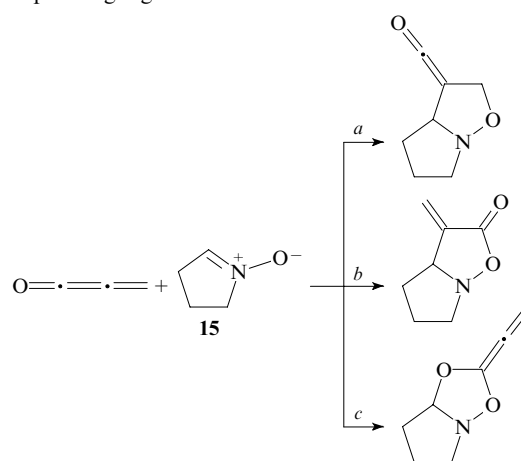
Figure 7. Primary and secondary orbital interactions.

Model reactions of nitrone $\text{CH}_2=\text{NHO}$ with vinylboranes $\text{CH}_2=\text{CHBR}_2$ were studied.¹³⁵ The [3 + 2]-cycloaddition reaction should show regioselectivity and *endo*-stereoselectivity and proceed at high rate *via* acyclic complex **13** with the formation of *ortho*-isomer **14**.



The regioselectivity and low activation barriers are due to strong interaction between the boron and oxygen atoms in complex **13** and in the corresponding transition state **TS2**. Other possible mechanisms of this process, namely, cyclisation with the formation of six-membered boron-containing ring, *O*-boration and oxidation are undoubtedly energetically less favourable compared to cycloaddition. The use of dimethyl-substituted vinylboranes $\text{CH}_2=\text{CHBMe}_2$ and $\text{Me}_2\text{C}=\text{CHBH}_2$ causes the activation energy to increase, whereas in the case of dichlorovinylborane $\text{CH}_2=\text{CHBCl}_2$ the activation barrier decreases consistently with the FMO theory predictions for the NED reactions. At present, these theoretical predictions cannot be substantiated or rejected due to the lack of corresponding experimental data.

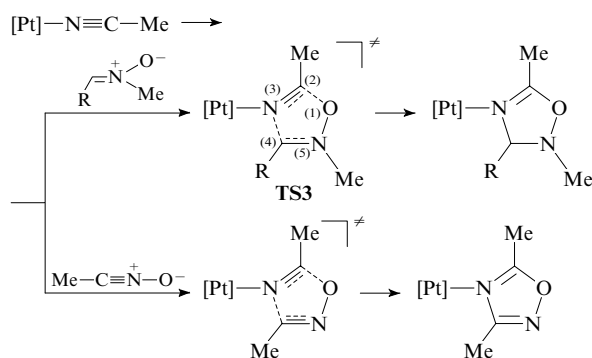
If the dipolarophile molecule has several multiple bonds, the dipole can selectively react at one of the bonds (this is called chemoselectivity). For instance, the chemoselectivity of the reaction of cyclic nitrone **15** with methyleneketene was studied.¹³⁶ The reaction can follow three pathways, among which the cycloaddition to the terminal $\text{C}=\text{C}$ bond is the most kinetically favourable (B3LYP/6-31G* calculated activation energies for the pathways *a*, *b* and *c* are 16, 23 and 87 kJ mol⁻¹, respectively). This agrees with experimental data on the isolation of the corresponding regioisomer.



e. Other dipolarophiles

The results of studies on the reactions of cyclic and acyclic nitrones with free nitriles $\text{RC}\equiv\text{N}$ and platinum-coordinated nitrile constituents of the complexes *trans*-[PtCl₂(NCMe)₂] (**16**) and *trans*-[PtCl₄(NCMe)₂] (**17**) (Scheme 3) were summarised in two recent studies.^{72, 137}

Scheme 3



[Pt] = *trans*-[PtCl_n(NCMe)]; *n* = 2, 4.

These studies were carried out to establish the reasons for the activation of nitriles in the complexes compared to free ligands and to thoroughly analyse the reaction mechanisms and the influence of various factors (solvent, nature of substituent, computational method) on the energy characteristics of the reactions. The experimentally observed^{138,139} enhancement of the reactivity in the series MeCN–**16**–**17** was interpreted as being due to a decrease in the nitrile LUMO energy in this series (orbital control) and an increase in the effective atomic charge of the nitrile β -carbon (charge control).¹⁴⁰ Analysis of the electron density distribution in the transition states **TS3** showed that the coordination of nitrile is accompanied by not only the change in the reaction type from the intermediate to the NED reaction but also a change in the reaction mechanism from synchronous for MeCN ($S_y = 0.92$) to intermediate between concerted cycloaddition and nucleophilic addition of the nitron oxygen atom to the nitrile β -carbon ($S_y = 0.69$ and 0.53 for the reactions of compounds **16** and **17**, respectively). It is this change in the reaction mechanism that provides an explanation for dramatic enhancement of nitrile reactivity upon coordination. Nevertheless, ring critical points were located for all transition states (Fig. 8), which indicates the

cyclic nature of the transition state even in the reaction of complex **17**.

The results of calculations confirmed that coordination of nitrile in complexes **16** and **17** is followed by dramatic decrease in the Gibbs free activation energy and by an increase, in absolute value, in the energy change (ΔG) in the reaction (Table 1). This is in excellent agreement with the experimentally observed changes in the reactivity of nitriles. Interestingly, the ‘electronic’ activation energy calculated relative to the total energy of reactants for the interaction of $\text{CH}_2=\text{N}(\text{Me})\text{O}$ with complex **17** is negative, being equal to -23 kJ mol^{-1} (obtained from B3LYP/6-31G* calculations). However, the E_a values calculated relative to the orientation complex that is formed in the early stages of the reaction and the Gibbs free activation energy calculated relative to the total energy of reactants become positive (20 and 34 kJ mol^{-1} , respectively). Thus, in the E_a scale (in essence, this parameter coincides with $\Delta H^\ddagger$ at 0 K) the energy of the orientation complex is lower than that of the reactants. Nevertheless, with allowance for the entropy factor one gets that the equilibrium is shifted towards formation of the initial compounds. This situation is typical of the cycloaddition reactions involving highly activated reactants (see, e.g., Refs 141–143).

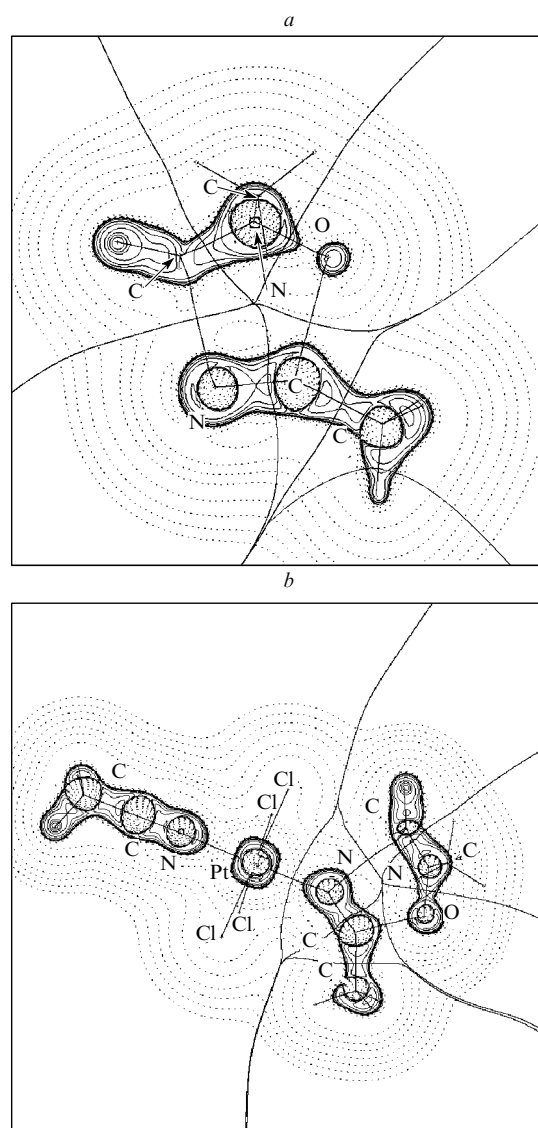


Figure 8. Contour map illustrating the distribution of the Laplacian of electron density $\nabla^2\rho(r)$, the bond pathway and the zero-flux surface for transition states of the reactions of nitron $\text{CH}_2=\text{N}(\text{Me})\text{O}$ with MeCN (a) and complex **17** (b).

Table 1. Relative energy characteristics (in kJ mol^{-1}) of the cycloaddition of $\text{CH}_2=\text{N}(\text{Me})\text{O}$ to MeCN and to complexes **16** and **17** (obtained from B3LYP/6-31G* calculations; ECP on Pt atom).^a

Reactant	E_a	$\Delta H^\ddagger$	$\Delta G^\ddagger$	ΔE	ΔH	ΔG
MeCN	59 (66) 67 [71] ^a [71 (78)] ^b	62 [74] ^b	116 [128] ^b	-100 (-83) -91 [-97] ^a [-97 (-81)] ^b	-88 [-86] ^b	-32 [-30] ^b
16	13 (19) 24 [27] ^a	14	82	-147 (-130) -136 [-129] ^a	-137	-64
17	-23 (-17) -15 [0] ^a	-16	34	-170 (-152) -163 [-151] ^a	-155	-93

Notes. 1. All values are given relative to the total energy of the reactants. 2. The values in parentheses and in square brackets denote the values corrected for zero-point vibrational energy and for solvation effect, respectively. The values corrected for the basis set superposition error are given in *italic*.

^a Obtained from CPCM calculations using the gas-phase equilibrium geometry. ^b Full geometry optimisation was carried out in the CPCM-B3LYP/6-31G* approximation.

Studies of the effect of the substituent nature on the energy characteristics of reactions showed that the process proceeds more easily upon introduction of electron-withdrawing groups into the nitrile molecule. Indeed, the activation energies obtained for the reaction of $\text{CH}_2=\text{N}(\text{Me})\text{O}$ with RCN are 59 and 54 kJ mol^{-1} at $\text{R} = \text{Me}$ and Ph , respectively. *C*-Alkyl nitrones are more reactive than *C*-aryl nitrones ($\Delta G^\ddagger = 127$ and 143 kJ mol^{-1} for the reactions of $\text{MeCH}=\text{N}(\text{Me})\text{O}$ and $p\text{-MeC}_6\text{H}_4\text{CH}=\text{N}(\text{Me})\text{O}$ with MeCN, respectively). The theoretical $\Delta H^\ddagger$ value for the reaction of $p\text{-MeOC}_6\text{H}_4\text{CH}=\text{N}(\text{Me})\text{O}$ with PhCN is 83 kJ mol^{-1} , being very similar to the experimental value determined for the interaction of cyclic nitron **18** with PhCN (84 kJ mol^{-1}).¹⁴⁴ Additionally, a linear correlation between the parameter $\Delta G^\ddagger$ and the synchronicity of cycloaddition was found (Fig. 9). Since both reactant molecules have high polarities, the use of a polar solvent should inhibit the reaction, namely, the activation energy increases by $12\text{--}23 \text{ kJ mol}^{-1}$ on going from the gas phase to solution in CH_2Cl_2 and the ΔE value for this reaction decreases by $3\text{--}20 \text{ kJ mol}^{-1}$ in absolute value.

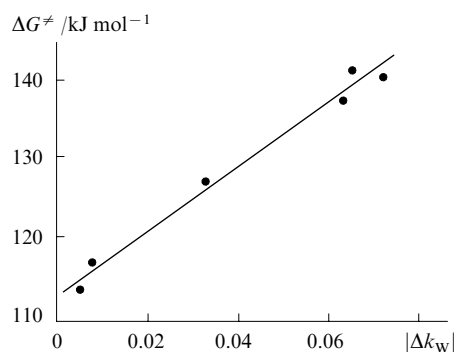
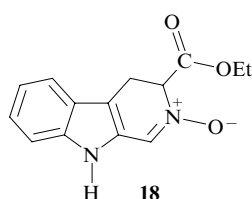


Figure 9. Parameter $\Delta G^\ddagger$ plotted vs. difference of the Wiberg indices (Δk_w) of the contacts O(1)N(5) and C(4)N(3) for the reactions of compounds R^1CN ($R^1 = H, Ph$) with $R^2CH=N(Me)O$ ($R^2 = H, Me, p\text{-MeC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4$); obtained from B3LYP/6-31G* calculations.

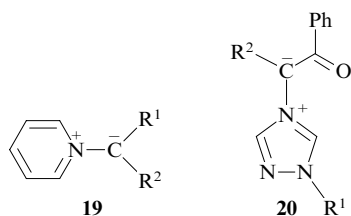


Salts with $[R^1C \equiv NR^2]^+$ cations, in which the nitrile is very electron-deficient, can be used to model the complexation of compounds RCN . The results of semiempirical AM1 calculations of the cycloaddition of pyridine *N*-oxide (C_5H_5NO) to $[MeC \equiv NMe]^+$ supported a stepwise reaction mechanism.¹⁴⁵

Reactions of nitrones $R^1CH=N(R^2)O$ with singlet oxygen $^1O_2$ and molecular anion O_2^- were studied.¹⁴⁶ The intrinsic reaction coordinate was calculated and application of the virial theorem to the molecular system along the reaction pathway was considered. All processes, except for the interaction of $CH_2=NHO$ with O_2^- , occur with the formation of five-membered heterocyclic products. For the last-named reaction, attempts to locate such a product failed.

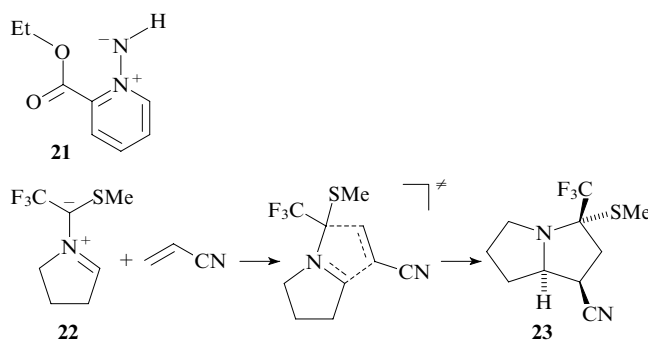
2. Ylides

Ylides are a large class of 1,3-dipoles. Most of them belong to allyl-type dipoles (except nitrile ylides). Azomethine ylides $[R^1_2C=N(R^2)CR^3]$, carbonyl ylides and thiocarbonyl ylides ($R^2C=XCR_2$, $X = O, S$) have been best theoretically studied. Additionally, the behaviour of cyclic ylides **19** and **20** in the [3 + 2]-cycloaddition reactions was studied based on the results of the MO calculations of these dipoles.^{147–149}



The reactions of ylides with dipolarophiles mainly belong to the NED processes.^{86,87} Indeed, the cycloaddition of azomethine ylides to alkenes,^{60,150,151} alkynes,^{63,152} aldehydes,¹⁵³ imino alcohols,¹⁵⁴ as well as the cycloaddition of carbonyl ylides and thiocarbonyl ylides to alkenes,^{155,156} aldehydes¹⁵⁷ and cyclopentenones¹⁵⁸ is governed by the $HOMO_{\text{dipole}} - LUMO_{\text{dipolarophile}}$ interaction. At the same time the reactions between *N*-arylazomethine ylides $R^1R^2C=N(Ar)CR^3R^4$ or carbonyl ylides $R^1R^2C=OCR^3R^4$ and dipolarophiles with electron-donating substituents represent IED processes.^{86,87,159}

The mechanisms of ylide reactions are strongly dependent on the nature of the dipole and dipolarophile and on the character of substituents in the reactant molecules. For instance, the [3 + 2]-cycloaddition reactions of 2-ethoxycarbonylpyridinium *N*-amidine (**21**)¹⁶⁰ and cyclic azomethine ylide **22**¹⁴¹ with acrylonitrile proceed by concerted asynchronous mechanism. The latter process shows regioselectivity and *endo*-stereoselectivity with preferred formation of isomer **23**, which agrees with experimental data, namely, the yield ratio of two *endo*-regioisomers is 24 : 1, whereas no *exo*-regioisomers were isolated.¹⁶¹ The activation energy for this reaction pathway calculated relative to the total energy of reactants is negative (-9 kJ mol^{-1} , obtained from B3LYP/6-31G* calculations), being positive when calculated relative to the energy of the orientation complex (15 kJ mol^{-1}). Moreover, augmentation of the 6-31+G** basis set with diffuse functions leads to positive E_a values relative to the total energy of reactants (5 kJ mol^{-1}). Low activation barriers are confirmed by the fact that this reaction occurs at low temperature (-78°C).¹⁶¹ At the same time it was reported¹⁶² that the addition of azomethine ylide ions $[CH_2=NCH_2]^-$ (and allyl and borallyl ions) to ethylene proceeds by stepwise mechanism, which is consistent with the results obtained by Sauer.¹⁶³



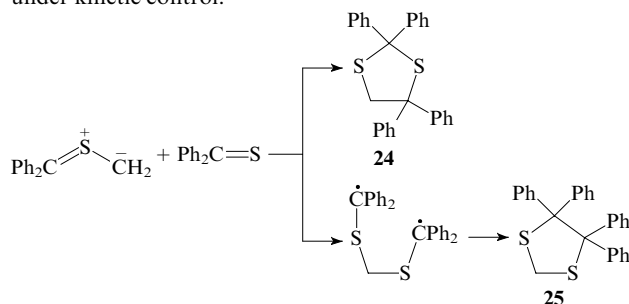
The substituent effects on the mechanisms of the reactions between ylides $R^1_2C=N(R^2)CHCHO$ and alkenes $CH_2=CHR^3$ were studied.¹⁶⁴ It was established that the reactions proceed by concerted mechanism at $R^1 = R^3 = H$ and $R^2 = H, Li$; by stepwise mechanism at $R^1 = H, R^2 = Li, R^3 = NO_2$ and $R^1 = Ph, R^2 = H, R^3 = NO_2$; and by an intermediate mechanism characterised by a synchronicity S_y of about 0.6 (for the reaction in acetonitrile) at $R^1 = R^2 = H, R^3 = NO_2$.

Butler *et al.*^{165,166} analysed the effect of association of water clusters $(H_2O)_4$ and $(H_2O)_6$ with the dipolarophile molecule on the energy characteristics of the cycloaddition of azomethine ylides to alkenes. It was shown that taking into account the formation of such associates leads to considerable decrease in the Gibbs free activation energy (by 22–28 kJ mol^{-1}).

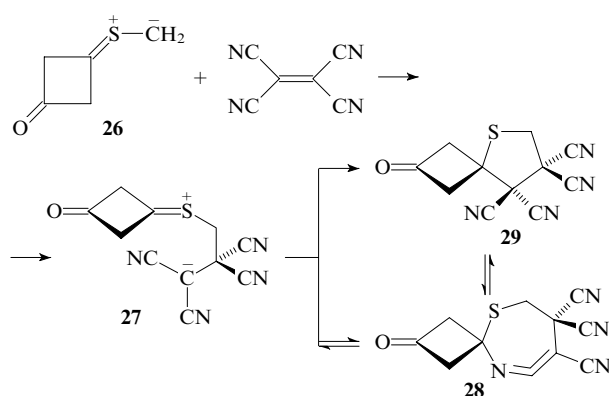
The mechanisms of the interaction of thiocarbonyl ylides $CR_2=SCH_2$ and thiocarbonyl imine $CH_2=SNH$ with symmetrical thioketones and ethylene were studied by the DFT, MCSCF, QCISD(T) and CBS methods.^{85,167–169} Concerted cycloaddition was shown to be energetically more favourable than the stepwise mechanism. It is believed that the reaction of $CH_2=SCH_2$ with $CH_2=S$ proceeds barrierlessly, whereas the activation barriers to the other processes amount a few kcal mol^{-1} . At the same time the activation energies for concerted and stepwise mechanisms differ insignificantly; as a consequence, the possibility of the stepwise mechanism in the presence of substituents stabilising the biradical structure cannot be ruled out.

B3LYP/6-31G*//HF/3-21G* calculations¹⁵⁷ of the activation energy and energy change for the concerted mechanism of the [3 + 2]-cycloaddition of diphenylthiocarbonyl ylide $Ph_2C=SCH_2$ to thiobenzophenone $Ph_2C=S$ revealed kinetic and thermodynamic preference of the formation of regioisomer **24** ($E_a = 27$ and $\Delta E = -172 \text{ kJ mol}^{-1}$). However, these results contradict experimental data, according to which product **25** is isolated in this reaction.¹⁷⁰ Further studies showed that the energetically most

favourable mechanism of this process is a stepwise mechanism with the formation of a C,C-biradical intermediate and regioisomer **25** as the end product. Thus, this reaction occurs under kinetic control.



A stepwise mechanism was also predicted for the reaction of thiocarbonyl ylide **26** with tetracyanoethylene.¹⁷¹ The cycloaddition involves the formation of a zwitterionic intermediate **27**.



This species can undergo cyclisation to the seven-membered cyclic product **28** and to the thermodynamically most stable end product **29** (compounds **28** and **29** are in equilibrium). The energy profile of this reaction pathway is shown in Fig. 10. The activation energies for cyclisation of intermediate **27** to compounds **29** and **28** differ by 5 kJ mol⁻¹, which is in reasonable agreement with experimental data on the formation of compounds **28** (more correctly, corresponding *spiro*-lactim ether) and **29** in a 2:1 ratio;¹⁷² hence, the process also occurs under kinetic control.

The regioselectivity of the reactions of azomethine ylides **30** with (*E*)-3-arylidene-4-chromanones **31** was studied⁶⁰ using the AM1 and PM3 semiempirical MO calculations. The results of calculations confirmed the experimental data on exclusive formation of product **32**. On the contrary, the FMO theory provides no explanation for the observed regioselectivity of dimerisation of thiocarbonyl ylide **33** ('head-to-head' addition pattern).¹⁷³

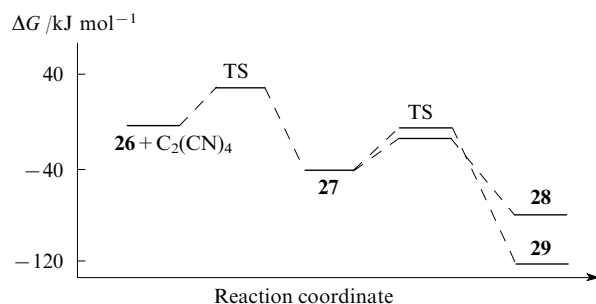
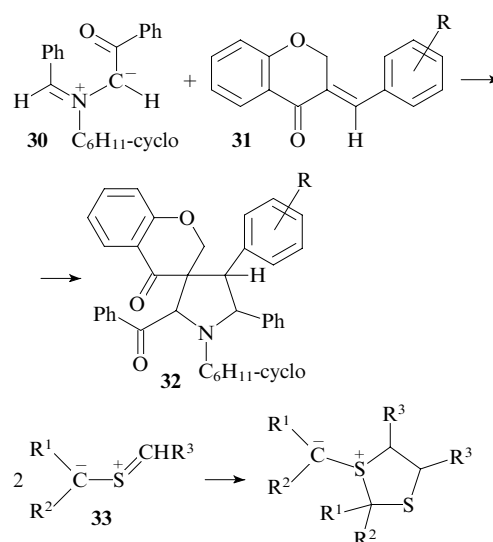


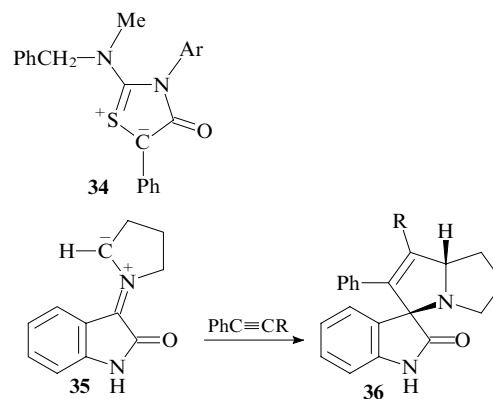
Figure 10. Energy profile of the reaction of thiocarbonyl ylide **26** with tetracyanoethylene.



R¹ = SMe, R² = SO₂Me, R³ = SiMe₃.

It was concluded that in this case the regioselectivity is governed by charge control, *i.e.*, the carbon atom bearing the negative formal charge attacks the positively charged sulfur atom.

Theoretical studies of stereoselectivity were reported for the reactions of (i) isomunchnones and thioisomunchnones (*e.g.*, compound **34**) with alkenes^{155, 174, 175} and alkynes,¹⁷⁶ (ii) azomethine ylides with olefins^{177, 178} and maleimides^{179, 180} and (iii) ylides **35** with phenylalkynes.¹⁵² In the last-mentioned case the equilibrium transition-state geometry was only determined for one out of eight possible stereoisomers (compound **36**). This suggests a selective formation of this structure and was confirmed experimentally.

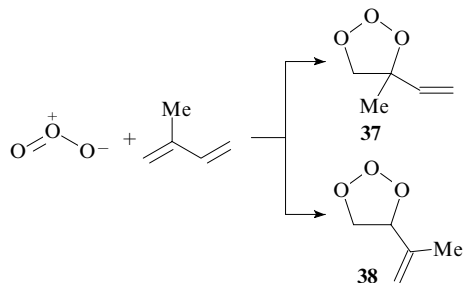


3. Ozone

The ozone molecule provides yet another example of allyl-type dipole, which can also undergo [3 + 2]-cycloaddition reactions. Analysis of the FMO energies showed that these reactions are governed by the HOMO_{dipolarophile} – LUMO_{ozone} interaction due to the low ozone LUMO and especially HOMO energies, thus being the IED processes. This reaction type remains unchanged even for the dipolarophiles containing electron-withdrawing substituents.^{86, 87} Here, the reaction rate is appreciably lower than in the case of the cycloaddition to dipolarophiles with electron-donating groups due to larger energy difference between the corresponding MOs.

Ozonolysis of isoprene was studied theoretically.⁷⁴ It was shown that the process begins with dipolar [3 + 2]-cycloaddition. According to calculations, the reaction proceeds by concerted mechanism. The energy changes and activation energies for the reactions strongly depend on the approximation employed. For

instance, the DFT and MP2 methods give negative E_a values, thus suggesting a barrierless reaction; more accurate CCSD(T)/6-31G* calculations led to $E_a = 14 \text{ kJ mol}^{-1}$ for both reactions. This value is in agreement with experimental kinetic data for these processes ($16\text{--}18 \text{ kJ mol}^{-1}$). Products **37** and **38** are similar in thermodynamic stability, the energy difference between them being 3 kJ mol^{-1} .

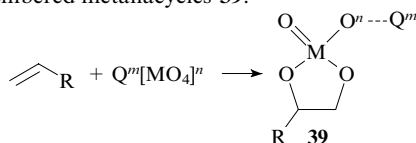


Similar results were also obtained for the ozone reactions with ethylene, benzene and phenol.⁸¹ According to calculations, the reaction with ethylene proceeds most easily [$E_a = 14$, $\Delta E = -220 \text{ kJ mol}^{-1}$, obtained from CCSD(T)/6-31G** computations], whereas the cycloaddition to benzene is characterised by much higher activation barrier and small energy change (66 and -79 kJ mol^{-1} , respectively). Ozonolysis of phenol occurs at positions 1 and 2 of the benzene ring with intermediate energies. The calculated energies are in reasonable agreement with experimental data. Namely, the E_a and ΔE values for the interaction $\text{O}_3 + \text{CH}_2=\text{CH}_2$ are respectively 21 and $-188 \pm 25 \text{ kJ mol}^{-1}$ (Refs 181 and 182) and the activation energy E_a for the interaction $\text{O}_3 + \text{C}_6\text{H}_6$ is 61 kJ mol^{-1} (Ref. 183).

The kinetics and mechanism were studied for the ozone reactions with ethylene, fluoroethylene and chloroethylene¹⁸⁴ and with acetylene.^{185,186} The activation parameters and rate constants for these reactions were estimated. The cycloaddition to haloalkenes should proceed 20 to 25 times slower than the reaction with unsubstituted ethylene [$E_a = 20 \text{ kJ mol}^{-1}$; obtained from CASPT2(10.9)/cc-pVTZ calculations], whereas the reactivities of chloroethylene and fluoroethylene are comparable ($E_a = 23$ and 24 kJ mol^{-1} , respectively). The results of calculations were also confirmed by experimental data [e.g., the calculated and experimental rate constants for cycloaddition to ethylene are 1.02×10^{-18} and $(1.75 \pm 0.52) \times 10^{-18} \text{ cm}^3 (\text{molecule s})^{-1}$, respectively]. It is believed that the reaction with acetylene proceeds by concerted mechanism because no biradical intermediates were located on the potential energy surface.¹⁸⁵ The theoretical rate constant for this process is $0.8 \text{ litre } (\text{mol s})^{-1}$ and $\Delta H^\ddagger = 31 \text{ kJ mol}^{-1}$ [obtained from CCSD(T)/CBS calculations]; the latter value is consistent with the experimental values obtained earlier ($29.7 \pm 4.2 \text{ kJ mol}^{-1}$).¹⁸⁷

4. Metal oxides

There is a number of theoretical studies on the reactions of cycloaddition of the permanganate ion MnO_4^- (Refs 188–191), associates $\text{Et}_4\text{N}^+ \cdots \text{MnO}_4^-$ (see Ref. 188), ruthenium oxide RuO_4 (Refs 192 and 193) and associates $\text{NH}_3 \cdots \text{RuO}_4$ (Ref. 192) to alkenes $\text{XC}_6\text{H}_4\text{CH}=\text{CH}_2$ and $\text{CH}_2=\text{CH}_2$, which result in five-membered metallacycles **39**.



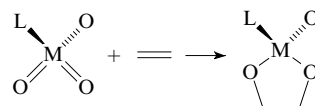
$\text{M} = \text{Mn}$: $n = 1-$, $m = 1$; $\text{Q} = \text{NEt}_4$; $\text{R} = \text{C}_6\text{H}_4\text{X}$ ($\text{X} = \text{H}$, 4-Me, 4-Cl, 3-Cl, 3-Br, 3,4-Cl₂, 3-NO₂, 4-NO₂);
 $\text{M} = \text{Ru}$: $n = m = 0$; $\text{Q} = \text{NH}_3$, $\text{R} = \text{H}$.

The effect of the substituent X on the energy characteristics of the reactions was studied and it was shown that the $\Delta G^\ddagger$ value decreases as follows for different X : 4-Me > H > 3-Br > 4-Cl > 3,4-Cl₂ > 3-Cl > 3-NO₂ > 4-NO₂. Good agreement between the theoretical and experimental activation parameters of the process was obtained (Table 2). For the reactions involving RuO_4 and MnO_4^- the [3 + 2]-cycloaddition processes were shown to be both thermodynamically and kinetically more favourable than [2 + 2]-cycloaddition.

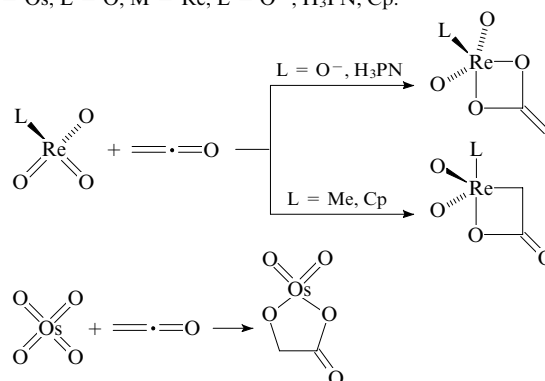
Table 2. Theoretical and experimental (in parentheses) activation parameters for the interaction of $\text{Et}_4\text{N}^+ \cdots \text{MnO}_4^-$ with $\text{XC}_6\text{H}_4\text{CH}=\text{CH}_2$ (B3LYP/6-311 + G**//B3LYP/LanL2DZ calculations; geometry optimised with inclusion of Et_4N^+ counterion).¹⁸⁸

X	$\Delta H^\ddagger / \text{kJ mol}^{-1}$	$\Delta G^\ddagger / \text{kJ mol}^{-1}$
4-Me	24 (20.3 ± 0.7)	79 (73.2)
H	21 (18.8 ± 1.5)	73 (72.7)
3-Br	18 (17.5 ± 1.1)	71 (70.7)
4-Cl	17 (15.9 ± 1.2)	69 (70.9)
3,4-Cl ₂	14 (10.7 ± 0.7)	68 (69.9)
3-Cl	18 (18.0 ± 1.5)	67 (71.0)
3-NO ₂	13 (11.4 ± 1.4)	61 (69.4)
4-NO ₂	7 (15.6 ± 1.7)	58 (67.2)

The cycloaddition of OsO_4 , MO_3^q and LMO_3^q [$q = 0, 1-, 1$; $\text{M} = \text{Mo}$, W , Mn , Tc , Re , Os ; $\text{L} = \text{O}$, H_3PN , Cl , Me , $\eta^5\text{-C}_5\text{H}_5$ (Cp)] to olefins and ketene ($\text{CH}_2=\text{C}=\text{O}$) were studied.^{193–200} The reactions of all compounds (except MeReO_3) with ethylene and the reaction of OsO_4 with ketene proceed by the [3 + 2]-cycloaddition mechanism, although the activation energies are high ($59\text{--}197 \text{ kJ mol}^{-1}$). Other oxides react with ketene by the [2 + 2]-cycloaddition mechanism ($E_a = 46\text{--}92 \text{ kJ mol}^{-1}$), ReO_4^- and $(\text{H}_3\text{PN})\text{ReO}_3$ being added to the $\text{C}=\text{O}$ bond and MeReO_3 and CpReO_3 being added to the $\text{C}=\text{C}$ bond. The most recent data on the cycloaddition of metal oxides to the $\text{C}=\text{C}$ double bond were summarised in a review by Deubel and Frenking.²⁰¹



$\text{M} = \text{Os}$, $\text{L} = \text{O}$; $\text{M} = \text{Re}$, $\text{L} = \text{O}^-$, H_3PN , Cp .



V. Reactions of propargyl–allenyl type dipoles

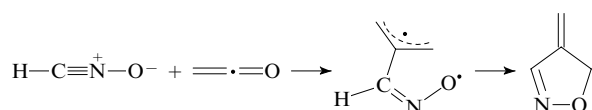
The propargyl–allenyl type dipoles include nitrile oxides, azides, diazoalkanes, nitrile ylides, nitrile imines and nitrous oxide (see Fig. 6).

1. Nitrile oxides

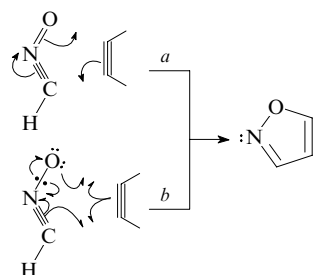
Following Sustmann's classification, reactions of cycloaddition of nitrile oxides $\text{RC}\equiv\text{N}^+-\text{O}^-$ are often treated as type III (IED) processes.^{86,87} At the same time, carrying out reactions with electron-deficient dipolarophiles causes the reaction type to

change to the NED process due to a decrease in the dipolarophile LUMO energies.^{92, 202, 203} For instance, the reactions of RCNO compounds with fluoroalkenes and fluoroalkynes⁹² and halo- and cyano-substituted *p*-benzoquinones²⁰² are governed by the HOMO_{dipole}–LUMO_{dipolarophile} interaction, their reactions with the methyl and methoxy derivatives of *p*-benzoquinone²⁰² and with 1,2,4-triazepine²⁰⁴ are controlled by both types of the orbital interaction, while the addition of RCNO to dihydrofuranones belongs to the IED processes.²⁰⁵

Most reactions involving nitrile oxides are assumed to proceed concertedly.^{35, 99, 100, 104, 204, 206–211} Quantum-chemical calculations predicted a high synchronicity for, e.g., the reactions of fulminic acid with ethylene and acetylene ($S_y = 0.79–0.81$ in the gas phase).^{99, 100} The calculated activation barriers to the former process strongly depend on the approximation used. The results of MP4/6-31G**/HF/6-31G* calculations³⁵ ($E_a = 38$, $\Delta G^\ddagger = 74$ kJ mol^{−1}) are in good agreement with the experimentally determined $\Delta G^\ddagger$ value (84 kJ mol^{−1}) for the cycloaddition of PhCNO to CH₂=CH₂.²¹² Various high-level calculations [B3LYP, MP2, CCSD(T), CASSCF, G2(CC)] of the interaction of HCNO with C₂H₂ give $E_a = 54–59$ kJ mol^{−1} (Ref. 213). This is consistent with the fact that alkynes are more inert than alkenes in the cycloaddition reactions with nitrile oxides.²¹⁴ These processes occur *via* planar aromatic transition states and the stabilising effect of π -aromaticity in them is insignificant. Similarly to nitrones, taking into account solvation effects causes an increase in the activation energy by 4–9 kJ mol^{−1} and a decrease in the synchronicity of the reaction. At the same time the energy of the transition state of the cycloaddition of fulminic acid to allene (CH₂=C=CH₂) following the biradical mechanism is 16 kJ mol^{−1} lower than the corresponding energy in the case of concerted mechanism.¹⁰⁵

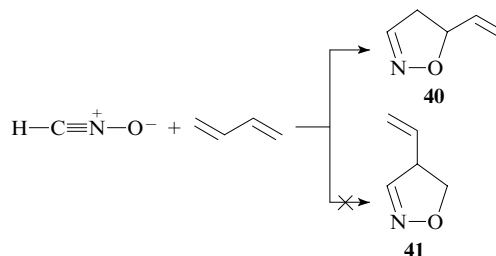


Some authors considered the reaction of fulminic acid with acetylene in terms of the valence bond approach.^{215, 216} In particular, this reaction was treated²¹⁵ as proceeding by ‘heterolytic’ mechanism (*a*) *via* a non-aromatic transition state in contrast to the Diels–Alder reactions characterised by ‘homolytic’ mechanism and aromatic transition state.²¹⁷ Yet another version of the reaction mechanism, namely, pathway *b*, is also available.²¹⁶ Clearly, a correct determination of the mechanism of this reaction requires further investigations. This process was also studied using the catastrophe theory.²¹⁸

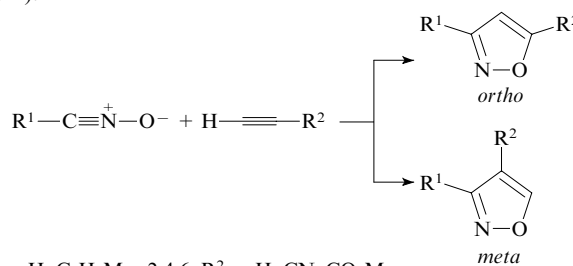


A number of studies are concerned with the regio- and stereo-selectivity of the cycloaddition of nitrile oxides to buta-1,3-diene,¹⁰⁰ alkenes^{35, 219–221} and fluoroalkenes,²²² acrylonitrile, methyl vinyl ether,^{35, 223} cyclobutenes,^{124, 224} dicyclopentadienes,²²⁵ alkynes,^{226–228} thionitroso compounds,²²⁹ anthracene and acridine,²³⁰ dihydrofuranones,²⁰⁵ adamantane-2-thiones, 2-methyleneadamantanes,^{231, 232} stilbenes²³³ and 4-methylenetetrahydrothiopyran.²³⁴ In the reaction with butadiene the activation energy for the formation of 5-vinylisoxazoline (**40**) is 14–15 kJ mol^{−1} lower than that needed for the formation of 4-vinyl-substituted product **41** both in the gas phase and in

solution.¹⁰⁰ This agrees with experimental data on selective formation of compound **40** in the reaction of buta-1,3-diene with fulminic acid prepared *in situ*.²³⁵ The aromaticity of the transition state does not determine the regioselectivity of the process. The cycloaddition to olefins, acrylonitrile and methyl vinyl ether shows regioselectivity with the formation of the *ortho*-isomers, which is also consistent with experimental facts.^{236, 237} Enhancement of electron-donating ability of the substituent at the dipolarophile enhances the *ortho*-selectivity as in the reactions of nitrones.³⁴

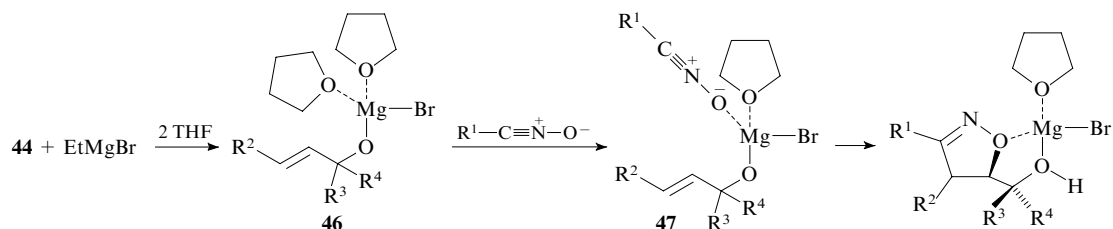
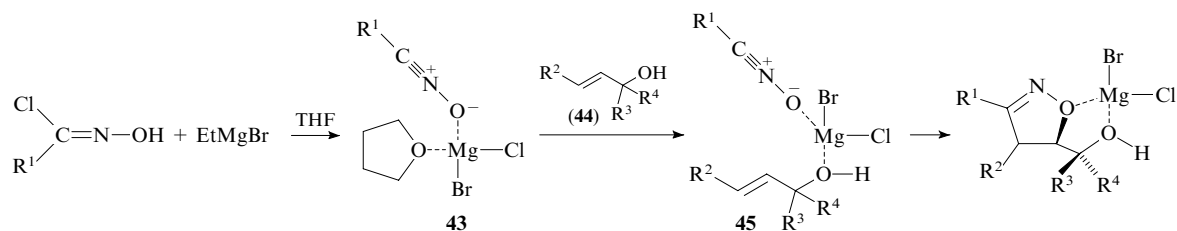


The regioselectivity of the cycloaddition of nitrile oxides to alkynes depends on both the nature of substituents in the dipole and dipolarophile molecules and on the solvent nature.^{226, 228, 230} For instance, quantum-chemical computations of gas-phase interaction of fulminic acid with cyanoacetylene (CH≡CCN) predicted preferred formation of the *ortho*-isomer of isoxazole; on the contrary, the reaction of 2,4,6-trimethylbenzonitrile oxide (mesitonitrile oxide) with CH≡CR (R = CN, CO₂Me) is expected to result in the *meta*-isomers (the activation energy difference, ΔE_a , between the *ortho*- and *meta*-pathways lies in the range 2–5 kJ mol^{−1}; obtained from B3LYP/6-31G* calculations).²²⁶ A similar change in the regioselectivity depending on the substituent at the nitrile oxide was also experimentally observed for the reaction of RCNO with CH≡CCO₂Me (ratio of *ortho*/*meta* isomers is 5.25:1 for R = H and 1:2.6 for R = 2,4,6-Me₃C₆H₂, see Refs 7, 10, 237). This can be interpreted as a result of enhancement of the nucleophilicity on going from HCNO to mesitonitrile oxide due to strong donor properties of the mesityl group. As a consequence the orbital coefficients on the oxygen atom increase and therefore the formation of the *meta*-isomer is facilitated (orbital coefficients at the unsubstituted carbon atom in the alkyne molecule are also larger than at the substituted carbon atom).



R¹ = H, C₆H₂Me₃-2,4,6; R² = H, CN, CO₂Me.

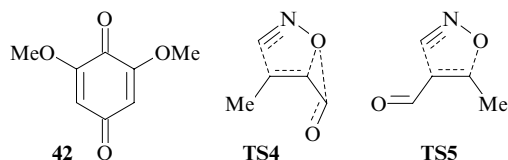
Solvation significantly facilitates the formation of the *ortho*-isomers (they should be the major products in high-polarity solvents, in particular, H₂O). This becomes understandable taking into account the fact that the TS of the reaction resulting in the *ortho*-isomer is characterised by a higher polarity than the TS on the pathway to the *meta*-isomer and therefore the former transition state is better stabilised in polar solvents. The theoretical ratio of the *ortho*- and *meta*-isomers in the reaction of mesitonitrile oxide with acrylonitrile in CCl₄ solution agrees with experimental data (2.3:1 and 1.3:1, respectively).²³⁸ At the same time an increase in the solvent polarity causes an increase in the activation energies, which leads to inhibition of the process. DFT calculations of the reactions of benzonitrile oxide with ethynyl- and propynylboronates (RC≡CBOCH₂CH₂O) predict a change in the regioselectivity from the formation of the *ortho*-isomer



$R^1 = \text{H, Ph}; R^2 = R^3 = R^4 = \text{H, Me.}$

($R = \text{H}$) to *meta*-isomer ($R = \text{Me}$),²⁰⁷ which is in agreement with experimental data.²³⁹

In some cases the chemo- and regioselectivity are influenced by the secondary orbital interaction. For instance, in the reaction of 2,4,6-trimethylbenzonitrile oxide with 2,6-dimethoxy-*p*-benzoquinone (**42**) the antibonding secondary orbital interaction between $\text{HOMO}_{\text{quinone}}$ and $\text{LUMO}_{\text{dipole}}$ is responsible for experimentally observed selective formation of the product of addition to the $\text{C}=\text{O}$ rather than $\text{C}=\text{C}$ bond.²⁴⁰ The same effect governs a decrease in the regioselectivity of cycloaddition of fulminic acid to crotonaldehyde $\text{MeCH}=\text{CH}-\text{CHO}$.²⁴¹ Due to the secondary orbital interaction between the nitrile oxide oxygen AOs and the carbonyl carbon AOs in the transition state **TS4**, the energies of the structures **TS4** and **TS5** become similar ($E_a = 57$ and 55 kJ mol^{-1} , respectively; the calculated ratio of regioisomers is 2.2 : 1 and the experimentally determined ratio of the isomers for the reaction of PhCNO with $\text{MeCH}=\text{CH}-\text{CHO}$ is 4.3 : 1).



The mechanisms and the regio- and stereoselectivity of the reactions of nitrile oxides with allyl alcohols controlled by magnesium ions were studied.^{242, 243} In particular, two reaction pathways were analysed. One of them (Scheme 4a) leads to the formation of a magnesium complex with nitrile oxide and one THF molecule **43** due to the interaction of hydroxyiminoyl chloride $\text{R}^1-\text{C}(\text{Cl})=\text{N}-\text{OH}$ with EtMgBr in THF solution. Subsequent interaction between **43** and **44** yields complex **45** with both reactant molecules coordinated to magnesium. The second pathway (Scheme 4b) begins with the formation of alkoxymagnesium complex **46** and then intermediate **47** containing coordinated nitrile oxide, alkoxide and THF molecules. Although the reaction between RCNO and compound **44** shows *ortho*-regioselectivity in the absence of Mg^{2+} (the activation energies for the formation of the *ortho*- and *meta*-isomers differ by 13 to 21 kJ mol^{-1}), the magnesium-controlled process (second pathway) results in exclusive formation of the *ortho*-isomer. This pathway is also kinetically more preferred. The coordination to magnesium also causes enhancement of the *syn*-stereoselectivity related to steric factors, but the activation energy changes insignificantly in this case.

The cycloaddition of benzonitrile oxides to alkenes $\text{CH}_2=\text{CHOC}(\text{O})\text{R}$ (**48**) and $\text{CH}_2=\text{C}(\text{Ac})\text{OC}(\text{O})\text{R}$ (**49**) ($\text{R} = 4\text{-NO}_2\text{C}_6\text{H}_4$) was also described using the hard and soft acids and bases principle.^{244, 245} Consideration of the global-

global interaction revealed that the term ΔE_v in Eqn (2) (see Section II) is much smaller than the term ΔE_μ at $\lambda = 1$ ($\Delta E_{\text{int}} = -4.83 - 209.75 \lambda$ and $\Delta E_{\text{int}} = -6.37 - 217.30 \lambda$ for the reactions with compounds **48** and **49**, respectively). Therefore, charge-transfer processes have little effect on the reactivities of compounds in the cycloaddition reactions of nitrile oxides.

The nucleophilic and electrophilic attack on the carbon and nitrogen atoms in the nitrile oxide molecule and on the double-bond carbon atoms in the alkene molecules were studied from the standpoint of local-global interactions. According to calculations, the energetically most favourable processes include the nucleophilic attack of alkene on the carbon atom in the dipole molecule and the electrophilic attack of the dipole on the terminal carbon atom in the alkene molecule. Thus, in accordance with experimental facts the hard and soft acids and bases principle correctly predicts the selective formation of the *ortho*-isomer.²⁴⁶ The FMO theory gives incorrect results in this case.

The mechanism of reactions of acetonitrile oxide (MeCNO) with nitriles (see Scheme 3) and the reason for the activation of RCN in the platinum complexes **16** and **17** have been studied.²⁴⁷ The activation of nitriles upon coordination was interpreted from the standpoint of orbital control as a result of a decrease in the nitrile LUMO energy. Indeed, if the reaction of free MeCN is described as an intermediate process [difference $\Delta E = \Delta E(\text{HOMO}_{\text{nitrile}} - \text{LUMO}_{\text{dipole}}) - \Delta E(\text{HOMO}_{\text{dipole}} - \text{LUMO}_{\text{nitrile}})$ is 2.10 eV ; obtained from B3LYP/6-31G* calculations], the cycloaddition to the nitrile complexes is more probably a NED process ($\Delta \Delta E = 3.70$ and 5.06 eV for the reactions of complexes **16** and **17**, respectively).

The reactions proceed by concerted mechanism, but the asynchronicity appreciably increases on going from MeCN to complex **17**. The energies of the transition states and intermediates in the case of stepwise mechanism are $33\text{--}218 \text{ kJ mol}^{-1}$ higher than the transition-state energies for the concerted mechanism. Calculations of the reactions of MeCNO with MeCN and complex **16** gave similar values of activation barriers (Table 3) in

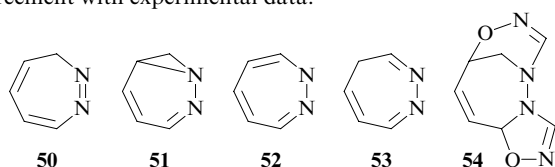
Table 3. Relative energy characteristics (in kJ mol^{-1}) of the cycloaddition of MeCNO to MeCN and to complexes **16** and **17** (obtained from B3LYP/6-31G* calculations; ECP on Pt atom).

Reactant	E_a	$\Delta H^\ddagger$	$\Delta G^\ddagger$	ΔE	ΔH	ΔG
MeCN	59 (63)	60	109	-224 (-205)	-212	-154
16	51 (54)	51	108	-255 (-236)	-245	-169
17	24 (28)	22	94	-251 (-231)	-241	-157

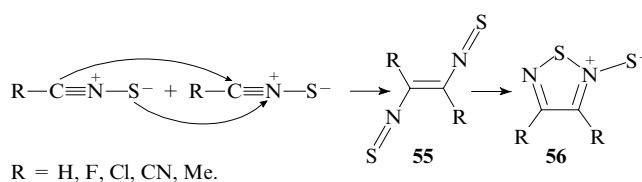
Note. All values are given relative to the total energy of the reactants. The values corrected for the zero-point vibrational energy are given in parentheses.

contrast to the results obtained for analogous reactions of nitron $\text{CH}_2=\text{N}(\text{Me})\text{O}$ characterised by considerable activation on going from MeCN to compound **16** (see Section IV.1.e).⁷² The activation energy for the cycloaddition of nitrile oxides to complex **17** also decreases much smaller than in the case of cycloaddition of nitrones. Probably, this difference between the nitron and nitrile oxide reaction kinetics is due to steric interaction of the methyl group in MeCNO with the platinum or chlorine atoms; this interaction is absent for $\text{CH}_2=\text{N}(\text{Me})\text{O}$. Clearly, additional theoretical and experimental investigations are needed for solving this problem. The cycloaddition of MeCNO to compound **16** is characterised by large negative ΔG value. Thus, high reactivity of complex **17** is governed by kinetic factors, whereas the cycloaddition of nitrile oxides to compound **16** occurs under thermodynamic control. Interestingly, the reaction of radical cation $\text{HCNO}^{+\bullet}$ with HCN proceeds in a stepwise manner.²⁴⁸

Possible reactions of nitrile oxides with 1,2-diazepine were considered.²⁴⁹ The dipolarophile can exist in two forms, **50** and **51**, whereas the formation of the other two forms (**52** and **53**) is kinetically unfavourable. Taking into account this fact, the thermodynamically most probable product of double cycloaddition of nitrile oxide to diazepine is compound **54**, which is in agreement with experimental data.²⁵⁰



Attempts to synthesise nitrile sulfides RCNS by thermolysis of 1,2,5-thiadiazoles were reported.²⁵¹ However, the reactions resulted in corresponding nitriles RCN and elemental sulfur instead of RCNS . To explain the experimental results, high-level quantum-chemical calculations [B3LYP, MPn, QCISD, QCISD(T), CCSD, CCSD(T)] of the decomposition mechanism of RCNS were carried out. It was shown that one of the key stages of the decomposition process is dimerisation of RCNS , which is in essence a reaction of dipolar [3 + 2]-cycloaddition in which one nitrile sulfide molecule acts as dipole and the other nitrile sulfide molecule plays the role of dipolarophile. The process proceeds by the stepwise mechanism and results in intermediate **55** (activation energy is 8 kJ mol^{-1} , obtained from B3LYP/6-31G** calculations). The low activation energy is due to low stability of RCNS in the condensed phase. With $\text{R} = \text{F}$ or Cl , the activation barrier disappears, whereas for $\text{R} = \text{CN}$ it increases to 53 kJ mol^{-1} . The reaction product, compound **56**, subsequently decomposes. Stepwise cycloaddition was also predicted for the dimerisation of nitrile oxides RCNO ($\text{R} = \text{Me}, \text{F}$).^{252–255}



$\text{R} = \text{H}, \text{F}, \text{Cl}, \text{CN}, \text{Me}$.

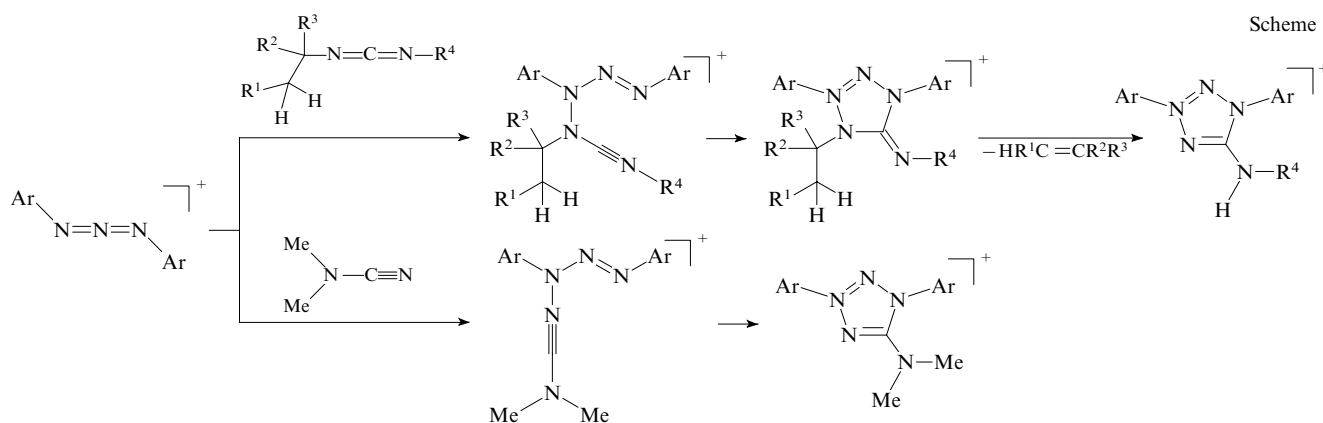
2. Azides

Another group of propargyl-allenyl type dipoles comprises hydrazoic acid derivatives $\text{RNN}\equiv\text{N}$. In the [3 + 2]-cycloaddition reactions involving these dipoles both types of orbital interaction, $\text{HOMO}_{\text{dipole}}-\text{LUMO}_{\text{dipolarophile}}$ and $\text{HOMO}_{\text{dipolarophile}}-\text{LUMO}_{\text{dipole}}$, often make similar contributions (type II processes according to Sustmann's classification).^{86,87} Therefore, by varying substituents in the reactant molecules one can readily change the reaction type.^{256,257} For instance, reactions of azides R^1N_3 ($\text{R}^1 = \text{H}, \text{Me}$) with alkenes $\text{CH}_2=\text{CHR}^2$ ($\text{R}^2 = \text{H}, \text{F}, \text{Cl}, \text{Me}, \text{OH}$) belong to the IED processes; however, if $\text{R}^2 = \text{CN}$ (strong electron-withdrawing substituent), the reaction proceeds as the NED process. Reactions of azides with N_2 , HCN , $\text{CH}_2=\text{NH}$, $\text{NH}=\text{NH}$, $\text{CH}_2=\text{CH}_2$, $\text{CH}\equiv\text{CH}$ and vinylpyridine derivatives^{258–260} also belong to the NED processes.

Calculations predicted a concerted mechanism for the [3 + 2]-cycloaddition of (i) methyl azide (MeN_3) to ethylene²⁶¹ and 1-nitropropene²⁶² and (ii) 1,3-diaza-2-azoniaallene cation $[\text{ArN}=\text{N}=\text{NAr}]^+$ to butyne.²⁶³ Reactions of azide anion with some symmetrical molecules (N_2 , *trans*- $\text{NH}=\text{NH}$, $\text{CH}_2=\text{CH}_2$, $\text{CH}\equiv\text{CH}$) are expected to proceed as synchronous processes; however, for *cis*-diazene (*cis*- $\text{NH}=\text{NH}$) high asynchronicity of the addition was predicted.²⁵⁸ The calculated activation energy increases in the order: *trans*- $\text{NH}=\text{NH} < \text{HCN} < \text{CH}\equiv\text{CH} < \text{cis-NH}=\text{NH} \approx \text{CH}_2=\text{NH} < \text{CH}_2=\text{CH}_2 \ll \text{N}\equiv\text{N}$, which is consistent with experimental data.²⁶⁴ At the same time the interaction of $[\text{ArN}=\text{N}=\text{NAr}]^+$ with *N,N*-dimethylcyanamide ($\text{Me}_2\text{N}-\text{C}\equiv\text{N}$) and carbodiimides $\text{R}^1\text{CH}_2\text{C}(\text{R}^2\text{R}^3)=\text{N}=\text{C}=\text{NR}^4$ is a stepwise process described by Scheme 5.²⁶³

As for other dipoles, the mechanism of cycloaddition of azides depends on the solvation effects and can be changed by varying the solvent. Baranski²⁶⁵ showed that the interaction of MeN_3 with $\text{MeCH}=\text{CHNO}_2$ in the gas phase and in non-polar solvent (toluene) proceeds synchronously, whereas the reactions in polar solvents (acetonitrile, water) proceed by the stepwise mechanism because the polar acyclic intermediate is stabilised in solution. Noteworthy is that replacement of the solvent has no effect on the regioselectivity of the process.

The activation barrier to the reaction of methyl azide with ethylene decreases by 3 kJ mol^{-1} on going from non-polar (CCl_4) to dipolar aprotic solvent (dimethyl sulfoxide); this is accompa-

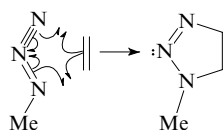


$\text{R}^1 = \text{H}, \text{R}^2 = \text{Me}; \text{R}^1-\text{R}^2 = (\text{CH}_2)_4; \text{R}^3 = \text{H}, \text{Me}; \text{R}^4 = \text{Pr}^i, \text{Bu}^t, \text{cyclo-C}_6\text{H}_{11}$.

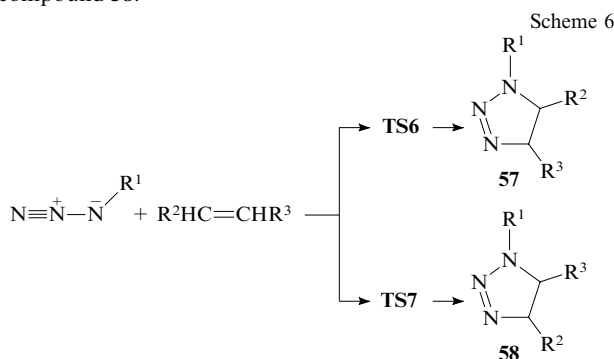
Scheme 5

nied by a fourfold increase in the reaction rate.²⁶¹ Interestingly, the activation barriers calculated with inclusion of polar solvents (water and methanol) are higher than that obtained for CCl₄. Thus, the experimentally observed acceleration of the reaction of phenyl azide with norbornene in water can be explained by the hydrophobic effect rather than an increase in the solvent polarity.

The mechanism of the reaction of methyl azide with ethylene was studied using the spin-coupled method of valence-bond theory.⁸⁰ The cycloaddition proceeds by the homolytic mechanism in contrast to the reactions of nitrile oxides and diazoalkanes that proceed by the heterolytic mechanism.^{73,215} The reaction is accompanied by synchronous cleavage of two π -bonds in the MeN₃ and C₂H₄ molecules, followed by formation of two new bonds. In the vicinity of the transition state the system behaves as a biradical structure.



The regioselectivity, mechanism and energy characteristics of the reactions of compounds R¹N₃ (R¹ = H, Me, NH₂) with alkenes R²CH=CHR³, thionitroso compounds (HN=S, H₂NN=S), nitriles and phosphalkynes [RC $\equiv$ N, RC $\equiv$ P (R = H, Br, Cl, F, Me)] were studied using the DFT approach.^{54, 229, 256, 262, 266} The calculated activation barriers to the reaction of hydrazoic acid with alkenes increase for different substituents R² as follows: CN < H < OH < F < Me < Cl; in the reaction of methyl azide the fluoroalkene becomes more reactive than vinyl alcohol. The reactions show regioselectivity and proceed with selective formation of isomer **57** (Scheme 6), except for the processes involving cyanoethylene and nitropropene that exhibit inverse regioselectivity, which leads to formation of compound **58**.



R¹, R³ = H, Me; R² = H, F, Cl, OH, Me, CN, NO₂.

The regioselectivity is related to the parameter

$$\Delta_{ij}^{kl} = (s_i^- - s_k^+)^2 + (s_j^- - s_l^+)^2,$$

where s are the local softnesses of the reacting atoms. This quantity is a criterion for validity of the hard and soft acids and bases principle. The Δ_{ij}^{kl} is smaller for *ortho*-cycloaddition at R² = H, F, Cl, Me, OH and for *meta*-cycloaddition at R² = CN.²⁵⁶

Molteni and Ponti⁵² studied the dependences of regioselectivity of the process and the interaction energy at constant external potential ΔE_v [see Eqn (3)] taking the reaction of 4-RC₆H₄N₃ with HC $\equiv$ CCO₂Me as an example. Based on a linear relationship between ΔE_a and

$$\Delta \Delta E_v = [\Delta E_v(i-k) + \Delta E_v(j-l)] - [\Delta E_v(i-l) + \Delta E_v(j-k)]$$

(ΔE_a is the difference between the activation energies for two regioisomeric reaction pathways, ΔE_v are the energies of the local-local interaction of the corresponding reaction centres i, j, k, l), one can assess the regioselectivity without locating transition

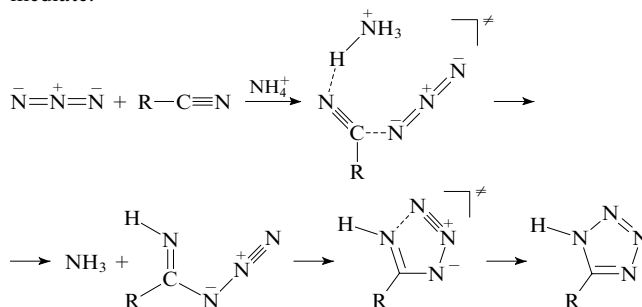
states on the potential energy surface only using the global and local properties of the reactant molecules.

The energy (E_{int}) of the interaction between reactant molecules R¹N₃ and CH₂=CHR² in the transition states was calculated²⁶⁶ as the sum

$$E_{\text{int}} = E_{\text{def}} + E_{\text{es}} + E_{\text{p}} + E_{\text{ex}} + E_{\text{ct}},$$

where the terms in the right side of the equation denote the deformation, electrostatic, polarisation, exchange and charge-transfer energy, respectively. The deformation energy makes the major contribution to E_{int} . The charge-transfer energy is sensitive to the nature of substituents R¹ and R², namely, it is maximum at R² = F, Me, OH, but is not responsible for regioselectivity. Inversion of the regioselectivity, which was found in the reaction of cyanoethylene (see above), can be explained by high polarisation energy for **TS7** and high deformation energy for **TS6** (see Scheme 6), whereas for other substituents the *ortho*-selectivity is controlled by the electrostatic component.

Reactions of azides with organonitriles (RCN) were studied more thoroughly than similar reactions of nitrones and nitrile oxides.^{267–272} It was shown²⁶⁷ that concerted mechanism is energetically most favourable for the cycloaddition of methyl azide and azide ion to non-activated nitriles. However, in the presence of acid catalyst (ammonium ion or some other proton donor) the reaction mechanism changes and the process proceeds in stepwise manner through transfer of a proton from NH₄⁺ ion to the nitrogen atom of RCN with the formation of acyclic intermediate.

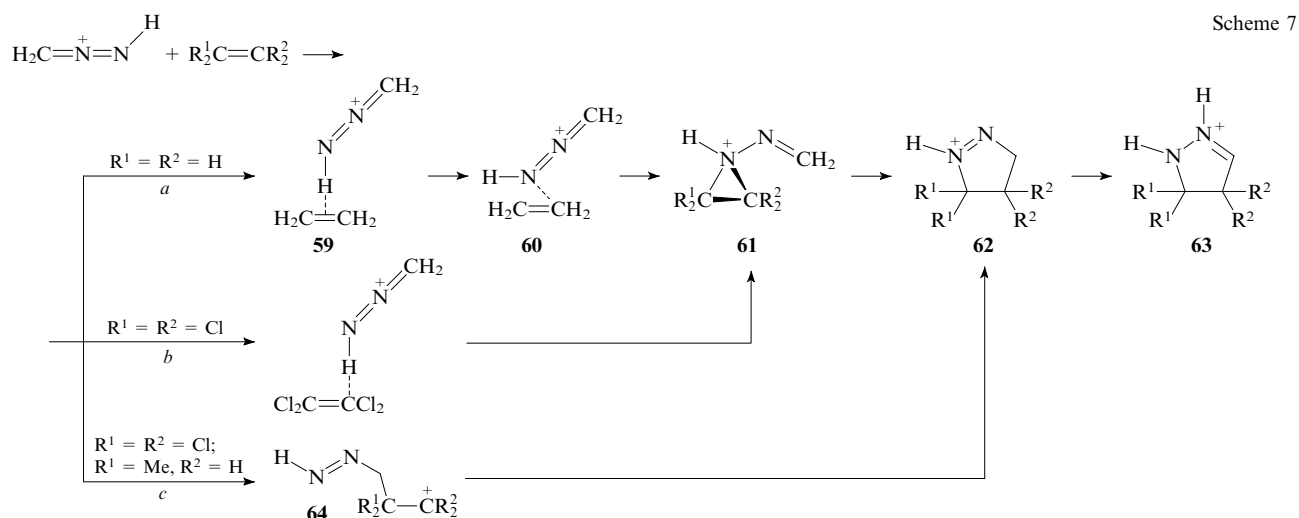


A similar change from concerted to stepwise mechanism and a considerable decrease in the activation barrier was also found for the BF₃- and BH₃-catalysed reactions of N₃⁻ with RCN.^{268,269} At the same time, B3LYP/6-31G** calculations gave a high activation barrier ($\Delta G^\ddagger = 275$ kJ mol⁻¹) to the reaction of nickel azide complex [Ni(η^1 -N₃)]⁺ with nitrogen, which is not surprising with allowance for high inertness of N₂.²⁷⁰

It was shown that coordination of the azide ion to zinc in complex [Zn(H₂O)_{*n*}N₃]⁺ ($n = 3, 5$) has little effect on the activation barrier of the reaction with acetonitrile compared to the thermally activated process [$\Delta H^\ddagger = 141$ kJ mol⁻¹ at $n = 3$ and 149 kJ mol⁻¹ at $n = 5$; 132 kJ mol⁻¹ for reaction MeN₃ + MeCN and 141 kJ mol⁻¹ for reaction N₃⁻ + MeCN; obtained from B3LYP/6-311+G(2d,2p)//B3LYP/6-311G** calculations].²⁷¹ When nitrile or both reactants are coordinated to zinc, the enthalpy of activation decreases by 8–36 kJ mol⁻¹. Thus, the catalytic acceleration of the reaction is due to complexation of dipolarophile, which is consistent with the results of qualitative FMO analysis (see Section II) and makes it possible to treat this reaction as a NED process. The activation of nitriles upon coordination to the Lewis acid in the [3+2]-cycloaddition reactions with azides was confirmed experimentally. In particular, a decrease in $\Delta G^\ddagger$ on going from thermally induced to zinc-catalysed reaction of NaN₃ with 2-cyanopyrazine is 23.8 kJ mol⁻¹ (Ref. 271).

3. Diazoalkanes, nitrile imines and nitrile ylides

Diazoalkanes (R₂C=N=N), nitrile imines (RC $\equiv$ N–NR) and nitrile ylides (RC $\equiv$ N–CR₂) also belong to propargyl-allenyl type dipoles. The [3+2]-cycloaddition reactions involving these

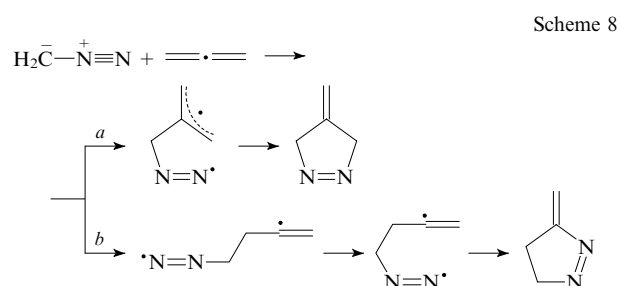


compounds result in such heterocyclic compounds, as pyrazolines and oxadiazolines. Since the LUMO energies in the diazoalkane and nitrile ylide molecules are high and, as a consequence, the HOMO_{dipolarophile}–LUMO_{dipole} interaction becomes ineffective, these reactions should be treated as type I (NED) processes,^{86, 87, 273–275} This particularly concerns the reactions with electron-deficient dipolarophiles (e.g., acrylonitrile³⁵ or imidoyl chlorides²⁷⁶). The reactions of compounds R_2CN_2 with propylene and methyl vinyl ether and those of nitrile imines with unsubstituted alkenes are controlled by both types of the HOMO–LUMO interaction,^{35, 86, 87} while the cycloaddition of nitrile imines to *N*-methylindole is an IED process.²⁷⁷

A number of studies on the mechanism of the [3 + 2]-cycloaddition reactions of these dipoles are available. An unexpected mechanism was calculated for the cycloaddition of 1-aza-2-azoniaallenyl ion ($CH_2=N^+=NH \leftrightarrow CH_2=N^+ \equiv NH$), which can be treated as a diazomethane derivative, with alkenes²⁷⁸ and carbodiimides $R^1N=C=NR^2$ (Ref. 279). The reaction with ethylene proceeds by the stepwise mechanism and begins with the formation of two orientation complexes **59** and **60** (pathway *a*, Scheme 7). This is followed by the formation of the three-membered intermediate **61**, which is transformed to pyrazolinium cation **62** and then to the end product **63**. The replacement of two hydrogen atoms in the ethylene molecule by methyl groups causes a change in the mechanism and now the reaction begins with the formation of acyclic intermediate **64** (pathway *c*). Finally, both pathways, *b* and *c*, are probable in the reaction with tetrachloroethylene. At the same time the addition of $R_2C=N^+=NR^2$ to ethynes $RC \equiv CR$ (Ref. 280) or to the CN bond of isocyanates $RNCO$ (Ref. 281) proceeds concertedly, although being asynchronous.

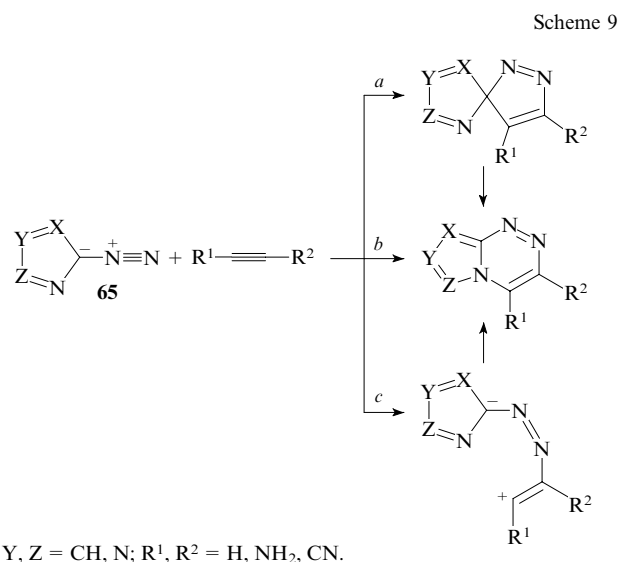
Different regioisomeric pathways of the reactions of diazomethane with allenes¹⁰⁵ are characterised by different mechanisms. For instance, the energetically most favourable mechanism of the addition of the terminal nitrogen atom in CH_2N_2 molecule to a terminal atom of $CH_2=C=CH_2$ molecule involves the formation of one intermediate (pathway *a*, Scheme 8). The addition of the nitrogen atom of diazomethane to the central atom of allene molecule proceeds via two intermediates (pathway *b*). Comparison of the activation barriers to the two regioisomeric pathways, *a* and *b*, showed that the former is 13 kJ mol^{−1} energetically more favourable than the latter. This was confirmed by experimental data on selective formation of the corresponding regioisomer.²⁸² Interestingly, the activation barrier is much higher for the concerted rather than stepwise mechanism.

The effect of the nature of substituents in the dipolarophile molecules on the energy characteristics of the reactions of $HC \equiv NCH_2$ with compounds $CH_2=CR_2$ ($R = NO, CN, Cl, OH, Me$) was studied.²⁸³ In accordance with predictions of the



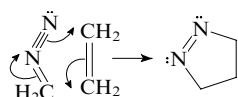
FMO theory, the electron-withdrawing substituents (NO, CN) should accelerate the NED processes, which was confirmed by activation energy calculations. By and large the synchronicity of cycloaddition changes in parallel with the activation energy and antiparallel with the acceptor properties of substituents. The lower activation barriers to most asynchronous processes seem to be due to a strong effect of the charge factor.

By varying substituents in the reaction of cyclic diazoalkane **65** with ethynes one can change the mechanism of the process. In particular, the first stage of the reaction with acetylene proceeds as either a [3 + 2] or [7 + 2] concerted addition with similar activation barriers²⁸⁴ (pathways *a* and *b* in Scheme 9). The reaction with ynamine $HC \equiv CNH_2$ most probably proceeds as a single-stage stepwise [7 + 2]-cycloaddition (pathway *c*). No transition states were located for the reaction with cyanoacetylene. Taking into



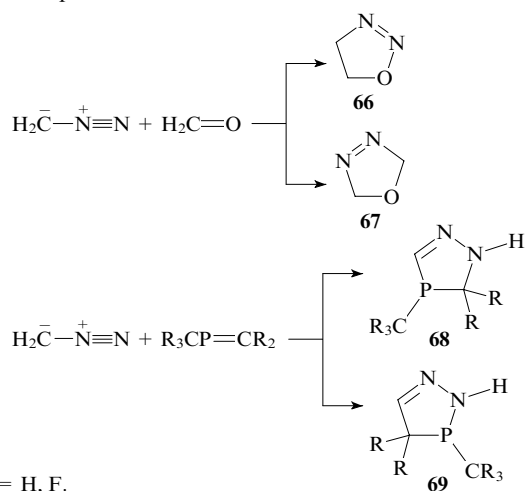
account this fact, it was concluded that no [3 + 2]-cycloaddition reactions of diazoazoles with cyanoacetylene should occur, which is indirectly confirmed by the lack of experimental data on these processes. However, unambiguous solution to this problem requires additional experimental and theoretical investigations of the cycloaddition to cyanoalkynes.

The interaction of diazomethane with ethylene was studied⁷³ using the spin-coupled method of valence-bond theory. It was shown that the reaction proceeds by the 'heterolytic' mechanism similar to that of the cycloaddition of fulminic acid to acetylene (see Section V.1).



A number of theoretical studies has been carried out on the regioselectivity of the reactions of (i) diazomethane with alkenes,³⁵ alkynes and phosphalkynes,^{54,285} formaldehyde,²⁸⁶ phosphapropenes²⁸⁷ and indenone,²⁷⁴ (ii) nitrile imines with fluorinated alkenes and alkynes,²⁸⁸ methyl propiolate,²⁸⁹ (arylsulfonyl)alkenes,²⁹⁰ methylidene-butyrolactone derivatives²⁹¹ and pyridazinones²⁹² and (iii) nitrile ylides with benzaldehyde and imidoyl chloride.²⁷⁶ For instance, calculations for the addition of CH₂N₂ to alkenes CH₂=CHR (R = H, Me, CN, OMe) predicted preferred formation of 3-substituted pyrazolines (*ortho*-isomer) both in the gas phase and in solution (with allowance for solvation effects).³⁵ The relative yields of the *ortho*- and *meta*-isomers and the $\Delta G^\ddagger$ values for the *ortho*-pathway (7.5 : 1 and 96 kJ mol⁻¹, respectively, for the reaction of CH₂N₂ with CH₂=CHMe; obtained from MP4//HF/6-31G* calculations; solvation effects were included for solution in CCl₄) agree with the corresponding experimental data (7.3 : 1 for the reaction of CH₂N₂ with propene²⁹³ and 103.3 kJ mol⁻¹ for the reaction of CH₂N₂ with hex-1-ene³⁵).

The reaction of diazomethane with formaldehyde results in oxirane as the end product. The reaction mechanism, which involves the formation of oxadiazoline as intermediate, was studied theoretically. The process occurs concertedly and yields 1,2,3-oxadiazoline (**66**) as kinetic product in the first stage; however, the other regioisomer, namely, 1,3,4-oxadiazoline (**67**) is thermodynamically more stable.²⁸⁶ Nevertheless, no oxadiazoline intermediates of these reactions were isolated so far and therefore substantiation of theoretical conclusions requires additional experimental studies.



R = H, F.

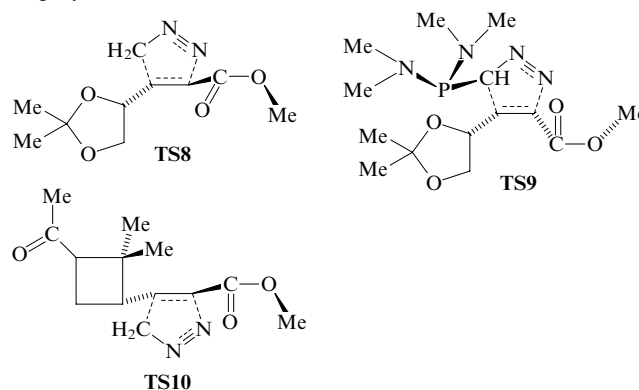
Calculations for the interaction of CH₂N₂ with phosphapropene MeP=CH₂ showed that 1,2,4-diazaphosphole (**68**) is kinetically most favourable while 1,2,3-diazaphosphole (**69**) is thermodynamically most stable.²⁸⁷ The reverse was found for the

reaction with perfluorophosphapropene F₃CP=CF₂. Thus, experimental isolation of regioisomer **69** in the latter case indicates that the process proceeds under kinetic control.

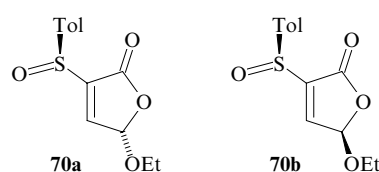
The stereoselectivity of the model reactions of diazomethane and bis(dimethylamino)phosphinodiazomethane [(Me₂N)₂P·CHN₂] with chiral alkenes was studied using the density functional theory (with BPW91 functional).²⁹⁴ It was shown that stereoselectivity depends on the nature of the substituents both in the alkene and in the dipole molecules. For the reaction of diazomethane with dioxolanyl-substituted alkene, the *syn*-cycloaddition was the kinetically most preferable pathway (ratio of the *syn*- and *anti*-isomers is 96 : 1) and the *E*-isomer of the olefin was more reactive than its *Z*-isomer (**TS8** is the corresponding transition state). On the contrary, the reaction of (Me₂N)₂PCHN₂ is characterised by the *Z*-*syn*-addition (**TS9**) (ratio of the *syn*- and *anti*-isomers is 518 : 1) and the reaction of CH₂N₂ with cyclobutyl-substituted alkene shows the *E*-*anti*-selectivity (**TS10**) (ratio of the *syn*- and *anti*-isomers is 1 : 8). The theoretical stereoselectivity qualitatively agrees with experimental data, namely, the ratios of the *syn*- and *anti*-isomers were 24 : 1, 16 : 1 and 1 : > 49 for the reactions of CH₂N₂ with (*E*)-OCMe₂OCH₂CHCH=CHCO₂Me, (Prⁱ)₂PCHN₂ with (*Z*)-OCMe₂OCH₂CHCH=CHCO₂Me and CH₂N₂ with (*E*)-OCH₂CH₂OC(Me)CHCH₂CH{CH=CHCO₂Me}CMe₂.^{294,295} In spite of some overestimation of the theoretical relative yields of the *syn*-isomers compared to the experimental data, the difference between the calculated and experimental (determined from the ratio of isomers) values

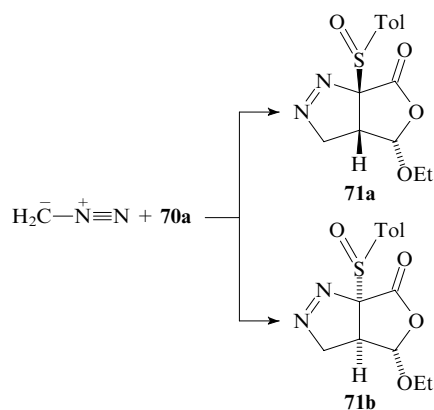
$$|\Delta\Delta G^\ddagger| = |\Delta G^\ddagger(\text{syn}) - \Delta G^\ddagger(\text{anti})|$$

is only 3–9 kJ mol⁻¹, which is quite reasonable for the method employed.



The stereoselectivity of the reactions of diazoalkanes with chiral furanones **70** depends on the stereoconfiguration of the dipolarophile.²⁹⁶ Namely, in the case of the (5*S*,5*S*) configuration (compound **70a**) the activation barrier to formation of the *syn*-isomer **71a** is 14 kJ mol⁻¹ lower than the barrier to formation of the corresponding *anti*-isomer **71b** (obtained from B3LYP/cc-pVTZ//B3LYP/6-31G* calculations). At the same time for the (5*R*,5*S*) configuration (compound **70b**) the stereoselectivity changes, which is consistent with experimental data. The stereoselectivity of the reaction of CH₂N₂ with oxazolone containing an acyclic double bond C=C was interpreted²⁹⁷ based on the results of AM1 and HF calculations.





4. Nitrous oxide

The cycloaddition of N_2O to alkynes was studied.²⁹⁸ The process is controlled by the $\text{HOMO}_{\text{dipolarophile}} - \text{LUMO}_{\text{dipole}}$ interaction, which is typical of this dipole.^{86, 87} Investigation of the regioselectivity showed that in the reactions with mono-substituted alkynes $\text{HC}\equiv\text{CR}$ ($\text{R} = \text{Me}, \text{Hal}, \text{OH}, \text{NH}_2, \text{PH}_2, \text{SH}, \text{SiH}_3, \text{CO}_2\text{H}, \text{CHO}$) the oxygen atom of the nitrous oxide molecule adds to the carbon atom bonded to the substituent R (the exception is $\text{R} = \text{NO}_2$; here the inverse regioselectivity was found). In the reactions with disubstituted alkynes $\text{MeC}\equiv\text{CR}$ ($\text{R} = \text{CHO}, \text{NO}_2$) the oxygen atom adds to the carbon atom bonded to the methyl group.

VI. Reactions of heterocumulenes

Compounds that are usually not treated as dipolar structures can also be included in the [3 + 2]-cycloaddition reactions. These are, in particular, heterocumulenes, *i.e.*, compounds with triatomic reactive fragments in which the central atom (most often, a carbon atom) forms the double bonds with adjacent atoms and the contributions of other possible boundary structures are small.

Concerted cycloaddition of heterocumulenes CX_2 , CSY , CY_2 ($\text{X} = \text{O}, \text{S}, \text{Se}; \text{Y} = \text{NH}, \text{PH}$) to acetylene is characterised by the following order of changes in the activation energies: $\text{O} > \text{S} > \text{Se}$ (from 259 to 113 kJ mol^{-1} according to B3LYP/6-311+G** calculations) and $\text{NH} > \text{PH}$ (from 152 to 107 kJ mol^{-1}) and the energy effects of the reactions change as follows: $\text{O} > \text{S} \approx \text{Se}$ (from 148 to -7 kJ mol^{-1}) and $\text{PH} > \text{NH}$ (from -54 to -134 kJ mol^{-1}) (Table 4).²⁹⁹ This is in qualitative agreement with the experimental data on higher reactivity of CSe_2 compared to that of CS_2 in the [3 + 2]-cycloaddition reactions. According to G3X(MP2) and B3LYP/6-311+G(3df) calculations, thermal decomposition of $\text{S}_2\text{O}^\ddagger$ begins with an exothermic or a weak endothermic (depending on the computational method employed) low-barrier [3 + 2]-cyclodimerisation [$\Delta H^\ddagger = 11$ kJ mol^{-1} , obtained from G3X(MP2) calculations] with the formation of a five-membered product $\text{OSSSS}=\text{O}$, which then decomposes to S_3 and SO_2 .^{300, 301}

Mass spectrometric and theoretical studies^{302, 303} concerned the mechanisms of the reactions of nitronium NO_2^+ and dithionitronium NS_2^+ ions with ethylene and acetylene, which result in O-nitrosated compounds $[\text{CH}_2=\text{C}=\text{O}\cdots\text{NO}]^+$, $[\text{MeCHONO}]^+$ and 1,4-dithia-7-azabicyclo[2.2.1]heptyl cations. Both reactions begin with concerted [3 + 2]-cycloaddition resulting in 1,3,2-dioxazol-2-yl-, 1,3,2-dioxazolidinyl- or 1,3,2-dithiazolidinyl cations as intermediate products. The cycloadduct of NO_2^+ with acetylene is aromatic in character, being therefore thermodynamically more stable than the product of addition to ethylene.

[‡] This compound is sometimes treated as a boundary structure $\text{S}=\text{S}^+ - \text{O}^-$, *i.e.*, as an analogue of ozone. In this case the corresponding reactions can be considered as dipolar [3 + 2]-cycloadditions.

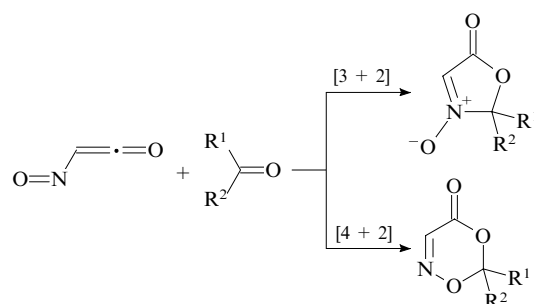
Table 4. Activation and reaction energies (kJ mol^{-1}) for heterocumulene reactions with C_2H_2 (obtained from B3LYP/6-311 + G** calculations).²⁹⁹

Reactant	E_a	ΔE
CO_2	259	148
CS_2	134	8
CSe_2	113	-7
$\text{S}=\text{C}=\text{NH}$	140	-68
$\text{S}=\text{C}=\text{NMe}$	142	-63
$\text{S}=\text{C}=\text{NPh}$	149	-44
$\text{C}(\text{NH})_2$	152	-134
$\text{C}(\text{NMe})_2$	140	-154
$\text{C}(\text{NF}_3)_2$	140	-118
$\text{C}(\text{PH})_2$	107	-54

The mechanism of radical [3 + 2]-cycloaddition of NCO to acetylene derivatives $\text{HC}\equiv\text{CR}$ ($\text{R} = \text{H}, \text{F}, \text{Cl}, \text{CN}, \text{Me}$) was studied.⁵³ All reactions, except that with $\text{R} = \text{CN}$, are controlled by the $\text{HOMO}_{\text{alkyne}} - \text{LUMO}_{\text{NCO}}$ interaction, show regioselectivity and proceed by the stepwise mechanism with the formation of acyclic intermediates $\text{OCNCH}=\text{CR}$ ($\text{R} = \text{Cl}, \text{CN}, \text{Me}$) or $\text{OCNC}(\text{R})=\text{CH}$ ($\text{R} = \text{F}$). The activation barrier increases in the following order of substituents: $\text{F} < \text{Cl} < \text{CN} < \text{Me} < \text{H}$. The regioselectivity was interpreted from the standpoint of the hard and soft acids and bases principle by comparing the Fukui radical functions on the reactive atoms (maximum f^0 and, hence, s^0 values were obtained for the unsubstituted carbon atom in the alkyne molecule).

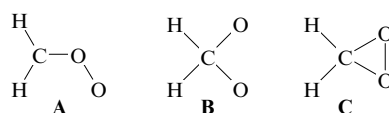
VII. Other reactions

The cycloaddition of nitrosoketene $\text{O}=\text{N}-\text{CH}=\text{C}=\text{O}$ to formaldehyde, acetone and acrolein was described by the *ab initio* methods HF/6-31G* (Ref. 304), MP2/6-31G* and MP4(SDQ)/6-31G**/MP2/6-31G* (Ref. 75). The [3 + 2]-cycloaddition is kinetically more favourable than its alternative, [4 + 2]-cycloaddition; however, the six-membered reaction product is thermodynamically more stable than the five-membered product. Thus, experimental isolation of the five-membered cyclic product of this reaction^{305, 306} indicates that the process occurs under kinetic control. The reaction proceeds concertedly and involves the formation of a planar pseudopericyclic transition state.



$\text{R}^1 = \text{R}^2 = \text{H}, \text{Me}; \text{R}^1 = \text{H}, \text{R}^2 = \text{CH}=\text{CH}_2$.

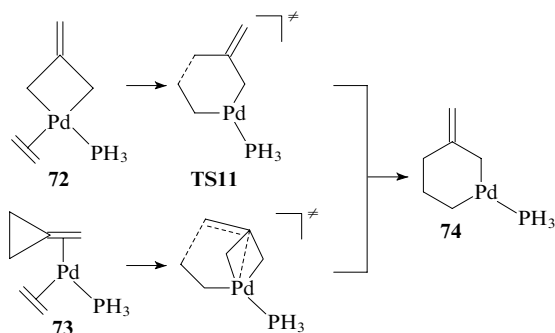
According to the results of high-level *ab initio* calculations, carbonyl oxide (A) and methylenebis(oxy) (B) react with ethylene to give 1,2-dioxolane and 1,3-dioxolane, respectively, and dioxirane (C) enters into the reaction of ethylene epoxidation.³⁰⁷



Some of these results were experimentally confirmed by Reiser *et al.*³⁰⁸ and Graziano *et al.*³⁰⁹ who observed the formation of 1,2-dioxolanes in the reactions of carbonyl oxides with alkenes.

Studies^{310, 311} of the [3 + 2]-cycloaddition of NO₃ radical to alkenes showed that in the first stage the concerted cycloaddition resulting in the five-membered intermediate is energetically more preferable than the addition of alkene to one oxygen atom of NO₃ reported earlier.

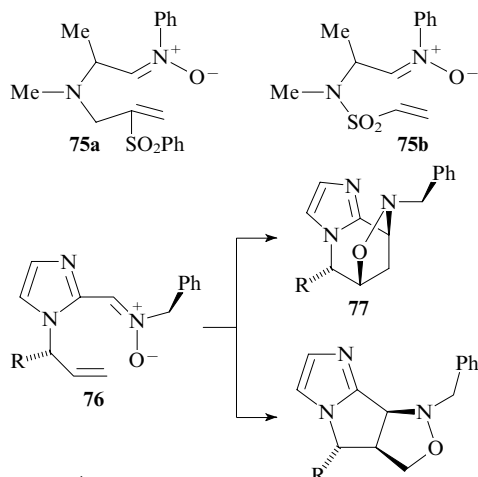
The mechanism of a palladium-catalysed reaction of methylenecyclopropane with ethylene was studied by high-level MP4(SDQ)/BS2//MP2/BS1 and B3LYP/BS2//B3LYP/BS1 calculations.^{312, 313} The concerted mechanism is kinetically unfavourable ($E_a = 186 \text{ kJ mol}^{-1}$) and the interaction between the palladium-coordinated reactants proceeds in a stepwise manner. Two mechanisms were considered, one involving an intermediate palladacyclobutane structure **72** and the other passing via η^2 -methylenecyclopropane complex **73**. Intermediate **73** is thermodynamically more stable than compound **72**. However, the addition of coordinated ethylene molecule to the palladacyclobutane fragment in compound **72** with the formation of methylenepalladacyclohexane **74** via transition state **TS11** followed by reductive elimination of methylenecyclopentane in the last stage is kinetically more preferable.³¹³ Interestingly, similar reactions of oxo- or azatrimethylenemethane with ethylene proceed by the [2 + 1] mechanism. This change in the cycloaddition mechanism depending on the nature of the reactants is consistent with experimental data.^{314–317}



VIII. Intramolecular cycloaddition reactions

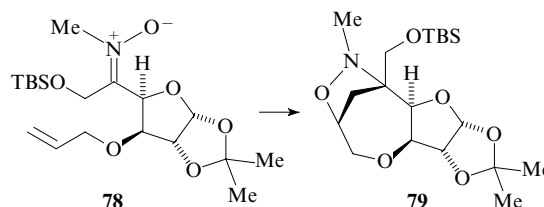
In addition to intermolecular cycloaddition, intramolecular cycloaddition reactions may also occur. Here, the reacting molecules or fragments are not isolated, being constituents of the entire molecular system that affects (sometimes, strongly affects) the course of these reactions. In this review, the cyclisation reactions with the formation of only one new bond upon ring closure are left out of consideration, because these processes do not belong to the cycloaddition reactions.

The regioselectivity³¹⁸ and stereoselectivity³¹⁹ of intramolecular cycloaddition reactions of nitrones **75a,b** and **76** were considered based on the results of semiempirical and *ab initio*



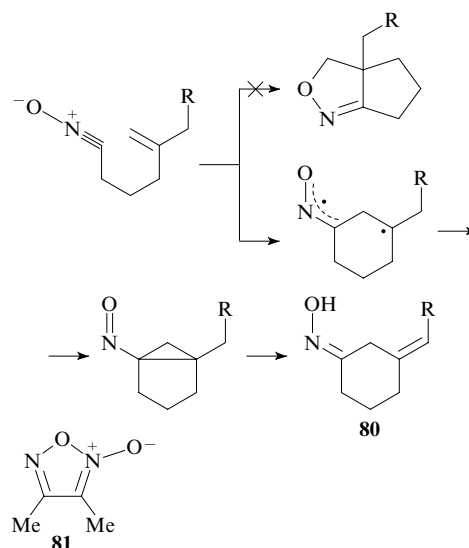
R = Me, Prⁱ.

calculations. The reaction of methyl derivative **76** results in isomer **77** as the kinetically and thermodynamically favourable product. Calculations³¹⁸ predicted a lower regioselectivity of the reaction with R = Prⁱ, which is consistent with experimental data. Calculations using the ONIOM(B3LYP/6-31(d): AM1) hybrid method followed by single-point B3LYP/6-31* energy calculations for the reaction of ketofuranonitrone **78** made it possible to interpret the experimentally observed selective formation of isomer **79**.³²⁰



TBS is *tert*-butyldimethylsilyl.

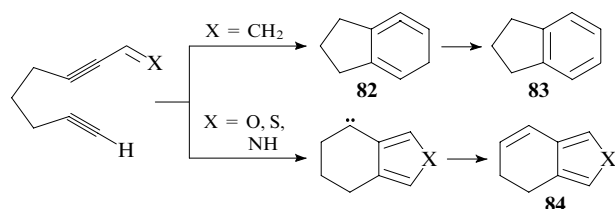
Intramolecular interactions between nitrile oxide and alkene fragments (including intramolecular cycloaddition) have been studied in detail.³²¹ If the initial molecule contains R = SiMe₃, the reaction proceeds by the mechanism leading to compound **80** as the end product instead of intramolecular [3 + 2]-cycloaddition. Replacement of trimethylsilyl group by hydrogen atom makes the [3 + 2]-dimerisation of the nitrile oxide fragments resulting in furoxan structure **81** the most favourable.



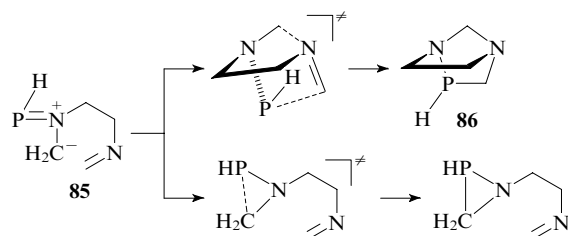
Azido-nitrile systems can enter into intramolecular cycloaddition reactions with the formation of condensed tetrazoles. However, unlike intermolecular processes, the electron-withdrawing character of substituents has little effect on the course of intramolecular reactions.³²² On the contrary, the length of the bridge connecting the azide and nitrile fragments is an important factor affecting the reactivity. For instance, the $\Delta G^\ddagger$ value for the cyclisation of $\text{N}\equiv\text{C}(\text{CH}_2)_n\text{N}_3$ increases with $n = 2, 3, 4$ (142, 143, 157 kJ mol⁻¹ respectively; obtained from B3LYP/6-311G** calculations) and the higher activation barrier obtained for $n = 4$ seems to be due to the formation of the seven-membered ring. This agrees with experimental data on isolation of the [5,5]- and [6,5]-type bicyclic adducts in the reactions of intramolecular cycloaddition of thiocyanates, whereas no [7,5]-type bicyclic products are formed under the same conditions.³²³

A comparative B3LYP, MP2 and MP4(SDTQ) study on the mechanisms of intramolecular cycloaddition of compounds containing conjugated enyne fragments $\text{C}\equiv\text{C}-\text{CH}=\text{X}$ (X = CH₂, O, S, NH) was reported.⁷⁶ According to calculations, the [4 + 2]-cycloaddition resulting in fused allene-type structure **82** is expected for X = CH₂. Structure **82** is stabilised by a double

1,2-proton shift and then transformed to a benzene-type system **83**. The heteroatomic fragments are involved in the [3 + 2]-cycloaddition reactions and eventually form condensed five-membered aromatic heterocycles **84**. The results of calculations agree with experimental data,^{324–327} namely, with the fact that the reactions of carboenynes proceed *via* a cyclic allene-type intermediate and that the intramolecular cycloaddition of heteroenynes involves formation of heterocyclic carbenes.



A study of the mechanisms of two possible reactions of intramolecular cycloaddition of ylides **85** was reported.³²⁸ The [3 + 2]-cycloaddition resulting in diazaphospholane **86** (its analogue was isolated experimentally) was shown to be kinetically and thermodynamically most favourable ($E_a = 45 \text{ kJ mol}^{-1}$; obtained from B3LYP/6-31G* calculations).



IX. Conclusion

Computational quantum-chemical methods provide a powerful tool for studying versatile chemical processes including the [3 + 2]-cycloaddition reactions. In some cases experimental studies of the reactivity of compounds and especially the reaction mechanisms are difficult or impossible at all (if, *e.g.*, the initial compounds are poorly soluble, the reaction rate becomes too high or, on the contrary, too low to carry out kinetic studies or if the process involves the formation of short-lived intermediates that cannot be characterised experimentally). In these situations theoretical calculations are put in the forefront, because they present the one and only alternative to experimental methods.

In this review we analysed the literature on the [3 + 2]-cycloaddition reactions and showed that the simplest qualitative models traditionally used in organic chemistry (first of all, the FMO theory) are still useful in interpreting experimental data. Moreover, in some cases they help to choose the reaction conditions. The overall reactivities of compounds depend on a bunch of factors, namely, the nature of substituents and solvent, the presence or the absence of catalyst, *etc.* Knowing the composition and the relative energies of the frontier MOs of the reactants, one can draw particular conclusions about the effects of these factors on the reactivity. In particular, the NED processes require the introduction of electron-donating substituents into the dipole molecule and electron-withdrawing groups into the dipolarophile molecule. The acceleration of such intermolecular reactions is achieved by selective coordination of catalyst to the dipolarophile. The reverse holds for the IED reactions.

However, this qualitative approach to the description of the reactivity is essentially simplified because it ignores, *e.g.*, steric effects. Additionally, changes in the FMO energies are not always related to the type of the substituent introduced. Finally, the activation barrier is affected by not only the relative orbital energies of reactants but also other factors, in particular, the

nature of the transition state and the energy balance between cleavage and formation of chemical bonds in the formation of transition states. Clearly, the cases where the FMO theory is inapplicable require detailed studies of the mechanisms of the processes and estimation of the activation energy. Thus, investigations on the reactivity of chemical compounds are often closely related to the reaction mechanisms, which play a key role for some reasons.

First, theoretical calculations of the activation barriers and reaction rates (this is of greatest value when experimental kinetic studies are impossible) have some sense only if the mechanism of the process is known, *i.e.*, the possible reaction pathways are elucidated and the energetically most favourable mechanism is available.

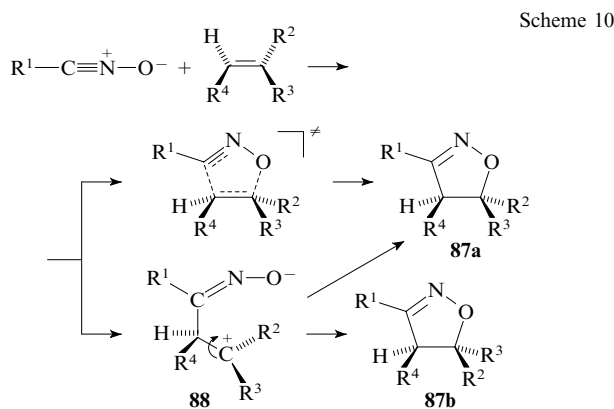
Second, the FMO theory predictions are usually applicable to the 'classical' synchronous processes that occur under orbital control. However, a [3 + 2]-cycloaddition reaction proceeding by the highly asynchronous mechanism behaves to some extent similarly to nucleophilic addition. Here, the role of the charge factors becomes significant. The need of taking into account the charge control complicates the choice of appropriate catalyst. On the one hand, the catalyst should provide selective coordination of the Lewis acid to the reactant (for intermolecular processes). On the other hand, it should provide a maximum possible degree of transfer of the electron density to the Lewis acid in order to attain the largest charge difference between the atoms in the reactant molecules. Therefore, experimental design in the field of catalytic syntheses requires knowledge of the reaction mechanisms.

Third, the nature of the solvent belongs to the factors responsible for the reactivity. By varying the solvent nature the reaction can be appreciably accelerated. Location of transition states in the minimum energy path and the inclusion of solvation effects in the course of quantum-chemical calculations make it possible to predict how the change in, *e.g.*, the solvent polarity will affect the rate of the process under study. It should also be noted that the type of the mechanism is related to the solvation effects, namely, in some cases a stepwise cycloaddition is accompanied by the formation of high-polarity intermediates and transition states, which favours acceleration of the reactions in polar media. Finally, in some cases the solvent forms strong complexes with reactants and thus becomes a constituent of the transition state, being involved in the reaction. Here, comprehensive theoretical studies of the mechanism with inclusion of coordinated solvent become even more important.

Fourth, the mechanism of the process governs the regio- and stereoselectivity of the reaction. Analysis of the available literature on the subject showed that these phenomena are controlled by a group of factors that can often be interpreted only using theoretical methods. First of all these are the electronic effects of substituents where the introduction of an electron-donating group into the dipolarophile molecule leads to preferred formation of the *ortho*-isomer, whereas the electron-withdrawing substituents are responsible for the *meta*-selectivity. Important factors also include the nature of the solvent, selective coordination of the Lewis acid to the reactant molecule, steric effects and the secondary orbital interaction. All of them act on the transition-state level.

Sometimes, the general type of the reaction mechanism (concerted or stepwise) is responsible for the stereoselectivity. The example presented in Scheme 10 shows that in the case of concerted cycloaddition only one stereoisomer **87a** can be formed, whereas the stepwise mechanism makes it possible to obtain two isomers (**87a** and **87b**) due to free rotation about the C—C bond in intermediate **88**.

The mechanisms of some [3 + 2]-cycloaddition reactions can be changed with ease. For instance, the inclusion of solvation effects or the use of high-polarity solvents, catalysts, or (in some cases) a simple replacement of substituents favour the change from concerted to stepwise reaction mechanism.



Therefore, if there is a need of carrying out stereoselective synthesis, it is possible to use the results of theoretical calculations of the reaction mechanisms for choosing the reaction conditions (catalyst, solvent, substituents) in such a way that they will provide a sufficiently high reaction rate on the one hand and will not change the reaction mechanism on the other hand. In this connection it should be noted that progress in computer science (computational methods) and hardware allows corresponding theoretical estimates to be obtained in a rather short time, *i.e.*, quantum-chemical methods become fast methods that help in experimental design.

Considering prospects for theoretical studies of [3+2]-cycloaddition, yet another two points should be noted. First, most publications are concerned with the reactions with alkenes and more rarely alkynes as dipolarophiles and nitrones, nitrile oxides, azides and diazoalkanes as dipoles. At the same time the number of theoretical studies devoted to the analysis of the reactivity of compounds with other multiple bonds ($C=N$, $C=O$, $C=S$, $C=P$, $C=Si$, $N=N$, $C\equiv N$, $C\equiv P$) or such dipoles as azimines, nitrile imines, azoxy compounds, carbonyl imines, carbonyl oxides, nitrosimines and nitroso oxides is relatively low and corresponding processes undoubtedly require more thorough investigations.

Second, theoretical studies aimed at analysing the role of catalysts and the mechanism of their action on the [3+2]-cycloaddition processes are also scarce compared to the literature on non-catalytic processes. Additionally, the importance of research into correlations between the nature of the catalyst, solvent and substituents, on the one hand, and the rate, regio- and stereo-selectivity of the reaction, on the other hand, becomes obvious.

Thus, knowledge of the mechanism and the driving forces of chemical reactions is very useful in the design of chemical experiments, attainment of optimum reaction conditions and in performing targeted synthesis. Modern computers and theoretical methods allow the [3+2]-cycloaddition reactions to be studied using high-level approximations, as indicated by dramatic increase in the number of publications on the title subject reported in the last five to seven years.

This work has been written with the financial support from the Russian Foundation for Basic Research (Project No. 05-03-32 504).

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Molecular similarity concept and its use for predicting the properties of chemical compounds

M I Skvortsova, I V Stankevich, V A Palyulin, N S Zefirov

Contents

I. Introduction	961
II. Interpretation of the 'molecular similarity' term in chemistry	962
III. Graph theory representation of molecules and descriptions of molecular structures based thereon	963
IV. The quantitative measures of the molecular similarity	966
V. Methods for the prediction of properties of chemical compounds based on the molecular similarity concept	969
VI. Formalisation of the postulate 'similar structures possess similar properties' and its analysis	970
VII. Examples of application of the molecular similarity concept	971
VIII. Conclusion	975

Abstract. Main methods for determination of the degree of molecular similarity used in modern theoretical chemistry are surveyed. Methods for predicting the properties of chemical compounds based on the statement 'similar structures possess similar properties' are described. Examples of using these approaches for the modelling of structure–property correlations for organic compounds are given. Bibliography includes 254 references.

I. Introduction

The similarity concept is very important in chemistry. Its essence can be expressed as follows: similar objects possess similar properties. The term 'similarity' is widely used when comparing different chemical objects (atoms, molecules, *etc.*) and reactions, chemical databases, molecular properties and so on. The popularity of the term 'similarity' in chemical literature is steadily increasing. Thus the number of abstracts in the *Chemical Abstracts* using the term 'similarity' has increased over 25 years from 233 (1967–1971) up to 1697 (from 1987 to the first half of 1992).¹ International conferences and workshops dealing with various aspects of the similarity concept in chemistry are being held (see, for example,^{2,3}); a number of books and reviews on this subject have been published.^{2,4–16} Commercial computer programmes based on the similarity methods of analysis have been developed.^{17–19}

The similarity concept in chemistry has a long-standing history and numerous interpretations. It is a scientific idea which is rather intuitive and is difficult to be clearly defined or formalised.^{20,21} However, formalisation of the main chemical terms and development of their quantitative description are required due to fast computerisation of the chemical studies, availability of enormous amounts of data on the structures, properties and chemical reactions, rapid development of mathematical chemistry, computer chemistry, combinatorial chemistry and medicinal chemistry. These main chemical terms include, in particular, the terms 'molecular structure', 'molecular similarity' and 'similarity of chemical reactions'.

The similarity concept is used for the solution of the following problems in chemistry:

- prediction of the physicochemical properties and biological activity of chemical compounds;^{22–33}
- classification and ordering of data in chemical information databases (like the *Beilstein's Handbook of Organic Chemistry*);³⁴
- planning of chemical experiments and the reactivity theory;^{35–40}
- search for biologically active analogues in chemical databases in order to optimise the structures of already known active compounds;^{41–51}
- clusterisation of databases and creation of representative subsets of compounds for further screening;^{16, 52–59}
- creation of databases with the highest structural variety for further search for new key compounds.^{18, 60, 61}

The present review discusses the concept of molecular similarity and the methods for predicting chemical properties based on this concept.

The so-called statistical approach is used most widely for determination of quantitative relationships between the structure and activity/property of compounds (QSAR/QSPR analysis).^{62–64} Some limitations of this technique have induced the development of a method based upon the similarity concept. Successful realisation of the statistical method requires a training set of compounds with known values of the studied property. The structures of studied compounds are described by a set of some molecular descriptors $x_1, \dots, x_N$ (topological, geometrical, electronic) and then the following equation can be written

$$y = f(x_1, \dots, x_N),$$

where f is a function of N variables, y is a property value. Usually the type of function f (for example, linear, quadratic, *etc.*) is

M I Skvortsova N D Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky prosp. 47, 119991 Moscow, Russian Federation. Fax (7-495) 135 53 28, tel. (7-495) 135 90 89, e-mail: stan@ineos.ac.ru

I V Stankevich A N Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, ul. Vavilova 28, 119991 Moscow, Russian Federation. Fax (7-495) 135 50 85, tel. (7-495) 135 79 98, e-mail: stan@ineos.ac.ru

V A Palyulin, N S Zefirov Department of Chemistry, M V Lomonosov Moscow State University, Leninskie Gory, 119992 Moscow, Russian Federation. Fax (7-495) 939 02 90, tel. (7-495) 939 39 69, e-mail: vap@org.chem.msu.ru (V A Palyulin), tel. (7-495) 939 16 20, e-mail: zefirov@org.chem.msu.ru (N S Zefirov)

Received 11 November 2005

Uspekhi Khimii 75 (11) 1074–1093 (2006); translated by D S Yufit

specified in advance and depends on a series of fitting parameters, which are determined using the training subset of compounds. The linear function f is the most frequently used one. The obtained equation is called a linear regression model. In order to calculate the properties of new compounds on the basis of this model, initially the values of the descriptors $x_1, \dots, x_N$ are calculated for the target compounds and then the value of the property y itself is calculated using the equation $y = f(x_1, \dots, x_N)$.

However, another approach to predicting the properties of compounds also exists. It is based upon the following hypothesis: 'similar' structures possess 'similar' properties.^{13, 29, 65} In order to estimate the property of a compound, another compound, 'similar' (in some sense) to the studied one but with known value of this property, has to be found in a dataset. Then it is assumed that the target properties of these compounds are the same (or just slightly different). The averaging of the properties of several 'nearest neighbours' is also possible. Some mathematical objects m_1 and m_2 (for example vectors, sequences, graphs, *etc.*) are assigned to the molecules M_1 and M_2 in order to make a quantitative comparison of their similarity. Then a scalar function $d(m_1, m_2)$ defined for the whole set of the objects is introduced. Calculating the values of this function for the pairs 'fixed compound M_1 – every other compound of the set' one can find the compound most similar to M_1 according to the measure $d(m_1, m_2)$.

There is a variety of methods for the description of molecular structures in mathematical terms. For each of them, in turn, a number of similarity may be defined. Thus, the similarity measures of molecules depend upon the method of their mathematical representation and on the selection of similarity criterion. It has to be noted that there is no universal similarity criterion, equally suitable for all properties and any class of compounds. Both the method of the description of compounds and the similarity criterion have to be specially selected for each individual problem. The result of a search for a 'similar' structure also depends on the dataset of compounds, through which the search is carried out.

While comparing the two above approaches to the modelling of structure–property relationships, one may notice that: (i) the latter provides more flexibility in the description of a molecular structure because molecules can be described not only by vectors of molecular descriptors ($x_1, \dots, x_N$) but also by graphs, sequences of symbols, sets, *etc.* Moreover, the number N of vectors ($x_1, \dots, x_N$) used in the former approach is usually not greater than the number of compounds in a dataset, while in the latter method, the value of N is unlimited. (ii) In the former method, the model takes into account the properties of all compounds of the training set; therefore, the value of a property of a new compound depends upon all the compounds, while in the latter method, this value depends only on the properties of a 'similar' compound. Both methods also have obvious shortcomings: in each case, there is a problem of adequate description of the molecular structure and of correct choice of the functions f and $d(m_1, m_2)$.

A huge number of papers based on the concept of molecular similarity have transformed this area into a new branch of theoretical chemistry. Analysis of these papers reveals that they differ by one or several of following points: (i) the studied subset of compounds; (ii) the studied properties; (iii) the method used for mathematical description of chemical structures; (iv) the quantitative criteria of molecular similarity; (v) the methods used to estimate the properties of compounds on the basis of the selected similarity criteria. The positions iii–v are the most methodologically interesting.

The aim of the present review is to discuss the most widespread methods of description and comparison of molecular structures and also the methods for prediction of properties of the chemical compounds based on the concept of molecular similarity. Some attention is also paid to the validity of the postulate 'similar structures possess similar properties' and to the possible ways of its formalisation. Besides, a series of examples illustrating the

advantages and shortcomings of these methods are given and related problems are discussed.

II. Interpretation of the 'molecular similarity' term in chemistry

The term 'molecular similarity' is used in chemistry in a very broad meaning, because molecules may be characterised by a number of structural and physicochemical properties and may exhibit various biological activities. The areas of chemistry that used the molecular (or atomic) similarity concept in some form are summarised in a paper.⁶⁶ In particular, the definitions of such fundamental chemical terms as isomerism, stereoisomerism, homology, periodicity of properties of the chemical elements, *etc.*, are based upon the similarity of some molecular (or atomic) properties.

Some examples of modern usage of the term 'molecular similarity' are given below.

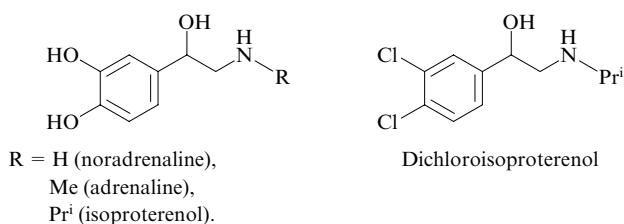
1. Classification of the organic compounds is based mainly upon the classical theory of chemical structure. The similarity of the chemical structures of molecules means some resemblance in the corresponding structural formulae and usually results in relatively small variations of some physicochemical properties and in similar methods of synthesis. However, it is obvious that there is no unique way for evaluation of molecular similarity based solely upon the structural formulae of molecules.

2. The molecules that possess identical skeleton and differ only by heteroatoms (for instance pyrrole and thiophene, benzene and pyridine) may be regarded as structurally related ones.

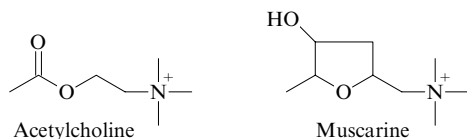
3. The members of homological series {for example, $\text{CH}_3-(\text{CH}_2)_n-\text{CH}_3$, $\text{R}^1-\text{CH}=\text{CH}-\text{R}^2$ } are also regarded as structurally related molecules. The physicochemical properties of the molecules in such series are usually linear functions of n .

4. The ability of atomic groups to form chemical bonds is described by analogy principle proposed by Hoffmann.⁶⁷ The valence properties of chemical groups are determined by their frontier molecular orbitals (FMO), namely by their number, symmetry, shape and energy. Two chemical groups are called isolobal if the number and symmetry of their FMO are identical and the shape and energy of these FMO 'are reasonably close'. The principle of isolobal analogy states that isolobal groups are mutually replaceable in chemical compounds regardless of the type of atoms in them. This principle links the valence theory of classical organic chemistry with the chemistry of organoelement compounds and provides a possibility of a unified explanation of the structural variety of chemical compounds and of the similarity of their properties.

The given examples illustrate the fundamental character of the chemical similarity concept. However, the very same definition of the term 'similarity' is ambiguous and, usually, intuitive.^{13, 68} The prediction of physicochemical properties or biological activity of compounds on the basis of the postulate 'similar structures possess similar properties' is one of the most important areas of the similarity concept application. However, the postulate is not always valid in the case of visual comparison of the structural formulae. For example, in the series of close analogues (noradrenaline, adrenaline, isoproterenol), the α -adrenergic activity decreases, but the β -adrenergic activity increases. Moreover, the replacement of the phenolic hydroxy groups of isoproterenol by chlorine atoms converts this agonist of β -adrenergic receptors into an antagonist, dichloroisoproterenol.⁶⁹

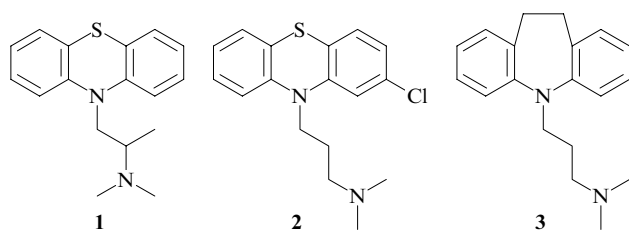


Yet another example is the poison muscarine, isolated from toadstools, and acetylcholine, which is produced in the human and animal bodies and takes part in the transfer of nerve impulses.⁷⁰

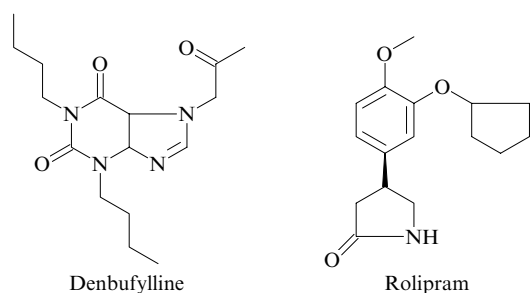


The structures of these compounds are similar and both of them affect the human cholinergic systems.

Sometimes, structurally similar compounds exhibit different types of biological activity. Thus, compound **1** is antihistamine, compound **2** is neuroleptic (antagonist of the dopamine receptors) and compound **3** is antidepressant.⁷¹



At the same time structurally different compounds may exhibit identical biological activity, as denbufylline and rolipram do, which both are phosphodiesterase inhibitors.



The electrostatic potential of a molecule may be used for the description of similarity degree of these compounds.^{69, 71}

These examples illustrate that in addition to the visual analysis of structural similarity, other methods of the molecular structure description are required and new approaches to determination of the molecular similarity degree have to be developed.

III. Graph theory representation of molecules and descriptions of molecular structures based thereon

1. Molecular graphs

According to the modern views, the molecular structure may be described at various levels of complexity. The simplest way of description is the molecular formula. The next step of complexity is the classical structural formula. Further steps include building of 3D molecular models and calculation of quantum-mechanical parameters.

However, there is yet another way of mathematical description of a molecular structure. A labelled molecular graph may represent a molecule. The vertices and edges of the graph will correspond to the atoms and bonds of a molecule and the labels of vertices and edges (numerical or alphabetical) mark the chemically different atoms and bonds. In fact, the classical structural formula is a particular type of labelled molecular graph, where the chemical symbols of corresponding atoms are used as the labels of the vertices and the edge labels correspond to bond orders. Generally, any atomic parameters (atomic charge, polarisability, atomic weight, atomic radius, *etc.*) may be used as vertex labels. Similarly, any bond parameters (bond length, bond order,

obtained from the quantum-chemical calculations, *etc.*^{29, 72}) may be used as edge labels. For example, so-called *be*-matrices (bond and electron matrices) have been proposed.⁷³ Their non-diagonal elements are equal to the bond orders and the diagonal elements, to the number of valence electrons of the corresponding atoms non-involved in bonding. A disconnected graph, *i.e.*, a graph which consists only of isolated labelled vertices without edges, formally corresponds to a molecular formula.

It is also possible to create complete molecular graphs where each pair of vertices is linked by an edge. In this case, a label (or weight) is assigned also to each pair of non-bonded atoms. The topological (or geometrical) distance between these two vertices may be used as such a label. In the latter case, the graph will correspond to the well-known matrix of geometrical distances.

Let us assume that the spatial coordinates of the atoms are known. In this case, one can construct a graph comprising isolated vertices labelled with sequences of three numbers, namely, the atom coordinates. A physicochemical parameter of the corresponding atom can be used as a label for a graph vertex.

Thus, according to the choice of labels, the molecular graphs may be grouped into three major types: calculated on the basis of the structure of the graph itself, taken from literature (for example, the standard physicochemical properties of atoms and bonds) or obtained experimentally (for example, determined by the X-ray crystallography). The combination of these methods is also possible.

In some cases, so-called 'simple' molecular graphs are used. The vertices of these graphs are represented by dots and edges are represented by line segments. Although a simple graph does not have obvious labels, it is assumed that labels of the vertices are equal to zero. If the atoms are chemically bonded, the corresponding edge is labelled by 1, while for nonbonded atoms the edge label is equal to zero. Such graphs are usually used to represent hydrocarbons structures.

2. Descriptions of molecular structures based on their theoretical graph representations

A labelled graph is determined by its topological matrix

$$A = (a_{ij}),$$

where a_{ii} is the label of vertex i , a_{ij} is the label of a pair of vertices (i, j) . (In the case of a simple graph, matrix A is usually called an adjacency matrix.) Obviously, the change of the vertex numbering scheme results, generally speaking, in a different matrix. This is a significant disadvantage of the chemical structure description in matrix terms. This problem leads to the concept of 'graph invariant'. A graph invariant is a number (or a function if the graph labels are symbols) calculated from graph matrix A , which does not depend on the vertex numbering scheme. In theoretical chemistry the invariants of simple graphs are usually called topological indices (TI). Quite often, this definition is also used for invariants of labelled graphs, which can represent not only the topology, but also the elements of electronic or spatial structure. Invariants of any subgraph of a graph can be determined by a similar way. They are called local TI. Topological indices are widely used in theoretical organic chemistry for quantitative characterisation of the molecular structure in a search for structure–property correlations, in the computer-aided synthesis and in creation and analysis of structure–property databases. The most well-known TI and their applications in chemistry are described in the reviews.^{63, 64, 74–76} The simplicity of calculations of TI, the possibility to take into account the electronic and spatial features of the structures and also numerous examples of successful property–TI correlations are the reasons for the popularity of this method of molecular structure description. At the same time, this approach has an obvious disadvantage: it does not differentiate between molecular configurations (*e.g.* stereoisomers) and does not take into account their conformational features.

Some examples of the most common named TI are given below.^{63, 64}

The Randić index χ is defined according to the following formula

$$\chi = \sum (v_i v_j)^{-1/2},$$

where v_i and v_j are the degrees of graph vertices i and j and the sum is taken for all the graph edges. The index χ has been generalised by Kier and Hall, who introduced the definition of m -order connectivity indices.

$${}^m\chi^v = \sum (\delta_i \delta_j \delta_k \dots)^{-1/2}, \quad m \geq 1, \quad \delta_i = \frac{Z_i^v - h_i}{Z_i - Z_i^v - 1},$$

where Z_i is a total number of electrons, Z_i^v is a number of valence electrons of atom i (corresponding to vertex i); h_i is a number of hydrogen atoms bonded to atom i ; the summation takes place along all the chains which consist of m graph edges; i, j, k are the numbers of vertices forming the chain.

The Wiener index W is defined as a sum over all pairs of vertices

$$W = 0.5 \sum d_{ij},$$

where d_{ij} is the shortest distance between vertices i and j . Matrix $D = (d_{ij})$ is called the matrix of topological distances of the graph.

The Hosoya index Z is defined as

$$Z = \sum p_k,$$

where p_k is a number of ways to choose k nonadjacent edges ($k \geq 1$) in a graph.

The Balaban index B [for acyclic graphs (trees)] is defined according to the following formula

$$B = \sum r_i^2,$$

where r_i is a number of the tree vertices cut out at step i of the 'tree pruning' procedure. This procedure consists of consecutive removal of the 1st degree vertices of the initial tree and the edges incident to them.

During the construction of informational topological indices,⁷⁷ a set of fragments (for example, a set of graph vertices) is selected and split into a number of equivalent classes according to some feature (for example, according to the first coordination type). Let assume that n is a number of graph vertices, n_i is a number of vertices in the equivalent class i , $i = 1, \dots, m$. The main informational TI is defined as

$$IC = - \sum \frac{n_i}{n} \log_2 \frac{n_i}{n}.$$

This TI characterises the inhomogeneity of the graph vertices set and has extreme values for the least homogeneous ($m = n$) and the most homogeneous ($m = 1$) sets of vertices. Instead of the set of vertices, a set of any other fragments can be used.

Another large class of TI is the spectral-type TI.⁶⁴ Let us call λ_i and $C^{(j)} = [C_1^{(j)}, \dots, C_n^{(j)}]$ the eigenvalues and the eigenvectors of the matrix of a graph with n vertices. They can be used for the construction of various TI, for example such as

$$J_1 = \max (\lambda_i),$$

$$J_2 = \lambda_r - \lambda_m,$$

where λ_r is the minimum positive and λ_m is the maximum negative eigenvalues, or

$$q_i = \sum C_i^{(k)} C_i^{(k)},$$

$$p_{ij} = \sum C_i^{(k)} C_j^{(k)}$$

(the summation in two latter formulae is over those eigenvectors to which the positive eigenvalues correspond). Spectral-type topological indices appear naturally in some quantum-chemical methods and usually have a quite clear physicochemical meaning.

It should be noted that even for a single fixed labelling scheme of a molecular graph an infinite variety of TI exists. For instance, the multiplication or summation of two TI results in a new TI. Therefore, it is impossible in principle to describe all TI, which can be constructed and used in the QSAR/QSPR analysis. The problem of reasonable choice of just a few TI out of infinite number of variants always arises during the construction of each particular model of structure–property correlation. This happens because it is often difficult to give a relatively clear physicochemical or structural interpretation of TI and to correlate it with the studied property. Moreover, some TI are related to each other by exact or approximate mathematical equations. These facts, as well as a common sense, prompt that for any finite set of the weighted graphs a finite set of TI $J_1, J_2, \dots, J_N$ should exist. This set is called a basic set. Then, any TI may be represented as

$$TI = F(J_1, J_2, \dots, J_N),$$

where $F(J_1, J_2, \dots, J_N)$ is a function of N variables. The type of the function depends on the given topological index. It was rigorously proved⁷⁸ that such basis always exists. The number of occurrences of some structural fragments in the graph may be taken as the basis invariants and F may be a linear function. Some examples of the expansion to a basis of various invariants of molecular graphs have been reported.⁷⁹ These results may be regarded as a mathematical foundation of the well-known principle of additive schemes, used for approximation of the physicochemical properties of compounds.^{80,81}

One more approach to the problem of selection of basic TI has been suggested.⁸² These basic TI are constructed relying on specially selected subgraphs and depend on variable parameters. Another, more QSAR/QSPR-friendly definition of the basis is also given in the same paper. The suggested method was successfully used for the estimation of various physicochemical properties of the hydrocarbons of different classes.

The number of occurrences of a structural fragment in the structure of a molecule is a particular case of TI. The simplest structural fragments have been used in the theoretical chemistry for a long time for the estimation of physicochemical properties by additive schemes.^{80,81} The QSAR/QSPR studies use more complicated fragments as well.^{62,83–85}

It is easy to notice that virtually all TI are somehow related to subgraphs. Fragmental descriptors are of great importance for QSAR/QSPR methods. Below we discuss some of these descriptors.

Let us assume that a chain of $L-1$ bonds (*i.e.* containing L atoms) 'links' together atoms i and j (with Y_i or Y_j codes). Such a chain fragment of the molecule is usually called 'an atomic pair (i, j)' and is coded by a symbol $Y_i - (L-1) - Y_j$.⁸⁶ The code Y_i (or Y_j) contains information about the type of the chemical element, the number of connected atoms (without hydrogens) and the number of π -electrons. As an example, Table 1 gives the 'atomic pairs' and the number of their occurrences in the structural formula of the acetone molecule.⁶⁹ The symbols C and O (see Table 1) correspond to carbon and oxygen atoms, the symbol X_n ($n = 1, 2, 3$) indicates that this particular atom is connected to n

Table 1. Atomic pairs in the acetone molecule.

Atom	Atomic pairs	Number of occurrences of the fragment in the structure
1	CX ₁ –1–C.X ₃	2
2	C.X ₃ –1–O.X ₁	1
3	CX ₁ –2–O.X ₁	2
4	CX ₁ –2–CX ₁	1

atoms (hydrogen atoms are ignored), the symbol ‘.’ indicates that this atom contains one π -electron. The number $L-1$ in this example is equal to 1 or 2. A different method of the description of atomic pairs based upon physicochemical parameters of the atom has also been suggested.⁸⁷

Below are examples of the descriptors, labelled MNA/ k , which are linked to the molecule fragments that are k -order neighbours of atoms of various types ($k = 0, 1, \dots$).^{69,88} The symbols ‘-’ in these descriptors are given to acyclic atoms; the zero order fragment is the atom itself; the first order fragment is the atom with the notification (in the parentheses) of its first-order neighbour, *etc.* The fragments MNA/0 and MNA/1 of the structural formula of phenol for three phenol atoms (labelled 1, 2 and 3) are given in Table 2 as examples.⁶⁹

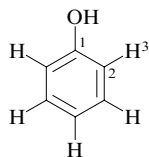
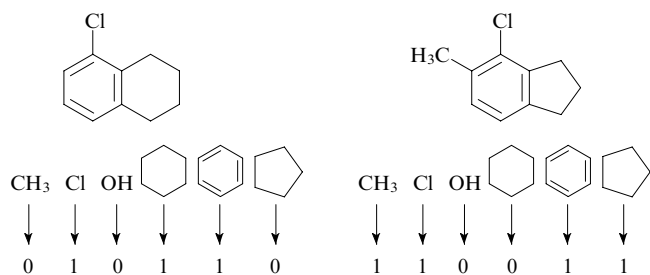


Table 2. Fragments MNA/0 and MNA/1 for atoms 1, 2 and 3 in the phenol molecule.

Atom	MNA/0	MNA/1
1	C	C(CC-O)
2	C	C(CC-H)
3	-H	-H(C)

The atom-centred fragments of various orders have been previously used a number of times.^{65,77,80,81} They have also been discussed in other publications.^{89,90}

Usually the vectors $X = (X_1, X_2, \dots)$, where $X_i = 0$ if the fragment i is absent in the structure and $X_i = 1$ if the fragment i is present, are composed on the basis of the selected fragment set. The number of occurrences of a fragment i (*i.e.*, an atom chain) in the structure also may be used as X_i .⁹¹ (Originally, this approach was suggested for alkanes.⁹²) Such (0,1) vectors $X = (X_1, X_2, \dots)$ are also called ‘a bit string’. Some relevant examples are given below.⁶⁹



Various TI X_i may be used for the construction of vectors $X = (X_1, X_2, \dots)$. Particularly, if the components of vector X are non-negative and $\sum X_i \neq 0$, then another vector $P = (P_1, \dots, P_k)$, where $P_i = X_i / \sum X_i$, may be constructed.⁹

Examples of vector construction have been reported.^{69,93} Two matrices P and C are introduced for a structure containing N atoms. P is a rectangular matrix of the $N \times 3$ size, where row i is given by $(1, p_i', q_i')$ (p_i', q_i' are specially normalised electronegativity and effective charge of atom i). The C is an (0,1)-adjacency matrix. Then a family of square 3×3 matrices TM_n , called electrotopological matrices, is defined:

$$TM_n = \frac{P^* C^n P}{N}, n = 1, 2, \dots, n_{\max},$$

where P^* is the transposed P matrix; C^n is the n -degree of matrix C ; $n_{\max}$ is the longest sequence in the corresponding graph. These matrices do not depend on the labelling of the vertices of the molecular graph; therefore, their elements may be used as descriptors called electrotopological indices. Vectors consisting of elements of these matrices for $n = 1, 2, \dots, n_{\max}$ may be constructed on the basis of these elements.

It was suggested^{94,95} to use specially formulated rectangular matrices dependent on fragment descriptors to construct vectors describing a molecular structure.

The vectors may also be constructed from quantum-chemical⁹⁶ and any other descriptors⁹⁷ and also on the basis of physicochemical properties of the compounds.⁹⁸

A molecular graph with indication of various sets of fragments, described by a sequence of symbols, may be used for characterisation of a molecular structure.⁹ Linear nomenclatures are examples of such graphs. In such a nomenclature the structural formula is coded by a string of symbols. Each symbol, in turn, determines the structural fragments. The works of Wissesser are at the origin of the linear nomenclatures.⁹⁹ For instance, for the compounds $\text{CH}_3-\text{CH}_2-\text{O}-\text{CH}_2-\text{CH}_2-\text{CH}_3$ and $\text{H}_2\text{N}-\text{CH}_2-\text{CH}_2-\text{C}(\text{O})-\text{OH}$ the Wissesser codes are (2O3) and (Z2VQ) respectively.⁶² The symbol ‘O’ indicates the oxygen atoms, not bonded to H atoms; ‘Q’ is a hydroxy group; ‘V’ is a carbonyl group; ‘Z’ is a nitrogen atom of an NH_2 group. Number 2 (or 3) indicates an unbranched chain of two (or three) CH_2 groups.

Yet another linear nomenclature is called SMILES.^{100,101} It is used, particularly, in search for the structural similarity of compounds. The examples of linear codes obtained by the FCSS (fragmentary code of substructure superposition) language have been reported.⁸⁵ The SLN code (SYBYL Line Notation) has been described.¹⁰² This code has been used¹⁰³ for protein similarity estimation.

Simple graphs may be coded with the minimum binary code. In order to do that, all possible ($n!$, where n is a number of graph vertices) adjacency matrices are constructed. Then each matrix is converted into one string of 0 and 1. This string may be regarded as a binary number. A minimum lexicographic sequence corresponding to the minimum decimal number is selected as a code.⁶⁴

There is one more method of sequences construction. Let us consider a set of N molecules $\{M_i\}$, $i = 1, \dots, N$, and assume that for each pair M_1 and M_2 of this set a symmetrical function $d(M_1, M_2) = d(M_2, M_1)$ is given. This function is regarded as a ‘distance’ between M_1 and M_2 . Then for each molecule M_k of set $\{M_i\}$ a sequence $\{d(M_k, M_i)\}$, $i = 1, \dots, N$, $i \neq k$ may be composed.^{9,29,104} as well as sequences consisting of local graph invariants, *i.e.*, the powers of graph vertices.¹⁰⁵ In contrast to the vectors, which are used for chemical structure descriptions, the sequences may be of various lengths.

Functions are also used for the description of a molecular structure. Let us assume that a molecule is described by a simple graph G and d_{ij} is a topological distance between vertices i and j . The function called topological transformation of graph G

$$t(s) = \frac{k(G) \sum \sum Z_i Z_j [\sin(s d_{ij})]}{s d_{ij}},$$

where s is real parameter, $k(G)$ is a normalising constant such that $\int [t(s)]^2 ds = 1$, Z_i and Z_j are charges of nuclei of corresponding atoms has been considered previously.^{106,107} A similar formula has also been suggested¹⁰⁸ for 3D structures, when d_{ij} is a geometrical distance between atoms i and j . In the latter case, functions of several variables, for example, charge densities, electrostatic potentials *etc.*, are also used.^{13,109}

An algorithm for the description and analysis of the molecular shape, based on quantum-chemical calculations of charge densities or electrostatic potentials, has been suggested.^{110–115} A study of the molecular surface is the starting point of the procedure. The charge density surfaces of various levels are calculated. A set of

these equal level surfaces are regarded as topological objects. The objects are characterised by homology groups, called shape groups. The shape groups are used for the description of molecular shapes and for the analysis of their similarity. This method may be successfully combined with the description of stereoisomers in terms of the knot theory and is easily programmable, which provides an opportunity for automatic non-visual analysis of the molecular similarity degree.

Spatial geometrical models of molecules may be constructed on the basis of structural formulae, using the molecular mechanics or quantum-chemical methods.⁶² These models are potential source of new molecular descriptors. Thus, for example, if the orthogonal coordinates (X_{i1} , X_{i2} , X_{i3}) of a molecule, containing N atoms of masses m_i ($i = 1, \dots, N$), are known, then the formulae

$$U_j = \frac{1}{M} \sum_{i=1}^N m_i X_{ij},$$

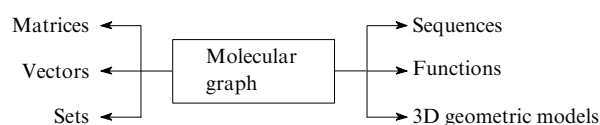
where $j = 1, 2, 3$; $M = \sum_{i=1}^N m_i$ is the molecular mass, determine

the coordinates of the centre of mass. Let us denote the inertia tensor as $R = (r_{jk})$

$$r_{jk} = \sum_{i=1}^N m_i (X_{ij} - U_j)(X_{ik} - U_k),$$

and the eigenvalues of matrix R as X , Y , Z . These eigenvalues and some of their functions, such as X/Y , X/Z , etc., were suggested⁶² as molecular geometrical descriptors. Some authors use the van der Waals volume or the surface area of the molecule for the description of the molecular spatial structure. The details of the calculations of these descriptors can be found in the literature.⁶²

Usually, methods for molecular structure description are subdivided into 2D and 3D methods. The bond angles and the Euclidean interatomic distances are not taken into account in the former case. Therefore, the methods, based on the matrices of topological distances of the molecular graph are 2D methods and the invariants determined by these methods are 2D descriptors. The methods based on the matrices of Euclidean distances are 3D methods and the invariants determined by these methods are 3D-descriptors. The degree of molecular similarity discussed below usually depends only on the mathematical representation of the molecules (graphs, sets, matrices, vectors, sequences, etc.) and does not depend on the information coded by these mathematical models. Therefore, we do not discuss separately the 2D and 3D methods of analysis of molecular similarity. The methods of representing the molecular structure, where those based on the graph theory are most important and the other ones are just its derivatives, may be illustrated in a form of the following Scheme.



IV. The quantitative measures of the molecular similarity

The quantitative measure of similarity of two molecules M_1 and M_2 is a scalar function $d(S_1, S_2)$ of two variables S_1 and S_2 . Its type depends on the method of description of the structures S_1 and S_2 of molecules M_1 and M_2 . The value of $d(S_1, S_2)$ for a pair of the structures is a measure of their similarity. Let us assume that the function $d(S_1, S_2)$ is such that:

$$d(S_1, S_2) \geq 0;$$

$$d(S_1, S_2) = 0 \text{ then and only then, when } S_1 = S_2;$$

$$d(S_1, S_2) = d(S_2, S_1) \text{ (symmetry);}$$

$$d(S_1, S_2) \leq d(S_1, S_3) + d(S_2, S_3) \text{ (the triangle inequality).}$$

In this case the function $d(S_1, S_2)$ is called a metric. Most of the measures of the molecular similarity are metrics. In this Section we will describe some similarity measures, developed for various mathematical methods of molecular representation, which are listed in the Scheme at the end of Section III.⁹

1. Let us assume that the structures S_1 and S_2 are represented by n -dimensional vectors $X = (x_1, x_2, \dots, x_n)$ and $Y = (y_1, y_2, \dots, y_n)$. The components of these vectors are some invariants of molecular graphs. The following similarity measures are described in literature:

$$d_1(X, Y) = \sum |x_i - y_i| \text{ (} L_1 \text{ is metric),}$$

$$d_2(X, Y) = \left(\sum |x_i - y_i|^p \right)^{1/p} \text{ (} L_p \text{ is metric);}$$

for $p = 2$, d_2 is a distance between points X and Y in the Euclidean space R^n . (Euclidean distances are widely used in the estimation of the molecular similarity degree^{24, 65, 116–122})

$$d_3(X, Y) = \frac{\sum (x_i - \bar{x})(y_i - \bar{y})}{\left| \sum (x_i - \bar{x}) \sum (y_i - \bar{y}) \right|^{1/2}},$$

$$\bar{x} = \frac{1}{n} \sum x_i, \quad \bar{y} = \frac{1}{n} \sum y_i$$

(correlation coefficient);

$$d_4(X, Y) = \frac{\sum x_i y_i}{\sum x_i^2 + \sum y_i^2 - \sum x_i y_i}$$

(Tanimoto coefficient).

The Tanimoto coefficient is one of the most common similarity measures in QSAR/QSPR studies as well as in the analysis of chemical databases.^{2, 53, 122–127} (0,1)-Vectors are usually used as vectors X and Y . The component values of these vectors depend on the presence (1) or absence (0) of some fragments in the structures S_1 and S_2 . In this case, the Tanimoto coefficient has the form

$$d_4(X, Y) = \frac{N_{xy}}{N_x + N_y - N_{xy}},$$

where N_x and N_y are the numbers of components in each of the vectors X and Y equal to 1; N_{xy} is the number of 'common' components of these vectors equal to 1.

$$d_5(X, Y) = \frac{\sum \min(x_i, y_i)}{\sum x_i^2 + \sum y_i^2 - \sum \min(x_i, y_i)} \text{ (Ref. 88),}$$

$$d_6(X, Y) = \sum (x_i - y_i) \log_2 \frac{x_i}{y_i} \quad (x_i, y_i > 0),$$

$$d_7(X, Y) = \frac{\sum x_i y_i}{\left(\sum x_i^2 \right)^{1/2} + \left(\sum y_i^2 \right)^{1/2}}$$

(cosine of the angle between the vectors),^{91, 121, 126, 127}

$$d_8(X, Y) = \frac{\sum \min(x_i, y_i)}{0.5 \left(\sum x_i + \sum y_i \right)}.$$

The metric $d_8(X, Y)$ was introduced for a case where the components of vector X (or Y) are equal to the number of occurrences of the special fragment, namely, an atomic pair, in the structure S_1 (or S_2) (see Section III).⁸⁶ The method for estimation of the similarity based on atomic pairs is sometimes called the 'atomic pairs method'.

The measure considered in a study⁶⁹

$$d_9(X, Y) = \left[1 + \frac{1}{n} \sum_i (X_i - Y_i)^2 \right]^{-1},$$

was defined for vectors constructed from the elements of electrotopological matrices^{70, 92} (see Section III).

2. Let us assume that the structures S_1 and S_2 are represented by finite sets D_1 and D_2 and denote the number of elements in the set D as $|D|$. The following similarity measures are described:⁹

$$d_{10}(D_1, D_2) = |D_1| + |D_2| - 2|D_1 \cap D_2| = |D_1 \setminus D_2| + |D_2 \setminus D_1|$$

(Hamming metric¹²⁸),

$$D_{11}(D_1, D_2) = \frac{|D_1 \cap D_2|}{|D_1 \cup D_2|}$$

(Ohia coefficient).

3. Let us assume that the structures S_1 and S_2 are represented by the labelled graphs G_1 and G_2 ; E is a set of graph vertices, $|G|$ is the total number of vertices and edges of the graph G ; $|\text{MACS}(G_1, G_2)|$ is the total number of vertices and edges in the maximum common subgraph G_1 and G_2 . The following measures were introduced for the graphs:⁹

$$d_{12}(G_1, G_2) = |E_2 \setminus E_1| + |E_1 \setminus E_2|,$$

$$d_{13}(G_1, G_2) = |G_1| + |G_2| - 2|\text{MACS}(G_1, G_2)|,$$

$$d_{14}(G_1, G_2) = \frac{|\text{MACS}(G_1, G_2)|^2}{|G_1 \cup G_2|}.$$

The methods of finding the maximum common subgraph have been reviewed.^{129, 130} It should be noted, that the subgraph may also be found for the edge graphs derived from these graphs.¹³¹ Eight similarity measures based on the maximum common subgraph have been reported.¹³²

In order to define the measure $d_{15}(G_1, G_2)$, let us choose a subgraph (fragment) H . Let $n(G) = 1$ if H belongs to the graph G , and $n(G) = 0$ if H does not belong to G . Let us consider the measure

$$d_{15}(G_1, G_2) = |n(G_1) - n(G_2)|.$$

Obviously, $d_{15}(G_1, G_2) = 1$ if one of the graphs contains the fragment H and another one does not (the graphs G_1 and G_2 are 'dissimilar'); and $d_{15}(G_1, G_2) = 0$ if H either belongs to both graphs or to none of them (G_1 and G_2 are 'similar'). This measure allows one to sort the structures of a set into two classes: those containing and not containing the fragment H . The application of this measure in QSAR results in a search for the fragment H present in all active compounds of a set and absent in the structures of inactive compounds.^{62, 85}

4. Let us assume that the structures S_1 and S_2 are represented by the sequences l_1 and l_2 ; $|l|$ is the length of the sequence; $|\text{LCS}(l_1, l_2)|$ is the length of the longest common sequence in l_1 and l_2 . For the sequences, the following similarity measures were suggested:⁹

$$d_{16}(l_1, l_2) = |l_1| + |l_2| - 2|\text{LCS}(l_1, l_2)|,$$

$$d_{17}(l_1, l_2) = \frac{2|\text{LCS}(l_1, l_2)|^2}{|l_1 \cup l_2|},$$

$$d_{18}(l_1, l_2) = \frac{1 - d_{17}(l_1, l_2)}{|l_1 \cup l_2|}.$$

Also, let us define the elementary 'editing' operations of the sequences: the removal of the element x , the addition of the element x , the replacement of x by y in the particular sequence.

The similarity measure of two sequences l_1 and l_2 may be introduced as the minimum number of such operations required to transform l_1 into l_2 .¹⁴

5. Let us assume that the functions f_1 and f_2 correspond to the structures S_1 and S_2 . The following similarity measures may be defined on this basis:

$$d_{19}(f_1, f_2) = \left(\int |f_1(x) - f_2(x)|^2 dx \right)^{1/2},$$

$$d_{20}(f_1, f_2) = \int |f_1(x) - f_2(x)| dx,$$

$$d_{21}(f_1, f_2) = \frac{\int f_1 f_2 dx}{\int |f_1|^2 dx \int |f_2|^2 dx}.$$

Similar formulae may also be written for the functions of several variables.

There are several 'named' similarity measures associated with the functions. Let us consider the measure¹³³ specified as

$$d(f_1, f_2) = \int \int f_1(r_1) \Omega(r_1, r_2) f_2(r_2) dr_1 dr_2,$$

where f_1 and f_2 are the functions of charge density, Ω is a positive definite operator. The measure $d(f_1, f_2)$ was used to specify other measures, for example:

$$d_C(f_1, f_2) = \frac{d(f_1, f_2)}{d(f_1, f_1)^{1/2} d(f_2, f_2)^{1/2}}$$

(Carbo's index^{134–140}),

$$d_{HR}(f_1, f_2) = \frac{2d(f_1, f_2)}{d(f_1, f_1) + d(f_2, f_2)}$$

(Hodgkin–Richards index^{109, 134–136, 141}),

$$d_P(f_1, f_2) = \frac{d(f_1, f_2)}{\max[d(f_1, f_1), d(f_2, f_2)]}$$

(Petke's index^{142, 143}).

Two sets of similarity indices, dependent on the parameters x and k , were suggested¹³³

$$D_1(f_1, f_2) = \left[\frac{k[d(f_1, f_1) + d(f_2, f_2)]}{2} - x d(f_1, f_2) \right]^{1/2},$$

$$D_2(f_1, f_2) = \frac{(k - x)d(f_1, f_2)}{D_1^2(f_1, f_2)}.$$

The indices D_1 and D_2 become equal to the Carbo and Hodgkin–Richards indices at some particular k and x values. The similarity measures listed above are usually called the quantum-chemical ones, because the functions f_i (charge density, electrostatic potential, etc.) are calculated by quantum-chemical methods.^{133, 135, 142, 144–171}

It was suggested¹⁷² to consider three- or four-atomic molecules similar if they have equal numbers of electrons. It was found that in this case the values of some physicochemical parameters (for example, the atomisation heats) of similar molecules are comparable. However, for other properties (for instance, for the ionisation potentials) this similarity measure does not work.

Various modifications of the above-mentioned quantum-chemical similarity measures have been proposed.^{173–175} These give rise to new, nonsymmetrical measures d'_{ij} for some sets of compounds. For example, so-called 'stochastic transformation' d'_{ij} of the similarity measure d_{ij} is suggested:

$$d'_{ij} = d_{ij}(d_{i1} + d_{i2} + \dots + d_{iN})^{-1},$$

where N is the number of compounds in a set. The quantity d'_{ii} called the self-similarity measure, is regarded as a molecular descriptor and is used for the modelling in QSAR/QSPR analysis.¹⁷⁶

6. Let us assume that the structures S_1 and S_2 are represented by matrices $A = (a_{ij})$ and $B = (b_{ij})$ of the same order k . In this case the measures $d_{22}(A, B)$, $d_{23}(A, B)$, $d_{24}(A, B)$ may be used for the comparison of the structures S_1 and S_2 .^{9, 177, 178}

Let us define the measure $d_{22}(A, B)$ as follows:

$$d_{22}(A, B) = \frac{1}{\sqrt{k(k-1)}} \left(\sum (a_{ij} - b_{ij})^2 \right)^{1/2}.$$

Obviously, the $d_{22}(A, B)$ depends on the atomic numbering scheme in the structures S_1 and S_2 . However, it is possible to design a numbering independent similarity measure $d_{23}(A, B)$. Keeping the numbering of atoms in the structure S_1 fixed, all possible numbering schemes of the structure S_2 are considered and all possible values of $d_{22}(A, B)$ are calculated. The minimum obtained value is regarded as a similarity measure $d_{23}(A, B)$ of the structures S_1 and S_2 .^{9, 177}

The measure $d_{24}(A, B)$ is often used to compare isomers described in terms of so-called *be*-matrices.⁷³ This measure is called 'the minimal chemical distance' and is determined by the following formula¹⁷⁸

$$\text{MCD}(A, B) = d_{24}(A, B) = \min_{i,j} \sum |a_{ij} - b_{p(i)p(j)}|.$$

Here the summation takes place over the indices i and j ; p are all possible combinations of n symbols, where n is the matrix order. Some combinatorial problems appear during the calculation of the $\text{MCD}(A, B)$ value. Methods for tackling these problems have been proposed.¹⁷⁸

A method of estimation of molecular similarity based on the matrices of the geometrical distances has been described.^{179, 180}

7. Let us discuss the similarity measures for the molecules represented by three-dimensional geometrical objects Γ_1 and Γ_2 .

In order to calculate these measures, the 3D molecular structures are spatially superimposed and a function of several variables is minimised. This function depends on the mutual orientation of the molecules. For instance, the following function may be used

$$R(\Gamma_1, \Gamma_2) = \left[\frac{1}{N} \sum_{i=1}^N \sum_{j=1}^3 \left(x_{ij}^{(1)} - x_{ij}^{(2)} \right)^2 \right]^{1/2},$$

where N is a number of atoms in the structures Γ_1 and Γ_2 , $x_{ij}^{(1)}$ [or $x_{ij}^{(2)}$] are the coordinates of atoms in Γ_1 (or Γ_2). The minimum $R(\Gamma_1, \Gamma_2)$ of all possible rotations and translations of the structure Γ_2 in the space R^3 (with a fixed position of the structure Γ_1) may be regarded as a similarity measure $d_{25}(\Gamma_1, \Gamma_2)$ of the structures Γ_1 and Γ_2 .

The following function may be used to evaluate the similarity of the structures Γ_1 and Γ_2 instead of the function $R(\Gamma_1, \Gamma_2)$

$$R'(\Gamma_1, \Gamma_2) = \left[\frac{1}{N} \sum_{i=1}^N m_i \sum_{j=1}^3 \left(x_{ij}^{(1)} - x_{ij}^{(2)} \right)^2 \right]^{1/2},$$

where m_i is the mass of the atom i . As in the previous case, the minimum of this function, determined by relative positions of the structures Γ_1 and Γ_2 , is calculated. The value of this minimum is regarded as a similarity measure $d_{26}(\Gamma_1, \Gamma_2)$ of the structures Γ_1 and Γ_2 .

In order to determine the Meyer's similarity index $S(\Gamma_1, \Gamma_2)$ (Ref. 181), a three-dimensional lattice with relatively small distances between the nodes (for example, 0.02 nm) is constructed in the space R^3 . The geometrical body formed by a system of atom-centred van der Waals spheres is regarded as a model of the molecule. Molecules Γ_1 and Γ_2 are placed in this three-dimensional latticed space and the numbers of the nodes $T(\Gamma_1)$, $T(\Gamma_2)$

and $T(\Gamma_1, \Gamma_2)$ are counted. These are the numbers of the nodes in the van der Waals areas of each molecule and in their overlapping region, respectively. Then the Meyer's index is calculated according to the following formula¹⁸¹

$$0 \leq S(\Gamma_1, \Gamma_2) = \frac{T(\Gamma_1, \Gamma_2)}{[T(\Gamma_1)T(\Gamma_2)]^{1/2}} \leq 1.$$

The superimposition is performed to ensure the highest possible value of $S(\Gamma_1, \Gamma_2)$.

The value of $d(\Gamma_1, \Gamma_2)$, calculated according to the following formula, is used as a similarity measure of two molecules

$$d(\Gamma_1, \Gamma_2) = \frac{V_{\Gamma_1 \Gamma_2}}{V_{\Gamma_2}},$$

where V_{Γ_2} is the volume of the molecule Γ_2 ; $V_{\Gamma_1 \Gamma_2}$ is the volume of the overlapping area of the molecules Γ_1 and Γ_2 .¹⁸² It should be noted that this measure is better to be used when the position of one of the molecules is fixed.

The elementary operations required to transform structure Γ_1 into structure Γ_2 during estimation of the molecular similarity are documented.¹⁸³ These operations include the addition and removal of atoms, the change of atomic labels, etc. The special measure of similarity of the structures Γ_1 and Γ_2 , which depends on the minimum number of operations for the transformation of one molecule into another, is introduced. The review of the methods for superimposition of three-dimensional structures is given. Another method of optimal superimposition of three-dimensional molecular structures was suggested in a study,¹⁸⁴ where the Carbo and Meyer indices were used for the molecular similarity measuring. The similarity measures based on the spatial superimposing of the molecules were also used¹⁸⁵ for the construction of 3D QSAR models.

The biological activity of molecules is closely related to their three-dimensional structure. As a result, the increased attention is attracted nowadays to the analysis of similarity of such structures.^{41, 42, 46, 186–202} The correct choice of the biologically active conformation of the molecule is the main problem of 3D analysis of similarity. Usually either the conformation obtained by X-ray structural study of the complexes of the ligand with the receptor or the conformation calculated on the basis of two-dimensional structure by a special converter program is taken. It was supposed that the biologically active conformation of the molecule corresponds to a global minimum of its potential energy. However, it was shown that it is not the case.⁶⁹ Therefore, the consideration of only one main conformation in the analysis of similarity of the compounds may produce erroneous results.

Most of the 3D databases contain just one conformation for each compound. Therefore the 3D methods of similarity analysis probably will not provide a significant advantage over the 2D ones without taking into account a conformational flexibility of the molecule. It requires either to generate and keep a set of conformations for each molecule or to perform conformational calculations in the process of similarity analysis, which significantly slows it down.⁶⁹

Superimposing (or overlaying) of two molecules in the similarity analysis is a limiting step, which restricts the application of 3D methods for the analysis of large databases. The superimposition procedure may be speeded up in several ways.^{202, 203} A 4D similarity measure, which depends on the conformation of the molecule, has been considered.²⁰⁴ The protein similarity measure²⁰⁵ is based upon their 2D representation.

Alongside with 2D, 3D, 4D representations, 1D representation is also in use.²⁰⁶ In this case the molecule is represented by a chain graph with labelled vertices, which correspond to the atoms of the molecule. The labels of the vertices include the atomic type, hybridisation and bonding of the corresponding atoms. The methods of the comparison of these chain graphs are identical to the methods for comparison of symbol sequences.

A comparative analysis of 2D and 3D methods was performed during the classification of four sets of compounds into the active and inactive ones.²⁰⁷ The possibility of application of 2D and 3D methods for the estimation of similarity of various experimentally measured and calculated physicochemical properties related to such interactions as hydrophobic, dispersion, electrostatic, steric and donor–acceptor ones has been discussed.¹⁸⁶ The best property predictions were made on the basis of 2D fragment descriptors.

In a study,²⁰⁸ various sets of 2D and 3D descriptors have been used for the classification of compounds according to their biological activity. It appeared that only 2D fragments provide effective sorting of the compounds to the active and inactive ones and, therefore, they are preferable for the analysis of similarity of chemical compounds.

The results of comparison of the 2D method of atomic pairs and its 3D modifications in the search for active analogues of morphine, cyclopamine, diazepam, apomorphine, serotonin, haboxadol, diethylstilbestrol in the database of 30 000 compounds are reported.⁵⁰ It is shown that the three-dimensional approach does not surpass the 2D method in the number of obtained biologically active analogues. At the same time, some active compounds, topologically different from the corresponding standard compound, were found only by 3D methods. A comparison of 2D and 3D descriptors for identification of active and inactive compounds was also carried out in other studies;²⁰⁹ both methods provide similar results. The comparison of the similarity measure defined by the Tanimoto coefficient and the measures based on the superposition of the structures has also demonstrated²¹⁰ that the efficiency of 2D and 3D methods is approximately the same.

The method of superposition of the structures has performed better in the search for analogues in the non-homogeneous 3D databases, while for more homogeneous databases the best results were obtained by the maximum common subgraph method.⁶⁸

A comparison of several similarity measures during the search for compounds in databases was performed;^{211–216} methods for determination of molecular resemblance based on 22 similarity measures were suggested.²¹⁶

The problem of analytical description of an arbitrary similarity measure specified for some finite set of the labelled graphs was discussed.^{217,218} The general analytical formula depending on two matrices A_1 and A_2 was obtained. These results imply that in the prediction of properties of chemical compounds by methods based upon a similarity measure the best matrices A_1 and A_2 have to be obtained. In order to do that, the measure should be selected by optimal way from the sample subset of the compounds. This method of measure selection is a universal one and may be programmed (in contrast to the usual approaches where the measure is often ‘guessed’). The method was applied²¹⁹ for the prediction of lipophilicity ($\log P$) of compounds, where P is a distribution coefficient in the n-octanol–water system. The advantages of this method were discussed.^{13,220}

Thus, there is a number of various molecular similarity measures. The new measures may be constructed on their base. The review by Sheridan and Kearsley²²¹ discusses the reasons for invention of such a variety of measures and their application in theoretical and computer chemistry.

In the conclusion of this Section it has to be noted that quantitative similarity measures used in the theoretical chemistry are commonly divided in the ‘similarity measures’ and ‘dissimilarity measures’. In the former case, the higher is the similarity (intuitive) of the molecules, the greater is the value of the corresponding similarity measure. In the latter case, the situation is opposite. By inverting the similarity measure $d(M_1, M_2)$ of the molecules M_1 and M_2 and calculating the value of $1 - d(M_1, M_2)$, the dissimilarity measure of these molecules may be obtained. A new molecular descriptor of the molecule M may be constructed on the basis of any similarity measure $d(M_1, M_2)$: $d(M) = d(M, M_0)$, where M_0 is a fixed molecule.⁹ Various methods

of determination of the molecular ‘diversity’ are discussed, for example, in the papers.^{12,222–234}

V. Methods for the prediction of properties of chemical compounds based on the molecular similarity concept

1. Method of k nearest neighbours

Let us take a set of N chemical compounds $M_1, \dots, M_N$ with known values $y_1, \dots, y_N$ of a chemical property. Then, according to the method of k Nearest Neighbours (k NN),^{24,69,235,236} the property y_0 of a compound M_0 may be calculated as follows:

$$y_0 = \frac{1}{k} \sum W(M_j) y_j,$$

where $W(M_j) = 1$ if M_j is among the nearest k neighbours and $W(M_j) = 0$ in the opposite case. Generally, $W(M_j)$ may be replaced by any other weighted functions, particularly a similarity measure $d(M, M_j)$ may be used instead. The advantages and limitations of the k NN method and some of its modifications have been discussed.^{235,236} The correct choice of k is a key problem of this method. For example, the optimal k was selected out of the series of values 1, 2, 3, 4, 5 in the prediction of lipophilicity;²³ the $k = 1$ was used for the estimation of boiling points and mutagenicity;^{25,69} the $k = 1, \dots, 10; 15, 20, 25$ were also applied.²⁴ The measure used for identification of the ‘nearest neighbours’ also affects the results of the k NN method. The composition of a set is also very important (there is a possibility that there are no ‘good’ neighbours in a set).

2. The estimation of a property on the basis of a system of equations

Zefirov and co-workers²¹⁹ suggested a method based on the optimal selection of a similarity measure $d(M_i, M_j)$ by the system of equations of the following type

$$|y_i - y_j| \approx d(M_i, M_j).$$

It was suggested to determine the property y_0 of a new structure M_0 on the basis of a system of equations in order to avoid the problem of selecting a correct number of neighbours k in k NN method:

$$|y_0 - y_i| \approx d(M_0, M_i),$$

where $\{M_i\}$ is a training set. In fact, this method is based on the assumption that the obtained model ‘similar structures–similar properties’ is also valid for the new compound M_0 .

3. The methods of pattern recognition theory

The background of the theory of pattern recognition (TPR)^{62,76,85,237–239} are as follows. There is a set of objects, each of them belongs to one of the classes (patterns). The main task of TPR is to produce the rules (usually written as inequalities) according to which the studied objects may be assigned to corresponding classes. If the class of an object is *a priori* known, then the problem is the learning strategy of pattern recognition. In the absence of the *a priori* knowledge the system has to train itself to recognise the classes. The quality of the rules is determined by the number of errors in the classification of a training set.

Let us discuss the geometrical interpretation of the TPR. In a number of cases the chemical objects are described as vectors $X = (x_1, \dots, x_n)$, i.e., any object is represented by a point in the Euclidean space R^n . The Euclidean distance $d(X_1, X_2) = [\sum (x_{1i} - x_{2i})^2]^{1/2}$ may be regarded as a measure of proximity of these points. If the choice of the recognition criteria is adequate, then the points of the same class occupy a compact area in the space R^n (so-called cluster) and the clusters of different classes do not intersect each other. The term ‘cluster’ is a fundamental one for the self-training procedure. It may be determined as a set of points $\{A\}$, where any point is closer to the point of the same set

rather than to a point that does not belong to $\{A\}$. In the simplest case, the recognition rule may be as follows: an object described by vector X belongs to the class that is located at the shortest distance from the object.

The TRP may also be described in the probability terms. In this case the selection rules are described in terms of the probability theory.

The theory of pattern recognition is widely used in the prediction of biological activity of the compounds. In the simplest case, the compounds are sorted into two classes: active and inactive ones. The vectors based on the descriptors are used for the description of the compounds.

The linear regression method, used for the quantitative description of properties, may be regarded as a specific case of TPR. Indeed, the range of the property values may be split into the non-intersecting intervals and the chemical compounds may be assigned to the corresponding classes. The regression equation determines the selection rule for the classification of the compounds of a training set. However, the method of linear regression is not usually regarded as one of the methods of molecular similarity in the prediction of properties of chemical compounds.

4. The methods of quantitative correlations between the similarity of compounds and their biological activity or property (QSiAR/QSiPR analysis)

The following type of correlations is established in these methods:

$$y_j = \sum a_i S(i, j) + a_0,$$

where $S(i, j)$ is a similarity coefficient between the compounds i and j , a_i , a_0 are regression coefficients. The principal component analysis or partial least squares method are used for the determination of significant variables in the correlation equation (*i.e.*, for determination of i values). Examples of applications of the QSiAR/QSiPR analysis can be found in the literature.^{29, 144, 240–243}

VI. Formalisation of the postulate ‘similar structures possess similar properties’ and its analysis

As it was mentioned above, the application of a concept of molecular similarity for the prediction of properties of chemical compounds is based on the statement ‘similar structures possess similar properties’ (SSPSP), which is accepted as an axiom, without being proved.

Naturally, the questions are: what is the correct interpretation of this postulate, how well is it justified, how to formalise it?

The hypothesis that similar structures possess similar properties originated from numerous experimental correlations between the properties of chemical compounds and the presence and number of some structural fragments in their molecules. Two structures are called similar if they have several common fragments, which mainly determine the value of a property, and differ by the fragments, which do not influence the value of a property. In this case one can expect that really ‘similar’ structures will possess ‘similar’ properties.

Nowadays very abstract and complicated similarity measures, not directly related to the studied properties (see chapter IV), are often used for the estimation of molecular similarity degree. In spite of this fact, the SSPSP statement is still applied; however, its interpretation and validity in these cases is not entirely clear.

Johnson²³⁵ reports the results of an empirical study of the validity of SSPSP postulate for various particular cases. Sixteen properties (both physicochemical properties and biological activity types), 16 databases and 72 quantitative similarity measures based on the vector representation of the molecular structures were investigated. The k NN method was used for the calculation of properties. It was shown that the measures based on the

correlation coefficients are the most successful ones. A vector whose components are equal to the number of appearances of some structural fragments in the molecule is the most preferable one for the description of the molecular structure.

Thus, the validity of SSPSP statement significantly depends upon the choice of the chemical descriptors, the similarity measures, the class of the chemical compounds, the studied properties and the method of property estimation.²³⁵ As the application of this postulate for the resolving of the particular problems of theoretical organic chemistry may turn out to be not always correct, the success of predictions of the properties of chemical compounds by the abovementioned methods is, generally, accidental. Therefore, a theoretical confirmation of the validity of SSPSP postulate is required.

In order to analyse the postulate, let us consider the most general case when the chemical structures $\{M_i\}$, $i = 1, \dots, N$, are represented by some mathematical objects $\{S_i\}$, $i = 1, \dots, N$, and for the pairs S_i and S_j of these objects a symmetrical function $d(S_i, S_j) \geq 0$ [such, that $d(S_i, S_j) = 0$ only when $S_i = S_j$], the similarity measure of the corresponding structures M_i and M_j , is specified. Besides, let us assume that the numbers $\{y_i\}$, *i.e.*, the values of some property of the structures $\{M_i\}$, $i = 1, \dots, N$, are also known. It is reasonable to propose, as a similarity measure, a quantity $|y_i - y_j|$. Let us assume that the numerical criteria of similarity of properties and structures are *a priori* known. The criteria are the numbers $\varepsilon \geq 0$ and $\delta \geq 0$, such that if $d(S_i, S_j) \leq \delta$, then the structures are regarded as similar and if $|y_i - y_j| \leq \varepsilon$, then the properties are also regarded as similar. Obviously, the number ε is always selected by a researcher according to the particular problem to be solved and $d(S_i, S_j)$ and δ are variable characteristics. Then the postulate SSPSP may be formulated as follows: if for any structures M_i and M_j $d(S_i, S_j) \leq \delta$, then $|y_i - y_j| \leq \varepsilon$.

For the analysis of the validity of the postulate, let us make the following simple statement: for any set of structures $\{M_i\}$ ($i = 1, \dots, N$), any property y and any similarity measure $d(S_i, S_j) \geq 0$ [$d(S_i, S_j) = 0$ only in the case where $S_i = S_j$] the following inequalities are valid

$$ad(S_i, S_j) \leq |y_i - y_j| \leq bd(S_i, S_j),$$

where a and b are constants depending on the measure, properties and the set of structures, namely

$$a = \min_{i, j, i \neq j} \frac{|y_i - y_j|}{d(S_i, S_j)} \geq 0,$$

$$b = \max_{i, j, i \neq j} \frac{|y_i - y_j|}{d(S_i, S_j)} \geq 0.$$

Several conclusions may be drawn from this statement.

1. The postulate will always be valid (in the abovementioned form) if $\delta = \varepsilon/b$ is selected.

2. Let us assume that for a given set, not all the values of the properties are close to each other, *i.e.*, that there is a pair S_i and S_j ,

such that $|y_i - y_j| > \varepsilon$. Therefore, if $\delta = \max_{i, j} d(S_i, S_j)$ is selected,

then the postulate will not be valid for the given set.

3. Earlier, we assumed ε to be specified. However, if ε is selected to be very large, then the postulate will be valid for any δ and $d(S_i, S_j)$.

4. From the obtained double inequalities, it follows that the lower is the value of $d(S_i, S_j)$, the smaller is the quantity of $|y_i - y_j|$, thus for the ‘very similar structures’ the properties are also ‘very similar’. This qualitative conclusion, drawn from the rigorous mathematical argumentation, is, in fact, a proof for the non-formal postulate typically used in theoretical chemistry.

Thus, we have shown that the validity of the postulate depends on the choice of ε and δ values if the measure $d(S_i, S_j)$ is fixed. However, the similarity measure of the properties is very seldom selected during the practical application of the molecular similarity concept. Therefore, without this criterion, it is very difficult to

judge if the structures really possess similar properties. Usually the experimental and calculated properties are listed in the QSAR/QSPR papers; however, the allowed error of prediction is never given. Therefore, a careful reader have to judge for himself the quality of methods applied.

An alternative method of selection of the measure $d(S_i, S_j)$ has been suggested.²¹⁹ This measure is selected using a set of structures on the basis of the conditions $d(S_i, S_j) \approx |y_i - y_j|$ at all i and j . In this case, the measure is represented by a special equation, depending on the variable square symmetrical matrix A . This equation is a scalar product of vectors AX and X , where X is a vector composed from certain descriptors. This method provides the validity of the SSPSP postulate for a given set with any values of ε and $\delta = \varepsilon$ and seems to be more efficient than 'guessing' of the measure.

Let us discuss the applicability of SSPSP postulate for the prediction of properties of the compounds that do not belong to the initial set. If this postulate is valid for the initial set with some δ , then for another set it cannot be valid with the same value of δ . Thus, it is obvious that the application of the postulate for estimating the properties of other compounds may be erroneous.

A 'training set' of compounds with known properties is always required for the estimation of the δ value. However, the standard regression equation may be written if the set is present and the problem of property prediction may be solved by other methods. Both these methods (regression analysis and similarity method) require the selection of the way of mathematical description of the molecular structure, the molecular descriptors, the type of the dependence between the descriptors and property or the similarity measure, and also the training set. The possibility of the analysis in the case of a non-linear structure–property correlation or even without a correlation at all is an advantage of the similarity method (the regression analysis usually uses the linear models). Moreover, the similarity method looks more attractive (in comparison with the regression analysis) because of the illusion that it

does not requires complicated computation and a training set. Measures that compare the structures as a whole and do not require any descriptors are also possible. For example, the maximum common subgraph and its characteristics (the number of vertices, edges, *etc.*) may be found. However, such simplification of the similarity method results in arbitrary character of the predictions.

VII. Examples of application of the molecular similarity concept

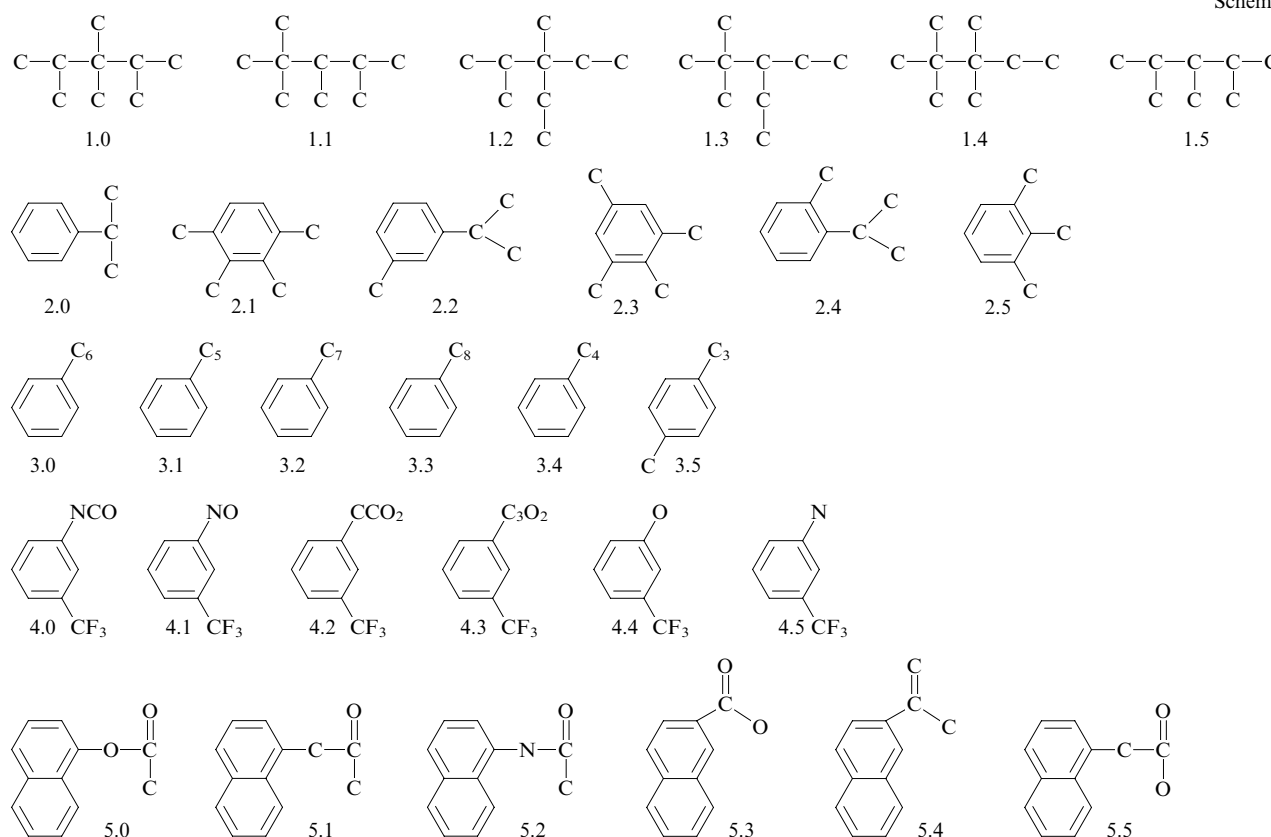
1. Determination of the structural similarity in terms of topological indices

The values of 90 topological indices (including the Randić index, the Wiener index, the series of informational indices, connectivity indices, *etc.*) have been calculated²⁴³ for 3692 organic compounds of various classes. Ninety-dimensional vectors were composed for each of the studied structures on the basis of these TI. Ten new TI $X_1, \dots, X_{10}$, which are linear combinations of the initial ones, were constructed as well, because some of the used indices were correlated by linear equations. Let us assume that $X^{(i)} = (X_1^{(i)}, \dots, X_{10}^{(i)})$ ($i = 1, 2$) are two such vectors corresponding to a pair of structures S_1 and S_2 . The similarity measure d of the structures S_1 and S_2 was determined²⁴⁴ as the Euclidean distance between two points in the space R^{10}

$$d[X^{(1)}, X^{(2)}] = \left\{ \sum [X_i^{(1)} - X_i^{(2)}]^2 \right\}^{1/2}$$

and the applicability of this measure in the search for structural analogues of some compounds in a specific database was studied. Five compounds were randomly selected and for each of them five nearest {according to the measure $d[X^{(1)}, X^{(2)}]$ } neighbours were found. The results of this procedure are shown in Scheme 1; indices 1.0, 2.0, 3.0, 4.0, 5.0 correspond to the selected compounds and indices of the i, j ($i, j = 1, \dots, 5$) type, to the found nearest

Scheme 1



'neighbours'. The compounds are listed according to increasing values of the measure $d[X^{(1)}, X^{(2)}]$. The compounds found are in agreement with the intuitive chemical ideas about the structural similarity of the molecules. In order to find 'good' compounds in a database, it is necessary, at least, to have them in the database.²⁴⁴

2. The dependence of the result of clusterisation of a set of compounds on the method of chemical structure description

The correlation between the toxic activity for mice and the structure has been studied²⁴⁵ for 25 ethers R^1-O-R^2 ($R^1 = \text{Me, Et, Pr}^n, \text{Pr}^i, \text{CH}_2=\text{CH}$; $R^2 = \text{Me, Et, Pr}^n, \text{Pr}^i, \text{Bu}$ and other). The electrotopic descriptor ε (Ref. 245) and valence-weighted connectivity index ${}^m\chi^v$ at $m = 1$ were used for the classification of compounds.

Clusters in the descriptor–property planes for ε and χ^v are shown in Fig. 1. Obviously, the quality of clusterisation depends on the selection of a descriptor and ε works better than χ^v .

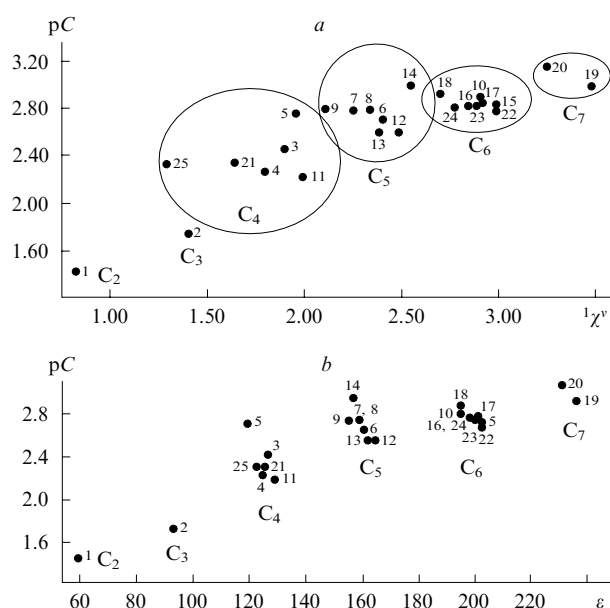
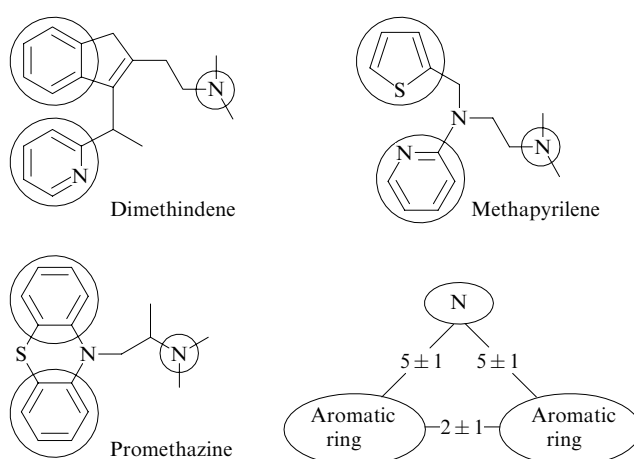
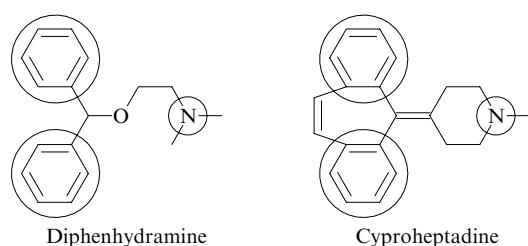


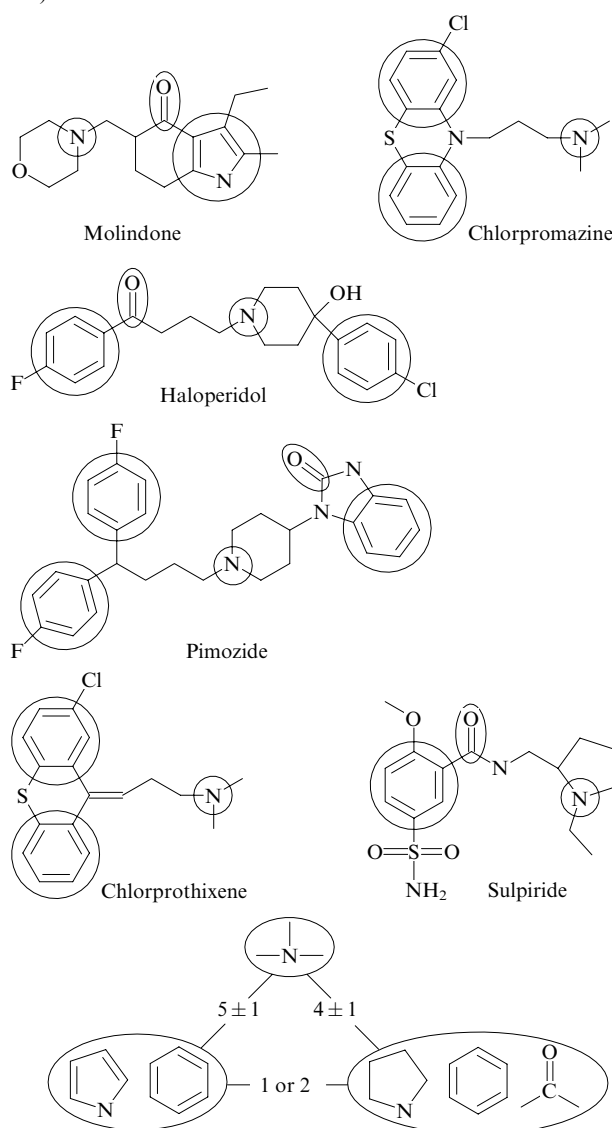
Figure 1. The clusterisation of the set of 25 esters, containing from 2 to 7 carbon atoms, on the planes descriptor ${}^1\chi^v$ –property (a) and descriptor ε –property (b).²⁴⁵ pC is a toxicity.

3. The search for similar structural fragments of compounds exhibiting similar properties

It appeared²⁴⁶ that the structural similarity of antihistamine agents (diphenhydramine, methapyrilene, cyproheptadine, dimethindene, promethazine) may be represented by a topological triangle of two aromatic rings and the tertiary nitrogen atom.



A common 'triangle' with some functional groups in the vertices has also been found for antipsychotic agents (molindone, chlorpromazine, haloperidol, pimozide, chlorprothixene, sulpiride).



4. Dependence of the result of property prediction by the *k*NN method on the choice of the similarity measure and number *k* of nearest neighbours

Two molecular similarity measures have been studied²³ for the estimation of lipophilicity ($\log P$) of 76 compounds of various classes. One of them was determined according to the following formula

$$d' = \frac{2C}{T_1 + T_2},$$

where T_1 , T_2 are the numbers of fragments that are atomic pairs in the first and second structures, respectively; C is the number of atomic pairs shared by these two molecules (see Sections III and IV). The second similarity measure was determined according to the following formula

$$d'' = \left\{ \sum [X_i^{(1)} - X_i^{(2)}]^2 \right\}^{1/2},$$

where $X^{(j)} = [X_1^{(j)}, \dots, X_9^{(j)}]$, $j = 1, 2$ are some vectors from the Euclidean space R^9 obtained by the main component analysis from 90 various TI (see part 1 of this Section).

Five nearest neighbours of each compound of the set have been found according to the measures d' and d'' and the values of $\log P$ have been calculated by *k*NN method in five variants (at $k = 1, 2, 3, 4, 5$). Thus, ten various estimations of the $\log P$ were obtained. The correlation coefficients r between the observed and calculated values of $\log P$ are listed in Table 3. The best results were obtained when the measure d' with $k = 4$ ($r = 0.874$) was used. According to a publication,²³ both methods provide good results.

Table 3. Correlation coefficients between experimental and theoretical $\log P$ values calculated by ten methods.²³

<i>k</i>	Correlation coefficient (<i>r</i>)	
	for d'	for d''
1	0.774	0.788
2	0.854	0.821
3	0.869	0.814
4	0.874	0.846
5	0.852	0.845

Another method of the similarity analysis based on the optimal selection of similarity measure d , has been applied for the same data.²¹⁹ A set of structural fragments has been selected for the description of the structures. It was established that according to some criteria, the obtained model is more precise than that used in the other publication.²³ Even more accurate model may be obtained by varying the set of fragments, however, no such studies were performed in the discussed paper.

5. The selection of structural analogues by various molecular similarity measures

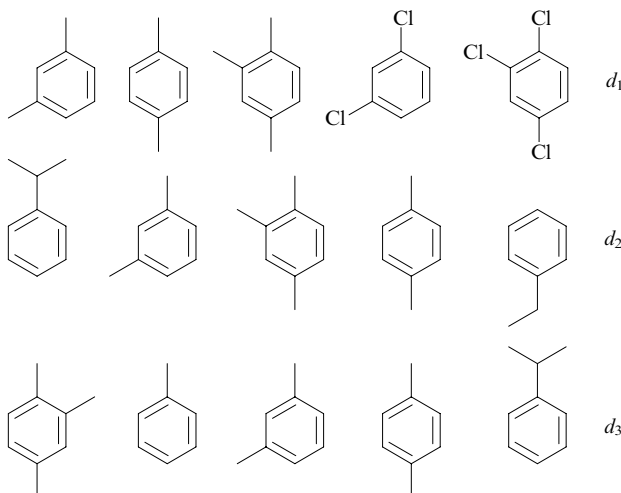
Three molecular similarity measures d_1 , d_2 and d_3 have been examined⁴³ and five structural analogues of *o*-xylene have been found according to these measures. Seven physicochemical properties (including molar volume, $\log P$, boiling point, *etc.*) were used for the description of molecules during the composing of measure d_1 . On the basis of the principal component analysis of these seven parameters, five new parameters were composed. These new parameters are linear combinations of the original ones. By coding the structures with the corresponding five-dimensional vectors, the measure d_1 was determined as a standard Euclidean metric in the space R^5 .

The measure d_2 is similar to d_1 and is based on 81 TI. Ten new descriptors were obtained from these TI by the principal compo-

nent analysis. Therefore, d_2 is defined as an Euclidean metric in the space R^{10} .

The d_3 measure is based on the atomic pairs and has been discussed earlier.

The structural formulae of the analogues of *o*-xylene selected with the help of the discussed similarity measures are listed below (the structures are arranged according to the decrease in the measure values). The result of the search for 'similar' structures depends on the measure selection. However, there are examples of coincidence between the structures found by using different similarity measures.



6. Revealing of the similarity of musk compounds by the pattern recognition theory method

A set of 300 compounds has been studied.⁶² Among these compounds 60 are musk odorants and 240 possess another fragrance (camphoric, floral, ester, mint, *etc.*). Also, the musk odorants belonged to various structural types: there were 23 macrocyclic compounds, 19 polynitrobenzenes, 11 steroids, 5 γ -butirolactones and two compounds of other types. Initially 68 descriptors (geometrical and fragmental) were used, further 13 of the most important among them were selected by TPR for

Table 4. The main descriptors used for the classification of compounds into musk and non-musk odorants.⁶²

Descriptor	Rate of correct classification
Number of O atoms	84.3
Number of double bonds	82.3
Number of aromatic bonds	80.0
Maximum eigenvalue of the inertia tensor	86.7
Minimum eigenvalue of the inertia tensor	80.0
Number of the fragments	
(see a)	80.0
(see a)	80.0
	86.0
	90.3
	80.7
	80.0
	80.0
	83.0

^a is an aromatic bond.

classification of these compounds into musk and non-musk odorants (Table 4). For testing of the predictive ability of the obtained descriptors, a test set of compounds has been used. This set contained 121 musk and 120 non-musk odorants not present in the initial set. As a result, 109 out of 121 musk odorants (90.1%) and 117 out of 120 non-musk odorants (97.5%) were recognised correctly.

The problem of correlation of the structure and electronic configuration with an ambergris fragrance has been studied.^{247, 248} The authors have used a combined approach based upon a combination of pattern recognition methods and quantum-chemical calculations with the precise electron-topological analysis of the potentially active parts of molecules. It appeared that the ambergris fragrance is associated with the presence in the molecular structure of so-called ambergris triangles.

7. Comparison of the accuracy of different methods of similarity analysis in the prediction of compound properties

The comparison of the prediction accuracy for various properties of chemical compounds by six methods (abbreviated as PCs, TIu, TIs, AP, TEI, MNA) of similarity analysis has been carried out.^{69, 88} The two initial sets consisted of 139 hydrocarbons with known boiling points and 15 nitrosamines with known values of mutagenicity. Three similarity methods (PCs, TIu, TIs) used the Euclidian distances as the similarity measures. In these cases various sets of the topological indices were used. These indices were obtained from 96 TI by various procedures, decreasing the dimensionality of the data.²⁵ The fourth method (AP) is based on the atomic pairs and the corresponding similarity measure (see Sections III and IV). Other methods (TEI and MNA) used the vectors composed from electrotopological indices and MNA descriptors based on the atom-centred fragments [see the measures $d_9(X, Y)$ and $d_5(X, Y)$ in Section IV and also the Section III]. The k NN method with $k = 1$ has been used for the estimation of properties.

The data of Tables 5 and 6 indicate that in the first case, the method TIs, which used the topological indices selected by the VARCLUS procedure, was the best one.²⁴ The informational indices and the connectivity indices of Kier and Hall of various orders were present in the selected set of ten TI (see Section III). This may be explained⁶⁹ by the fact that the boiling point mainly

Table 5. The comparison of efficiency of six methods of similarity analysis in the prediction of hydrocarbons boiling points.⁶⁹

Method	r	s
TIs	0.993	19.34
AP	0.986	26.26
MNA	0.985	27.89
TIu	0.983	29.36
PCs	0.966	41.29
TEI	0.959	45.37

Note. Here and in the Table 6, r is a correlation coefficient, s is a mean square deviation.

Table 6. Comparison of the efficiency of six methods of similarity analysis in the prediction of mutagenicity of nitrozoamines.⁶⁹

Method	r	s
MNA	0.945	1.25
AP	0.944	1.26
TEI	0.931	1.43
TIu	0.923	1.47
PCs	0.830	2.33
TIs	0.740	2.67

depends on the shape and the degree of branching of molecules. Both these characteristics are described well by topological indices. In the case of mutagenicity prediction (see Table 6), the MNA and AP methods based on the fragments performed better and the TEI method was at the third place. In this particular case, the TEI method is better than TI-based methods because the prediction of mutagenicity requires additional information about physicochemical characteristics of the molecules and exactly this information is contained in the electrotopological indices.⁶⁹

8. Construction of QSiAR models

The QSiAR model of affinity of fourteen *N*-substituted 3-(3-hydroxyphenyl)piperidines (Table 7) towards a σ -receptor (pIC_{50}) has been created.¹⁰⁴ The Meyer index S_{AB} (see Section IV) has been used as a measure of similarity of the structures A and B, where A is the initial (unsubstituted) compound, B are all other compounds of the set. The *R* and *S* enantiomers of the corresponding compounds were also taken into account. Two models have been composed, each of them on the basis of seven sets of compounds:

for *R* isomers ($r^2 = 0.750$)

$$pIC_{50} = -0.04 S_{AB} + 2.29,$$

for *S* isomers ($r^2 = 0.974$)

$$pIC_{50} = -10.21 S_{AB} + 9.30.$$

Table 7. The values of affinity towards σ -receptor (pIC_{50}) and of the Meyer indices (S_{AB}) for the series of *N*-substituted 3-(3-hydroxyphenyl)-piperidines.¹⁰⁴

Compound		S_{AB}	pIC_{50} (see ^a)
substituent	configuration		
H	<i>R</i>	1.000	−0.66
	<i>S</i>	1.000	−1.19
Me	<i>R</i>	0.952	0.43
	<i>S</i>	0.950	−0.28
Et	<i>R</i>	0.917	0.95
	<i>S</i>	0.912	−0.01
Pr ⁿ	<i>R</i>	0.881	1.52
	<i>S</i>	0.877	0.81
Pr ⁱ	<i>R</i>	0.884	0.61
	<i>S</i>	0.877	0.68
Bu ⁿ	<i>R</i>	0.849	2.05
	<i>S</i>	0.845	1.51
EtC ₆ H ₄	<i>R</i>	0.792	2.10
	<i>S</i>	0.786	1.80

^a IC_{50} is expressed in $\mu\text{mol litre}^{-1}$.

9. Study of the efficiency of the similarity analysis methods in the prediction of biological activity

The cross-validation method has been used for the estimation of efficiency of the similarity analysis methods in the prediction of biological activity.⁶⁹ One compound (numbered k) was excluded from the database at each step of the procedure, and the probability $P(k)$ of this compound to be active was estimated:

$$P(k) = \frac{A_k}{A_k + B_k},$$

$$A_k = (n-1)^{-1} \sum S_i^1,$$

$$B_k = (m-1)^{-1} \sum S_j^0,$$

where S_i^1 and S_j^0 are the values of similarity measure between the compound k and the active compound i and the inactive compound j , respectively; n and m are the numbers of active and inactive compounds in the training set, respectively. The summation in the expression for A_k takes place over all i values from 1 up to n (except for $i = k$). Similarly, the summation in the formula of B_k takes place over all j from 1 to m (except for $k = j$).

Let us assume that for each pair of compounds M_i and M_j , where M_i is an active compound and M_j is an inactive compound ($i = 1, \dots, n$; $j = 1, \dots, m$), the values of probabilities $P(i)$ and $P(j)$ are calculated, and N is the number of pairs, such that $P(i) > P(j)$. The quantity $IAP = N/mn$ ($0 \leq IAP \leq 1$) was used for the estimation of the prediction quality. A set of 17124 compounds with known values of 16 types of biological activity were selected from the database MDDR 96.2 (MDL Information System) as a training set for similarity analysis methods. Two modifications of similarity methods (using the Tanimoto coefficient as a similarity measure), based upon the electrotopological indices (TEI) and on the substructural descriptors (MNA), have been studied. The average accuracy of the prediction in the first case is equal to 86%, and in the second case, to 96%.

10. The optimal choice of k value in the k NN method

The efficiency of the clusterisation of molecules of various chemical databases based upon the method of k nearest neighbours depends on the choice of the parameter k .

The boiling points of 267 haloalkanes containing from 1 to 4 carbon atoms have been studied.²⁴⁹ The molecular similarity (dissimilarity) was estimated in terms of Euclidian metrics in eight-dimensional space of topological descriptors composed by the principal component analysis from a set of 59 TI. The correlation coefficients between the experimental and calculated values are in the range of 0.85 – 0.94. The chosen k values were equal to 1–10, 15, 20, 25. It was shown that the best standard deviation corresponds to $k = 5$ and equals to 23.7 °C. Similar results were obtained in other studies.^{23, 250}

11. Comparison of the efficiency of 2D and 3D descriptors in the estimation of properties of compounds

Three new databases were created on the basis of Medchem 94b database:¹⁸⁶ (i) 8651 compounds with known $\log P_{\text{octanol/water}}$; (ii) 762 compounds with known $\log P_{\text{cyclohexane/water}}$; (iii) 8416 compounds with known pK_a . Both 2D and 3D descriptors (four types) were used for coding of the structures. Particularly, the vectors, components of which were equal to the numbers of occurrences of fixed small fragments in the structures (in one case 153 fragments called MACCS, in another case 960 fragments called SSKEYS) were used. In order to estimate the properties of compounds, the preliminary clusterisation of corresponding databases has been performed by various methods and using the similarity measures. The property was calculated as an average value of all the property values of the corresponding cluster. The cross-validation procedure was employed for the estimation of the prediction quality. For this purpose, the compounds were taken out of the database one by one, and then the value of a property for this compound was calculated. These experimental and calculated property values were compared and then the correlation coefficient and the root-mean-square deviation of corresponding regression were calculated. It was found that 2D descriptors MACCS performed better in all cases. Also, the comparison of the results of calculations of $\log P$ for 7054 structures (out of 8651) was carried out by the above-mentioned methods and by a special programme CLOGP. The methods of molecular similarity yielded the values of $r = 0.95$ and the root-mean-square deviation $rmse = 0.60$, which is almost as accurate as the results of the calculations by the well known program CLOGP ($r = 0.96$, $rmse = 0.49$).

VIII. Conclusion

The molecular similarity concept ('similar compounds possess similar properties') is very popular in theoretical and experimental chemistry. One of the areas of its application, discussed in the present review, is the prediction of properties of chemical compounds on the basis of the 'molecular similarity' concept. The widespread computerisation of the chemical studies requires the formalisation of this concept and the development of methods for quantitative description of the degree of molecular similarity. Nowadays there is a number of various similarity measures, which usually deal with the structures only and are not related to any physicochemical properties or biological activity of the molecules. However, the measures may be optimally tuned to a specific task.

An important problem is the formalisation and approval of the validity of concept 'similar compounds possess similar properties'. As it was shown, the validity of this statement depends on the class of compounds, on the studied property, on the selected similarity measure, etc. The problem of formalisation of the concept is discussed in the present review for the first time. It was found that under certain conditions, this postulate is always valid, and a qualitative proof of the unformalised postulate was given.

On the basis of the analysis of published data, one can draw a conclusion that the molecular similarity method used for the prediction of properties of chemical compounds quite often yields satisfactory results. In particular, one of the advantages of the method is that the *a priori* knowledge of the type of the structure – property functional dependence is not required. Besides, the whole structural formula (a molecular graph) is used for the determination of some similarity measures and there is no need to calculate any molecular descriptors. The discovery of fullerenes is an example of usefulness of the similarity concept in chemistry: these unusual allotropes of carbon were first obtained in 1985,²⁵¹ while their existence had been predicted approximately 15 years earlier^{252, 253} on the basis of a hypothesis about similarity of electronic properties of planar polycondensed aromatic hydrocarbons and spherical polyhedral polycyclic conjugated molecules. This led to successful application to fullerenes of the mathematical models based on the resonance theory and on the Hückel method.

At the same time, it should be noted that the similarity method has some problems. Among them are the correct choice of the mathematical description of the structure, the selection of the similarity measure and the choice of the method for estimation of the properties of a compound on the basis of a similarity measure. Analysis of literature shows that there are no strict and approved methods for the solution of these problems and the selection is intuitive. Probably, here is the right place to quote a remark given by R Feynman in his Nobel lecture: 'I think equation guessing might be the best method to proceed to obtain the laws for the part of physics which is presently unknown'.²⁵⁴

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Regularities in the molecular structures of stable fullerenes

V I Kovalenko, A R Khamatgalimov

Contents

I. Introduction	981
II. Stable higher fullerenes: the analysis of their structures according to the experimental and theoretical quantum-chemical data	982
III. Conclusion	987

Abstract. The literature data on the stability of fullerenes from C_{60} to C_{84} are generalised. The distribution of the π bonds in the isolated and characterised fullerenes is analysed. General regularities in the molecular structures of fullerenes are considered. It is concluded that closed electronic shells and a uniform distribution of pentagons over the molecule are characteristic of stable fullerenes. The bibliography includes 96 references.

I. Introduction

The first suggestion on the probable existence and relative stability of fullerenes was made in 1970 by Osawa,¹ who described the C_{60} molecule and substantiated its stability. This problem was also addressed in a classical study by Bochvar and Gal'pern² and, more recently, by many other authors, both experimentalists and theoreticians within various approximations.^{3–18} Fullerenes with the number of atoms in a molecule ≥ 60 can have thousands of isomers, but only those isomers that comply with the isolated pentagon rule (IPR), which is the most important condition for the stability of fullerenes, have actually been isolated and characterised. According to this rule, each of twelve pentagons of a fullerene molecule have to be surrounded by five hexagons. Nevertheless, several fullerenes with the structures violating the IPR are known, *i.e.*, obtained, isolated and characterised. These include, for instance, endohedral metallofullerenes based on C_{66} and C_{68} , which are unusual complexes containing a metal atom inside the fullerene cage.^{19–23} These complexes are rather scarce but they are a subject of intense investigations.

The meanings of the terms 'obtained', 'extracted', 'isolated' and 'characterised' (identified) have to be explained in more detail. A fullerene is considered as obtained if a signal (peak) of a certain fullerene molecule was detected in a mass spectrum of a carbon soot sample. A fullerene is called extracted if it was successfully transferred to a solution with some solvents. A fullerene is considered as isolated when a specific isomer was separated from a mixture of isomers and obtained in the individual form. Then this fullerene isomer can be characterised or identified by some experimental techniques (*e.g.*, ^{13}C NMR,

X-ray crystallography, *etc.*). Sometimes, only a minute quantity of a compound sufficient exclusively for its identification is available. In other cases, a larger amount of a fullerene isomer can be isolated for a further use.

The total number of fullerenes with the IPR structures is 51 for fullerenes from C_{60} and C_{70} to C_{84} and increases to 300 if the series is extended to C_{94} (Ref. 9). Meanwhile, the number of the obtained fullerenes does not exceed thirty. The extension of the range of the obtained fullerenes is a result of extremely laborious and resource-consuming studies conducted during the last two decades (starting from the discovery of fullerenes in 1985). Nevertheless, according to our estimates, the number of the obtained isomers of fullerenes from C_{60} to C_{94} is less than 10% of the total number of possible IPR isomers (for a series of fullerenes from C_{60} to C_{84} , this fraction is slightly smaller than 30%).

Presently, only C_{60} and C_{70} are produced on a large scale (hundreds kilograms), whereas the vast majority of higher fullerenes (with more than 70 carbon atoms) complying with the IPR are available only in milligram quantities.

The possibility of the isolation of a fullerene in the individual form is governed by its stability (both thermodynamic and kinetic). Taking into account that the term 'fullerene stability' is not obvious, its definition has to be given. For the further discussion, we shall refer those fullerenes that can be synthesised (the thermodynamic stability) and that possess reactivities allowing them remain unchanged for a long time under normal conditions, *i.e.*, in air at room temperature, (the kinetic stability) to as stable fullerenes. The fullerenes that are detected by mass spectra, but cannot be isolated will be considered unstable.

The fullerenes C_{60} and C_{70} meet the stability conditions most comprehensively. Their properties and reactivities have been thoroughly studied, since they are the most accessible compounds among all fullerenes. In particular, C_{60} remains unchanged under normal conditions for years, whereas some of higher fullerenes undergo decomposition within hours, minutes or even seconds. Still, we shall refer all fullerenes that have successfully been isolated and characterised to as stable ones leaving their finer classification for the future. Other IPR fullerenes can be subdivided into two groups. The first group includes those fullerenes that can be obtained in principle, but have not been isolated so far. The second group includes the fullerenes that cannot be obtained due to their intrinsic instability related to the specific molecular structures.²⁴ It is apparent that the first group will extend as a result of the research efforts. However, it is important to know, which fullerenes belong to these two groups and why.

A fullerene can be unstable due to an unfavourable electronic structure (an open electronic shell or the presence of one or several unpaired electrons in the molecule) or topology-related strained geometry for the closed electronic shell. In the former case, the

V I Kovalenko, A R Khamatgalimov A E Arbuzov Institute of Organic and Physical Chemistry, Kazan Research Centre of the Russian Academy of Sciences, ul. Arbuzova 8, 420088 Kazan, Russian Federation.
Fax (7-843) 273 22 53, tel. (7-843) 273 22 83,
e-mail: koval@iopc.kcn.ru (V I Kovalenko), tel. (7-843) 63 26 60,
e-mail: ayrat_kh@iopc.kcn.ru (A R Khamatgalimov)

Received 8 February 2006

Uspekhi Khimii 75 (11) 1094–1102 (2006); translated by Ya V Zubavichus

radical species can be stabilised by converting them into endohedral metallofullerenes.^{10, 12, 24} The discussion below is devoted to structural features of stability of proper (or 'empty') fullerenes containing no guest atoms inside the fullerene cage.

To date, a number of reviews^{3–9, 14, 15, 18, 25, 26} summarising the literature data on structural studies, functionalisation, prospective applications, *etc.* have been published. The structures and properties of most stable endohedral metallofullerenes have been analysed and surveyed by several authors.^{10–13, 16, 17, 24} Nevertheless, no general analysis of the structures of the obtained (isolated and characterised) fullerenes within the context of the search for regularities in their molecular structures has been performed so far. This review represents an attempt to accomplish such an analysis.

II. Stable higher fullerenes: the analysis of their structures according to the experimental and theoretical quantum-chemical data

1. Isolated and characterised isomers of higher fullerenes C₇₂–C₈₄

As has been mentioned above, only some of possible isomers of higher fullerenes have been detected and isolated so far. For instance, the first representatives of higher fullerenes, which are also named lost, C₇₂ and C₇₄, are still missing^{27–32} (their signals were revealed only in mass spectra of soot extracts^{27–29}). Meanwhile, their different endohedral derivatives have been characterised, such as Ca@C₇₂, La@C₇₂, La₂@C₇₂, Ca@C₇₄, Sc@C₇₄, Sc₂@C₇₄, *etc.*^{10, 19, 28, 33–38} Furthermore, the existence of fullerenes C₇₂ and C₇₄ in reduced forms was suggested, which can be explained by the fact that both the C₇₂^{2–} and C₇₄^{2–} dianions are characterised by significant energy gaps between their frontier orbitals.^{30, 31, 33}

Only one of two isomers of the fullerene C₇₆ has been isolated.^{40–42} This is characterised by a chiral structure belonging to the point symmetry group D₂.⁴³ Meanwhile, both isomers have been isolated as endohedral metallofullerenes.^{35, 37, 38, 42, 44}

Three of five isomers[†] of the fullerene C₇₈ (Ref. 39) have been isolated, *viz.*, 1 (D₃), 2 (C_{2v}) and 3 (C_{2v}).^{40, 45} According to the first report,⁴⁶ a mixture of two isomers with symmetries C_{2v} and D₃ in a 5:1 ratio was detected experimentally. However, the presence of three isomers, C_{2v}, C_{2v} and D₃, in a 5:2:2 ratio was proven later.⁴⁷ Taylor *et al.*⁴⁸ also observed the C_{2v}, D₃ and C_{2v} isomers in a ratio 5.2:3:1.8. The earlier results were qualitatively supported⁴⁹ by an analysis of the ³He NMR spectra of the endohedral fullerene He@C₇₈. Only one isomer, *viz.*, 5 (D_{3h}), has been isolated as the endohedral metallofullerene Sc₃N@C₇₈.⁵⁰

The fullerene C₈₀ attracts special attention, since this is the first higher fullerene after C₆₀ that has an isomer with the highest symmetry of a truncated icosahedron (I_h) as that of C₆₀. In contrast to the best studied buckminsterfullerene C₆₀, this isomer of C₈₀ has not been isolated as the 'empty' molecule so far. In total, the fullerene C₈₀ has seven IPR isomers:³⁹ 1 (D_{5d}), 2 (D₂), 3 (C_{2v}), 4 (D₃), 5 (C_{2v}), 6 (D_{5h}) and 7 (I_h). Up to date, two isomers have been obtained.^{50, 51} First, the isomer 2 (D₂)⁵² and then the isomer 1 (D_{5d})⁵³ have been isolated and characterised. The isomers 6 (D_{5h}) and 7 (I_h) could be isolated as endohedral metallofullerenes.^{50, 54–60}

Dozens of fullerene C₈₂ derivatives with different numbers of metal atoms inside the cage are known (*i.e.*, have been isolated and studied). Among them, four isomers were identified, *viz.*, 5 (C₂),^{61, 62} 6 (C_s),⁶³ 8 (C_{3v})⁶⁴ and 9 (C_{2v}).^{10, 65, 66} Meanwhile, only one out of nine possible isomers, *viz.*, 3 (C₂), has been isolated as the empty molecule.^{15, 67–69}

The fullerene C₈₄ takes the third place after C₆₀ and C₇₀ as regards its occurrence and abundance in fullerene-containing soots. Two of its major isomers, 23 (D_{2d}) and 22 (D₂), out of twenty-four possible isomers complying with the IPR³⁹ were identified as a 2:1 mixture by ¹³C NMR spectroscopy.^{47, 70} An analysis of the ³He NMR spectra of He@C₈₄ revealed the presence of eight isomers.⁷¹ The first attempt at their identification was performed by Taylor and co-workers.⁷² Following the separation of the isomer mixture, two less accessible high-symmetry isomers, 24 (D_{6h}) and 19 (D_{3d}), were identified.⁷³ Five isomers were then separated by multistage HPLC:⁷⁴ two isomers with the C_s symmetry and isomers with the C₂, D_{2d} and D₂ symmetries, which were ascribed to the isomers 4 (D_{2d}), 5 (D₂), 11 (C₂) and 16 (C_s), respectively. One of isomers with the C_s symmetry was not unequivocally identified (there are five possible isomers with this symmetry). Thus, only ten out of twenty-four isomers of C₈₄ have been isolated so far,^{15, 47, 70–78} including two unidentified isomers with the C₂ and C_s symmetries. Additionally, isomers 7 (C_{2v}), 10 (C_s) and 23 (D_{2d}) have been isolated as endohedral metallofullerenes.^{19, 36, 56, 79, 80}

Table 1. Experimental studies on the IPR isomers of higher fullerenes.

TP	Ref. (EM)	Ref. (EMF)	TP	Ref. (EM)	Ref. (EMF)
Fullerene C ₇₂ (1)			Fullerene C ₈₂ (9)		
1 (D _{6d})	—	19, 28, 34, 44	8 (C _{3v})	—	64
			9 (C _{2v})	—	10, 65, 66
Fullerene C ₇₄ (1)			Fullerene C ₈₄ (24)		
1 (D _{3h})	—	10, 28, 33–38	1 (D ₂)	—	—
			2 (C ₂)	—	—
Fullerene C ₇₆ (2)			3 (C _s)	—	—
1 (D ₂)	40–42	35, 37, 42, 44	4 (D _{2d})	15, 74–76	—
			5 (D ₂)	15, 74–76	—
2 (T _d)	—	38	6 (C _{2v})	—	—
Fullerene C ₇₈ (5)			7 (C _{2v})	—	36, 79
1 (D ₃)	40, 45	—	8 (C ₂)	—	—
2 (C _{2v})	40, 45	—	9 (C ₂)	—	—
3 (C _{2v})	40, 45	—	10 (C _s)	—	36, 79, 80
4 (D _{3h})	—	—	11 (C ₂)	75–78	—
5 (D _{3h})	—	50	12 (C _i)	—	—
Fullerene C ₈₀ (7)			13 (C ₂)	75 (?), 78	—
1 (D _{5d})	50, 51	—	14 (C _s)	—	—
2 (D ₂)	50, 51	—	15 (C _s)	75 (?), 78	—
3 (C _{2v})	—	—	16 (C _s)	75–78	—
4 (D ₃)	—	—	17 (C _{2v})	—	—
5 (C _{2v})	—	—	18 (C _{2v})	—	—
6 (D _{5h})	—	50, 54–60	19 (D _{3d})	15, 73, 75, 76	—
7 (I _h)	—	50, 54–60	20 (T _d)	—	—
Fullerene C ₈₂ (9)			21 (D ₂)	—	—
1 (C ₂)	—	—	22 (D ₂)	15, 47, 70, 75, 76	19, 36, 56, 79–80
2 (C _s)	—	—	23 (D _{2d})	15, 47, 70, 75, 76	—
3 (C ₂)	15, 67–69	—	24 (D _{6h})	15, 73, 75, 76	—
4 (C _s)	—	—			
5 (C ₂)	—	61, 62			
6 (C _s)	—	63			
7 (C _{3v})	—	—			

Notes. (1) The following notations for fullerenes are adopted: TP is theoretically possible, EM is isolated experimentally as 'empty' molecules, EMF is isolated experimentally as endohedral metallofullerenes. (2) The numbers in parentheses are the numbers of theoretically possible IPR isomers of the fullerene. (3) The numbering and symmetries of fullerene isomers are given according to Ref. 39. (4) The symbol '?' marks those isomers of the fullerene C₈₄ that have presumably been isolated (taking into account their symmetries, structural and energy parameters) but not unequivocally identified.^{75, 78}

[†] Hereinafter, the enumeration of fullerene isomers, which uniquely define their molecular symmetry and bonding topology, is given according to Ref. 39.

The literature data on fullerene isomers isolated to date as 'empty' molecules and endohedral metallofullerenes are summarised in Table 1. As can be seen, the isomers that preferably occur as endohedral metallofullerenes differ, as a rule, from those that occur as 'empty' molecules.²⁴

2. The results of quantum-chemical calculations of stable fullerenes

Quantum-chemical calculations is the primary tool used to establish the stability of a specific fullerene. An analysis of the literature and our own results^{24,30,31} demonstrates that the order of the relative stabilities of isomers is reproduced in the majority of cases, irrespective of differences in the accuracy and predictive power of semiempirical and *ab initio* methods (performed either in minimum or extended basis sets, with account for the electron correlation or neglecting it). A comparative analysis of the relative total energies of *m* isomers of a fullerene C_n complying with the IPR makes it possible only to estimate probability of the isolation of a particular isomer. The total energy of the fullerene molecule and, respectively, its stability or instability depend on the mutual arrangement of pentagons, which defines the surface curvature of the molecule, the presence of fused hexagons and electronic effects. According to correlation of the calculated total energies for fullerene isomers the isolated fullerenes possess the minimum total energies among the IPR isomers of the fullerene in question. This is a reliable test for stability. Meanwhile, for fullerenes with only one IPR isomer, nothing but total energy value can be stated.

However, the total energies alone are insufficient for the prediction of probability of the synthesis of IPR isomers. In particular, 8 isomers of the fullerene C_{84} have been isolated and characterised. On the scale of relative energies, they all are located from 0 to 18 kcal mol⁻¹ with respect to the energetically most favourable isomer, 23 (D_{2d}).⁷⁵ The number of stable fullerenes from C_{70} to C_{84} estimated by taking this energy range as the stability criterion and extending it to other higher fullerenes should be significantly larger. And it remains unclear whether the missing isomers can be synthesised at all.

Unfortunately, there are currently no satisfactory criteria for the evaluation of the stability and possibility of the synthesis of fullerenes. Diener and Alford suggested³³ to subdivide all fullerenes into two groups: fullerenes with a large energy gap between the highest occupied and the lowest unoccupied molecular orbitals (HOMO–LUMO) (these include fullerenes C_{60} and C_{70}) and fullerenes with either a small HOMO–LUMO energy gap or even a radical structure (*i.e.*, with one or more unpaired electrons). A similar classification was proposed by Stevenson and co-workers⁸¹ based on electrochemical studies of fullerenes. In other words, the HOMO–LUMO energy gap was suggested as a simple criterion for the stability of fullerenes. Indeed, a large gap between the frontier orbitals implies a high stability and low reactivity of the molecule. However it was found that this criterion, the HOMO–LUMO energy gap, alone is not always sufficient for the prediction of the stability of fullerenes. To provide a more unambiguous estimate for the kinetic stability of fullerenes, the HOMO–LUMO energy gap should be correlated to the number *n* of conjugated carbon atoms in the fullerene molecule C_n and supplemented with other parameters,⁸² such as the bond resonance energy (which represents the contribution of a given π bond of the molecule to the total topological resonance energy⁸³) or the localisation energy (which characterises the heat of protonation of the respective fullerene⁷⁶). Using such a scheme, Aihara⁸³ concluded that fullerenes with the bond resonance energies smaller than $-0.100|\beta|$ and with small or zero HOMO–LUMO energy gap multiplied by the number of carbon atoms in the fullerene molecule are unstable. Nevertheless, the values of these parameter for some higher fullerenes that have not been isolated so far are nearly the same as those for C_{60} . In particular, this scheme fails to explain the impossibility of isolation of fullerenes C_{72} and C_{74} or

isomers 1 (D_2) and 20 (T_d) of the fullerene C_{84} , despite these molecules meet the above criteria.

Thus, the conventional quantum-chemical calculations and the stability criteria considered above fail to fully explain the instability of some fullerenes. This may be due to the lack of analysis of the local stability, *i.e.*, the stability of substructures that constitute the fullerene molecule. Such substructures were ignored in the earlier theoretical calculations predominantly focused on the molecules as a whole.⁸⁴ It might be hoped that the analysis of the electronic structures of stable (*i.e.*, isolated) fullerenes from this viewpoint will help revealing common regularities in their molecular structures.

3. Analysis of molecular structures of stable fullerenes

According to an approach developed by Kovalenko and Semyashova,^{85,86} the distribution of π bonds over the fullerene molecules in the series from C_{60} to C_{84} can be represented as the Schlegel diagrams. These diagrams show the positions of localised double and delocalised π bonds. A number of characteristic substructures with distinct electronic structures (as in their aromatic analogues: naphthalene, indacene, pyrene, perylene, corannulene, coronene, *etc.*) can be identified by analysing the local symmetry in the distribution of single, double and π bonds delocalised over the hexagons of the fullerene molecules. These substructures retain their electronic properties irrespective of the fullerene molecule they belong to.

Two types of bonds occur in the C_{60} molecule (Fig. 1 *a*): the five-membered rings are composed of single bonds, whereas single and double bonds alternate in the six-membered rings.⁸⁷ The C_{60} molecule (I_h) comprises exclusively corannulene substructures (Fig. 2 *a*) and is characterised by a uniform distribution of the pentagons over the molecule. The C_{70} molecule (Fig. 1 *b*) can be regarded as two poles with the same pattern of the bond distribution as in C_{60} and an equatorial belt composed of five hexagons with the delocalised π bonds^{10,88} forming five indacene substructures (Fig. 2 *b*). Thus, only two substructures, *viz.*, corannulene and indacene, occur in these two fullerenes. It would be reasonable to suggest that these substructures constituting the stable fullerenes C_{60} and C_{70} are characterised by the highest stability.⁸⁸

As has been mentioned above (see Table 1), two next fullerenes, C_{72} (D_{6d}) and C_{74} (D_{3h}), have not been isolated so far as 'empty' molecules.^{27–32} In the case of C_{72} , this can be explained by the presence of two coronene substructures in the molecule (Fig. 2 *c*), which induce large sterical strains: these substructures are planar, whereas the fullerene cage tends to be spherical.^{24,31} The instability of C_{74} can be explained by its biradical structure due to the presence of two phenalenyl radical substructures (Fig. 3).^{24,30,32}

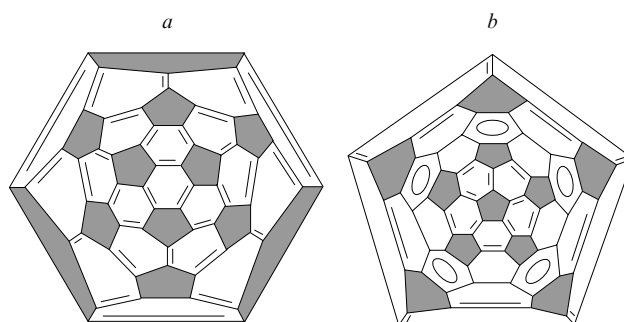


Figure 1. The Schlegel diagrams of the fullerenes C_{60} (*a*) and C_{70} (*b*). Hereinafter, all pentagons are marked grey; single and double bonds are marked with single and double lines, respectively. The hexagons with the delocalised π bonds are marked with circles.

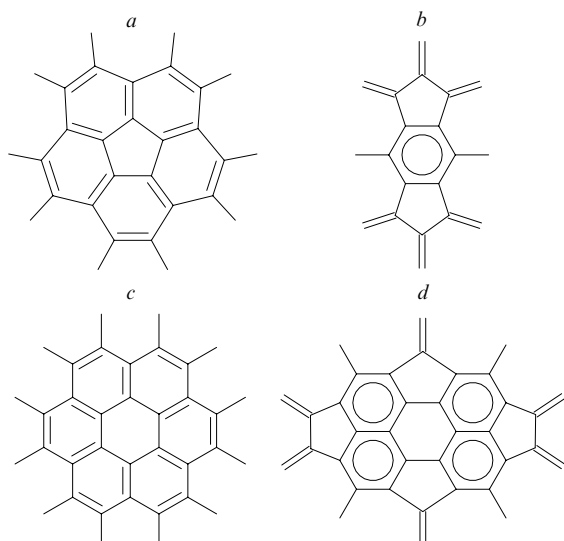


Figure 2. Characteristic substructures of stable fullerenes: corannulene (a), indacene (b), coronene (c) and perylene (d).

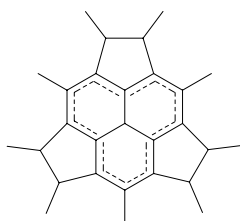


Figure 3. The phenalenyl radical substructure.

According to quantum-chemical calculations,⁸⁹ the difference in the total energies of two possible isomers of fullerene C_{76} (see Table 1) exceeds 12 kcal mol^{-1} . An analysis of the molecular structure of the energetically most favourable isomer 1 (D_2) (Fig. 4), which has been obtained experimentally, demonstrates that the distribution of the π bonds therein is similar to that in the C_{70} molecule: it includes four corannulene (see Fig. 2 a) and four indacene (see Fig. 2 b) substructures. The presence of four phenalenyl radical substructures (see Fig. 3) is a possible reason for the instability of the second isomer, 2 (T_d), which has not been obtained.

According to theoretical calculations reported in the literature^{9, 18, 40, 45, 90, 91} and our own data^{24, 30, 31} (Fig. 5),[‡] five possible isomers³⁹ of fullerene C_{78} can be arranged in the following series of decreasing stability: 3 (C_{2v}), 2 (C_{2v}), 1 (D_3), 5 (D_{3h}) and 4 (D_{3h}). Up to date, three most stable isomers of the above series (see Table 1) have actually been obtained and isolated experimentally.^{40, 45–49} The distribution pattern of the π bonds in the isomer 1 (D_3) (Fig. 6 a) is similar to that in C_{70} . Meanwhile, one coronene substructure occurs in the isomer 2 (C_{2v}) (Fig. 6 b) in addition to four indacene substructures (see Fig. 2 c). The isomer 3 (C_{2v}) (Fig. 6 c) contains one perylene substructure (see Fig. 2 d).

Although two coronene substructures make the fullerene C_{72} unstable,^{31, 92} their presence becomes less critical for larger fullerenes, which can remain stable. Nevertheless, the occurrence of three or more coronene substructures in one molecule dramati-

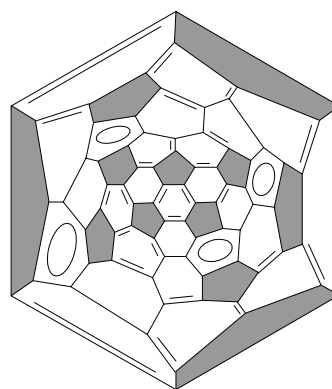


Figure 4. The Schlegel diagram of the fullerene C_{76} [the isomer 1 (D_2)].

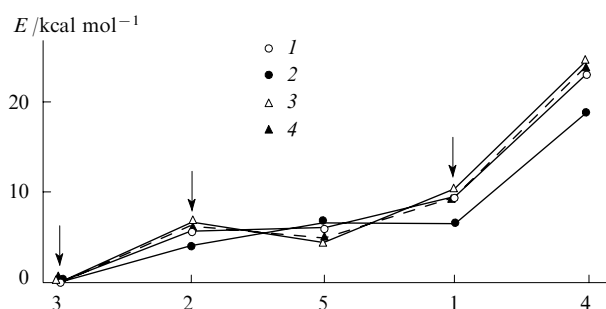


Figure 5. Relative energies of IPR isomers of the fullerene C_{78} calculated at the following theory levels: B3LYP/STO-3G (1), B3LYP/3-21G (2), B3LYP/6-31G* (3), B3LYP/6-31G (4); (1–3) from Ref. 40, (4) the present authors' data. Hereinafter, the arrows point to the obtained isomers.

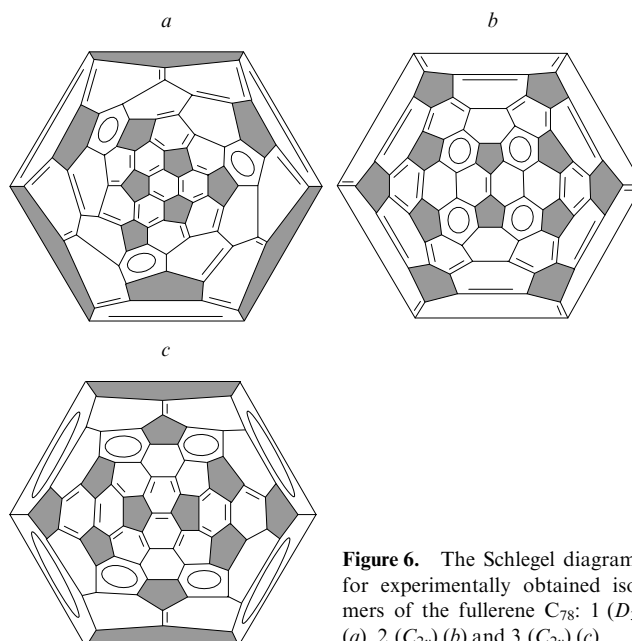


Figure 6. The Schlegel diagrams for experimentally obtained isomers of the fullerene C_{78} : 1 (D_3) (a), 2 (C_{2v}) (b) and 3 (C_{2v}) (c).

cally destabilise it due to the development of substantial strain. Thus the calculations the isomer 4 (D_{3h}) of the fullerene C_{78} , which includes three coronene substructures, is the least stable. High kinetic instability of the isomer 5 (D_{3h}) of the fullerene C_{78} is probably⁹⁰ the rationale for the fact that it cannot be obtained.

In the case of the fullerene C_{80} , the isomers 1 (D_{5d}) and 2 (D_2) (Fig. 7) are characterised by the lowest total energies according to calculations.^{9, 18, 51, 93–95} It is these two isomers (out of seven

[‡] Hereinafter, all calculations were performed using the DFT/B3LYP method with the full geometry optimisation in the 6-31G basis set; the total energies were recalculated for the optimised geometries in the 6-31G* basis set.

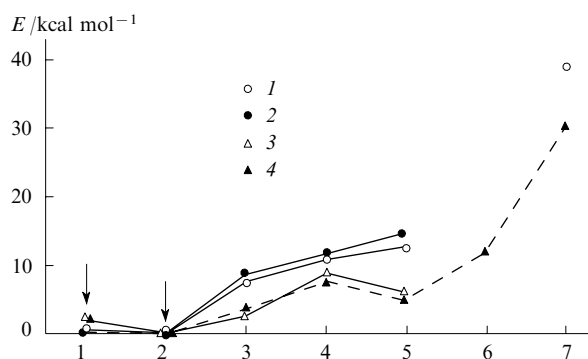


Figure 7. Relative energies of IPR isomers of the fullerene C_{80} calculated at the following theory levels: B3LYP/STO-3G (1), B3LYP/3-21G (2), B3LYP/6-31G* (3), B3LYP/6-31G (4); (1–3) from Ref. 93, (4) the present authors' data.

possible ones³⁹) that have actually been isolated and identified^{50–53} (see Table 1). The energy of the isomer 3 (C_{2v}), which has not been synthesised so far, is higher by ~ 5 kcal mol^{−1} than those of the isolated isomers 1 (D_{5d}) and 2 (D_2). This is rather surprising taking into account that the respective energy difference between the most stable isomer and other experimentally obtained isomers for other fullerenes, *e.g.*, for C_{84} , by far exceeds this value.

As for the distribution pattern of the π bonds in the isomers under discussion, the molecular structure of the isomer 1 (D_{5d}) (Fig. 8a) is similar to that of C_{60} since it contains only corannulene substructures (see Fig. 2a). The molecular structure of the isomer 2 (D_2) (Fig. 8b) is analogous to that of C_{70} : it contains two indacene substructures in addition to the corannulene structures (see Fig. 2b). Molecules of all other isomers contain different number of phenalenyl radical substructures^{24,30} (see Fig. 3). The isomer 7 (I_h) probably represents an unusual radical structure with the π bonds delocalised over all fused hexagons; this has no analogues. Undoubtedly, the number of unpaired electrons in a fullerene molecule affects its kinetic stability.

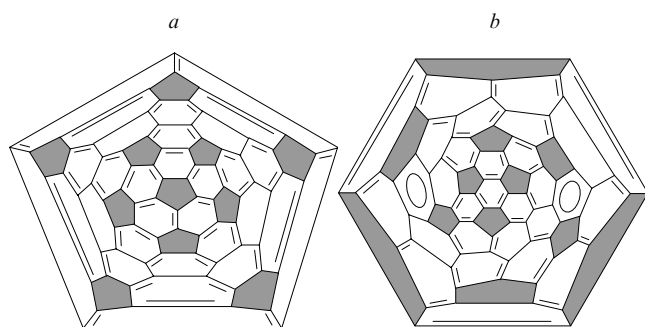


Figure 8. The Schlegel diagrams of the experimentally obtained isomers of the fullerene C_{80} : 1 (D_{5d}) (a) and 2 (D_2) (b).

According to numerous calculations,^{9,15,18,67–69} the isomer 3 (C_2) of the fullerene C_{82} is characterised by the minimum total energy among its nine IPR isomers³⁹ (Fig. 9a). Accordingly, it is the only isomer that has been obtained to date^{15,67–69} (see Table 1). Its molecular structure (Fig. 9b) features a combination of four corannulene (see Fig. 2a) and four indacene (see Fig. 2b) substructures. Despite the isomers 1 (C_2), 2 (C_s) and 4 (C_s) possess similar structures (in addition to the corannulene substructures, they include two, three and two indacene substructures, respectively²⁴), they have not been obtained so far. Other five isomers²⁴ are described by the molecular structures with

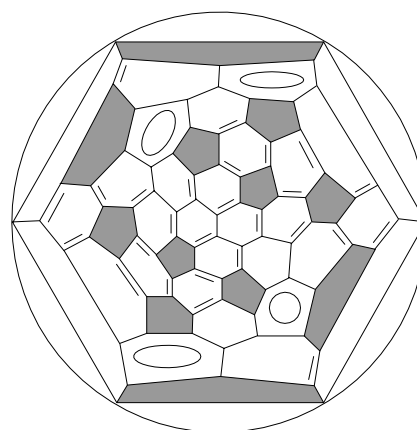
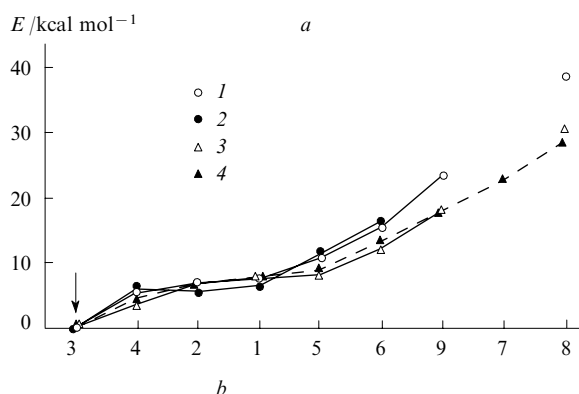


Figure 9. Relative energies of IPR isomers of the fullerene C_{82} (a) and the Schlegel diagram of the experimentally obtained isomer 3 (C_2) (b). The calculations at the following theory levels: (1) B3LYP/STO-3G, (2) B3LYP/3-21G, (3) B3LYP/6-31G*, (4) B3LYP/6-31G; (1–3) from Ref. 67, (4) the present authors' data.

phenalenyl radical substructures (see Fig. 3), which are responsible for their instability.

The results of quantum-chemical calculations for 24 isomers of the fullerene C_{84} are depicted in Fig. 10. Only 10 of them have been isolated. The isomers 4 (D_{2d}), 5 (D_2), 11 (C_2), 16 (C_s), 19 (D_{3d}), 22 (D_2), 23 (D_{2d}) and 24 (D_{6h}) have been reliably identified, whereas only point symmetry groups, *viz.*, C_2 and C_s , have been determined for the remaining two isolated isomers^{15,47,70–78} (see Table 1). Indeed, according to calculations,^{9,15,18,75,76,89} the

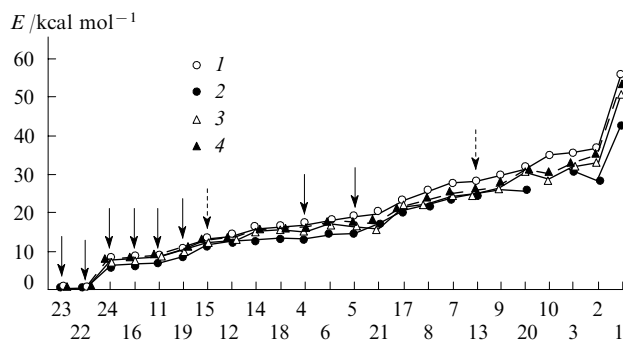


Figure 10. Relative energies of IPR isomers of fullerene C_{84} calculated at the following theory levels: (1) B3LYP/STO-3G, (2) B3LYP/3-21G, (3) B3LYP/6-31G*, (4) B3LYP/6-31G; (1–3) from Ref. 75, (4) the present authors' data. Dashed arrows indicate the most probable candidates for the isolated, but not identified isomers.^{75,78}

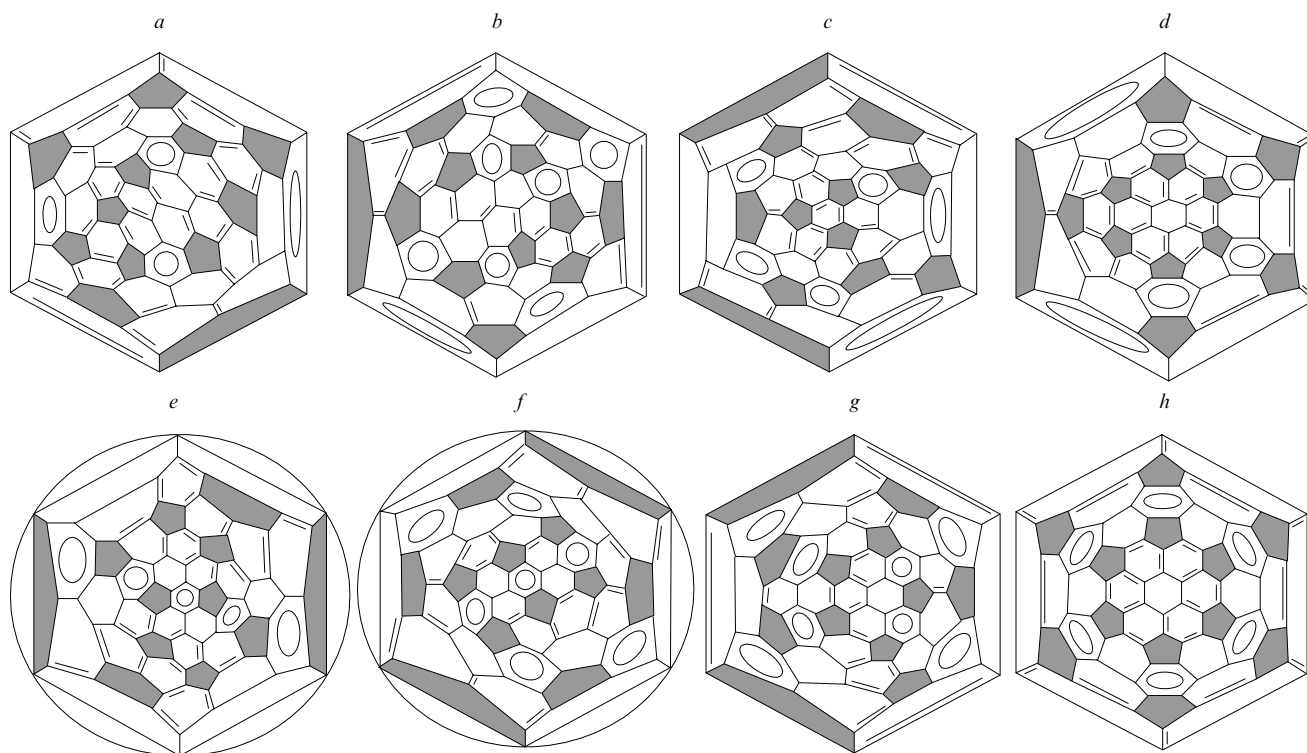


Figure 11. The Schlegel diagrams of the experimentally obtained isomers of the fullerene C_{84} : 4 (D_{2d}) (a), 5 (D_2) (b), 11 (C_2) (c), 16 (C_s) (d), 19 (D_{3d}) (e), 22 (D_2) (f), 23 (D_{2d}) (g) and 24 (D_{6h}) (h).

isomers 11, 16, 19, 22, 23 and 24 are the most energetically stable. Meanwhile, the total energies of other two isolated isomers, 4 and 5, are comparable to that of the isomer 15 (C_s). Presumably, the latter is the unidentified isolated isomer with the C_s symmetry. The second unidentified C_2 isomer can then be interpreted as the isomer 13, which is the most stable one among molecules with this symmetry containing no radical substructures [in contrast to the isomer 8 (C_2), which is characterised by a somewhat lower total energy]. The energy difference between the most stable isomer and other isomers obtained for this fullerene lies in the range⁷⁵ of 10–15 kcal mol⁻¹, which by far exceeds the aforementioned value of ~ 5 kcal mol⁻¹ for C_{80} .⁹³

The molecular structures of eight identified isomers are shown in Fig. 11. It is apparent that only corannulene (see Fig. 2a) and indacene (see Fig. 2b) substructures occur in the isomers 4, 5, 11, 19, 22 and 23. In the isomer 16, one coronene substructure (see Fig. 2c) appears, and the isomer 24 contains two such substructures, which supports the suggestion that the destabilising influence of the coronene substructure attenuates with an increase in the fullerene size. Taking into account the results of computation discussed above, a fullerene appears unstable if it includes radical substructures (*i.e.*, it has one or more unpaired electrons) or planar substructures with a large number of fused hexagons (*e.g.*, coronene, ovalene, *etc.*).

The question ‘why the number of isolated isomers of certain fullerenes is larger than that for some others, despite a larger scatter in the total energies in the former case?’ has no clear answer up to now. Nevertheless, some comparisons can be made based on the available data. Let us consider the general correlation between the stability of a fullerene and its total energy. The total energies and standard enthalpies of formation per carbon atom (*i.e.*, TE/n and $\Delta H_f/n$, respectively) are useful for such a comparative analysis. Trends in TE/n and $\Delta H_f/n$ as a function of n have been analysed by Khamatgalimov and Kovalenko⁹⁶ based on the literature data^{9,15,18} and own computation results (Fig. 12). This graph reveals a specific ‘beam’ of stability. Its top border is defined by the minimum total energies and enthalpies of forma-

tion (TE/n and $\Delta H_f/n$, respectively) typical of the most stable fullerenes, including C_{60} , C_{70} , C_{84} [the isomers 23 (D_{2d}) and 22 (D_2)] and the isomer 133 (C_2) of fullerene C_{94} . The bottom border of the ‘beam’ is defined by the maximum total energies and enthalpies of formation for all known stable isomers of fullerenes C_n . The instability region lies just below this border.

The prominent trend towards a decrease in the energy with an increase in the number of carbon atoms (*i.e.*, in the fullerene size) is of particular note. Apparently, this trend reflects a progressive relieve of strains in spherical molecules on going from C_{60} to larger

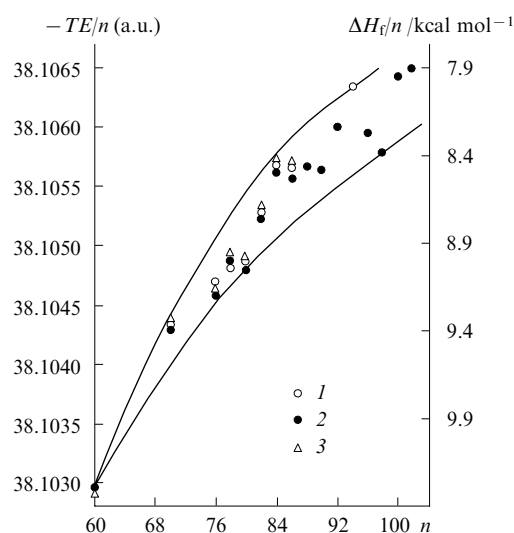


Figure 12. Changes in the total energies (1, 3) and standard enthalpies of formation (2) per carbon atom for the synthesised, isolated and characterised stable fullerenes C_n as a function of n ; (1) from Ref. 96; (2) from Refs 9, 18; (3) from Ref. 15.

higher fullerenes. We emphasise that it is the C_{60} and C_{70} molecules that are the most strained and, at the same time, the most stable in the series. Probably, a rather uniform distribution of the local strains over the entire molecule is realised therein due to a respective uniform distribution of the pentagons. For other fullerene molecules, despite their larger sizes, steric strains can be localised in specific regions of the sphere thus destabilising the entire molecule. Yet another important feature of the plot shown in Fig. 12 is that the 'beam' of stability encompasses all known stable fullerenes complying with the isolated pentagon rule.

Based on this 'beam' of stability, a simple scheme for the prediction of the number of stable isomers for any fullerene can be suggested. If the most energetically favourable isomer of a fullerene C_n is located at the upper border of the 'beam', the isolation of other stable isomers of this fullerene might be expected with total energies falling in the interval between the upper and the lower points of the 'beam'. For instance, for C_{84} , this interval amounts to 25 kcal mol^{-1} (and 10 isomers of this fullerene with a total energy gap of 20 kcal mol^{-1} have been obtained and characterised). It might be assumed that within the range of 25 kcal mol^{-1} , several other isomers of this fullerene might be isolated in future, including 6 (C_{2v}), 15 (C_s), 12 (C_1), 14 (C_s), 17 (C_{2v}), 7 (C_{2v}), 13 (C_2) and 21 (D_2) with closed electronic shells. At the same time, only two isomers of the fullerene C_{80} with a total energy difference of only 5 kcal mol^{-1} have been obtained, although their calculated total energies are located near the bottom border of the 'beam' of stability. Under these circumstances, the isolation of any other isomers is hardly possible. And to the contrary, the probability of the isolation of new isomers is high for the fullerenes with the most energetically favourable isomer lying near the upper border of the 'beam' of stability (as in the aforementioned case of C_{84}). Despite the evident predictive power of this scheme, this is based on the use of the integral molecular parameters, *viz.*, their total energies, which prevents the analysis of reasons underlying the stability or instability of certain isomers.

The energies, geometric and electronic structures of fullerene molecules can be calculated irrespective of whether they have experimentally been obtained. However, analysis of the total energies (or enthalpies of formation) cannot confidently predict the possibility of the isolation of a specific fullerene isomer. The newly suggested approach summarised in Fig. 12 enables such a prediction. A fullerene may be unstable due to a number of factors related to its geometric and electronic structures. The 'beam' of stability reflects the net result of all these effects, thus making it possible to estimate the possibility of isolation (*i.e.*, the stability) of a target isomer based solely on its energy characteristics. In particular, this plot that also includes the data for the most stable fullerene isomers from C_{86} to C_{102} predicts stability of isomers of the fullerenes C_{86} , C_{88} , C_{92} , C_{94} and C_{100} and instability of C_{98} . Supplementation of this plot with new points for the fullerenes discussed already and its extension to larger fullerenes C_n with $n > 84$ will allow prediction of the stability of particular isomers.

III. Conclusion

Owing to the detailed analysis of the electronic structures of stable (isolated) fullerenes, common regularities of their molecular structures have been revealed. In particular, all stable fullerenes

(1) represent molecules with closed electronic shells, which are characterised by a relatively uniform distribution of pentagons over the sphere;

(2) comprise corannulene and indacene substructures typical of the most stable fullerenes C_{60} and C_{70} . The presence of perylene and coronene substructures is also possible. The latter substructures substantially destabilise the molecules of the first members of higher fullerenes, but their destabilising effect attenuates with an increase in the number of carbon atoms in the molecule.

It has been shown that the possibility of the synthesis and isolation of an isomer of a higher fullerene is governed by the

location of the energetically most favourable isomer of this fullerene in the suggested 'beam' of stability that has been constructed by correlating the theoretical and experimental data on stable of fullerenes with closed electronic shells.

This study was performed within the framework of the programme 'Theoretical and experimental investigations into the nature of chemical bonding and mechanisms of the most important chemical reactions and processes' supported by the Division of Chemistry and Materials Science of the Russian Academy of Sciences and partially supported by the U.S. Civilian Research and Development Foundation (CRDF) within the programme 'Basic Research and Higher Education' (BRHE).

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Light-created chemiluminescence

R F Vasil'ev, Yu B Tsaplev

Contents

I. Introduction	989
II. Photosensitised chemiluminescence	989
III. Photochemical synthesis of chemiluminescent reagents	995
IV. Photoinduced chemiluminescence	998
V. Analytical applications	1000
VI. Conclusion	1000

Abstract. The results of studies of light-created chemiluminescence are described systematically. Conditions for the transformation of a dark chemical reaction into a chemiluminescence reaction are considered. Examples of photosensitised and photo-induced processes as well as of analytical applications are given. The bibliography includes 161 references.

I. Introduction

In darkness at ambient temperatures, electronic excitation of molecules involved in chemical reactions is not a routine event. However, if such an event happens, it has a reliable witness, namely, light emission. No matter how intricate and unclear the chemical processes in the reactor may be, the observation of chemiluminescence (CL) unambiguously points to electronic excitation. Chemiluminescence is a remarkable example of the conversion of chemical energy into light energy. Electronic excitation in the chemiluminescence is due to the energy liberated in an elementary act of the reaction on the way from the activated state to the products and, broadly speaking, is rather improbable. Correspondingly, relatively few chemiluminescence reactions are known.

It can be assumed that the effect of light on reactants or a reaction mixture (*i.e.*, the delivery of additional energy) will allow overcoming the energy limitations and transform a dark reaction into chemiluminescence. Indeed, over the last 40 years compounds have been found that, being preliminarily illuminated, give rise to CL. The diversity of such systems is associated with the variety of types of interaction of light with matter and their different chemical consequences.

This review is aimed at the systematisation of the results of studies of light-created chemiluminescence systems, their classification and the refinement of terminology used for their description. The latter problem is associated with the fact that along with already accepted terms, for example, photosensitised CL, photochemiluminescence and light-induced CL, exotic terms such as

optically pumped CL, photostoragechemiluminescence, *etc.*, are encountered.

The interaction between reactants that constitute a chemiluminescence system results in the electronically excited products or intermediates and light emission; this is why all starting components of a chemiluminescence system are justly referred to as chemiluminescent reactants. Among the components of a liquid-phase chemiluminescence reaction, one can single out a reactant that according to its composition and structure is the precursor of the primarily excited species and the light emitter.[†] It is this reactant that brings in individual features into the chemiluminescence system. To distinguish it from other reactants, it is called 'chemiluminophore'.[‡] For liquid-phase CL, molecular oxygen [its concentration in aerated solutions varies from 0.2 (in H₂O) to 4 mmol litre⁻¹ (in Et₂O)] and the solvent are the key reactants.

The present review deals with photosensitised oxidation of chemiluminophores with molecular oxygen. Attention is focused on chemiluminophores obtainable from precursors by photochemical mechanisms involving oxygen and solvent, as well as on chemiluminescence systems in which the light-induced intramolecular rearrangement of a molecule occurs.

II. Photosensitised chemiluminescence

Molecules and supramolecular structures can store for a while the energy of absorbed light quanta, being converted into the electronically excited state. The excitation energy is usually lost upon non-radiative transition of the molecule into its ground state; however, in certain cases the energy can be emitted as a luminescence quantum or transferred to other molecules, namely, quenchers. In the latter case, luminescence of the primary excited compound is quenched. The question of what happens if dissolved oxygen acts as the quencher, was raised by Kautsky back in the 1930s.⁵ The studies of luminescence quenching with oxygen led to the discovery of singlet oxygen⁶ and gave rise to a concept of 'active oxygen forms' (species OH[•], O₂H[•], O₂^{•-}, ¹O₂). Combined studies of photooxidation⁵ and chemiluminescence, which, as a

R F Vasil'ev, Yu B Tsaplev N M Emanuel Institute of Biochemical Physics, Russian Academy of Sciences ul. Kosygina 4, 119991 Moscow, Russian Federation. Fax (7-495) 137 41 01, tel. (7-495) 939 73 58, e-mail: vasil'ev@sky.chph.ras.ru (R F Vasil'ev), tsap_04@mail.ru (Yu B Tsaplev)

Received 13 February 2006

Uspekhi Khimii 75 (11) 1103–1118 (2006); translated by T Ya Safonova

[†] For chemiluminescence reactions in the gas phase, such a reactant can be singled out only in rare cases, *e.g.*, in reactions involving volatile low-molecular dioxetanes, whereas the involvement of all reactants of the chemiluminescence system 'on equal terms' is typical.

[‡] This term, which was introduced by analogy with 'luminophores', *i.e.*, substances that emit light upon activating radiation, is encountered with increasing frequency in the literature (see Refs 1–4).

rule, was observed in the oxidation,⁷ initiated studies on the phenomenon of photosensitised chemiluminescence (PSCL).

1. Photooxidation

IUPAC defines photooxidation as the oxidation reactions initiated by light. In a more general form, these are the reactions in which a reactant loses an electron upon the absorption of a photon and also the light-induced reactions of substances with oxygen (a process in which a chemical bond is formed between oxygen and the substance is called photooxygenation).

Two types of photosensitised oxidation processes in liquid phase are distinguished.⁸ Type I processes include reactions of the substrate (RH, R) with a sensitizer in the electronically excited triplet state (³S), or photoionisation reactions. Type II processes correspond to the interaction of an electronically excited sensitizer with an oxygen molecule. Each type includes reactions of several kinds (Table 1).

Table 1. Classification of photosensitised oxidation processes.

Type I	Type II
a. Free-radical oxidation $^1S_0 + h\nu \longrightarrow ^1S^* \longrightarrow ^3S$, $^3S + RH \longrightarrow SH^\cdot + R^\cdot$, $(R^\cdot + ^3O_2 \longrightarrow ROO^\cdot)$	a. Oxidation involving singlet oxygen $^1S_0 + h\nu \longrightarrow ^1S^* \longrightarrow ^3S$, $^3S + ^3O_2 \longrightarrow ^1S_0 + ^1O_2$, $RH + ^1O_2 \longrightarrow \text{products}$
b. Oxidation with electron transfer $^1S_0 + h\nu \longrightarrow ^1S^* \longrightarrow ^3S$, $^3S + R \longrightarrow S^{\cdot-} + R^{+\cdot}$, $(S^{\cdot-} + ^3O_2 \longrightarrow S + O_2^{\cdot-})$, $R^{+\cdot} + O_2^{\cdot-} \longrightarrow \text{products}$	b. Oxidation with electron transfer $^1S_0 + h\nu \longrightarrow ^1S^* \longrightarrow ^3S$, $^3S + ^3O_2 \longrightarrow [^1S_0 \cdots ^1O_2]^? \longrightarrow$ $\longrightarrow S^{+\cdot} + O_2^{\cdot-}$, $RH + O_2^{\cdot-} \longrightarrow \text{products}$
c. Single-photon ionisation $^1S_0 + h\nu \longrightarrow S^{+\cdot} + e^-$, or two-photon ionisation $^1S_0 + h\nu \longrightarrow ^1S^* \longrightarrow ^3S$, $^3S + h\nu \longrightarrow S^{+\cdot} + e^-$	c. Oxidation to form a biradical $^1S_0 + h\nu \longrightarrow ^1S^* \longrightarrow ^3S$, $^3S + ^3O_2 \longrightarrow ^\cdot SOO^\cdot$, $RH + ^\cdot SOO^\cdot \longrightarrow \text{products}$

Note. ¹S₀, ¹S*, ³S are ground (non-excited), excited singlet and triplet states of the sensitizer molecule, respectively. In parentheses, the possible subsequent reactions are shown.

Several relatively simple tests allow one to determine the type of a photosensitised oxidation process in a system under study.

(1) The formation of singlet oxygen is inhibited by quenchers among which 1,4-diazabicyclo[2.2.2]octane (DABCO), carotenoids and sodium azide are the most popular.

(2) Radical processes are sensitive to scavengers, *i.e.*, traps of free radicals.

(3) Free-radical oxidation depends on the temperature, whereas oxidation that involves singlet oxygen is temperature independent.

(4) Involvement of singlet oxygen in the oxidation reaction can be confirmed by an independent synthesis using singlet oxygen formed in a chemical reaction [*e.g.*, from triphenyl phosphite ozonide P(OPh)₃O₃].

(5) Reactions that involve a superoxide ion are sensitive to superoxide dismutase.

(6) Reactions that involve solvated electrons are sensitive to the presence of N₂O (trap).

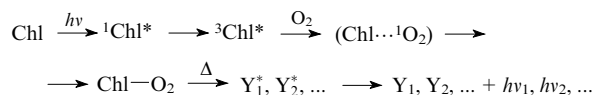
The phenomenon of sensitisation, which is associated with the enhanced reactivity of a molecule in the excited state, occurs also when the substrate itself plays the role of the sensitizer (S = RH). In this case, the process is referred to as autosensitisation.

2. Pigments and dyes

In 1951, persistent afterglow of chlorella photosynthesising cells following their illumination at 420–700 nm was discovered.⁹ Studies of this phenomenon were continued with simpler objects. It was noticed¹⁰ that red CL observed upon mixing of a chlorophyll solution with a formaldehyde solution in alkaline methanol, becomes more intense when the reaction mixture has been illuminated. Persistent afterglow was also observed¹¹ in aerated solutions of chlorophyll and pheophytin.

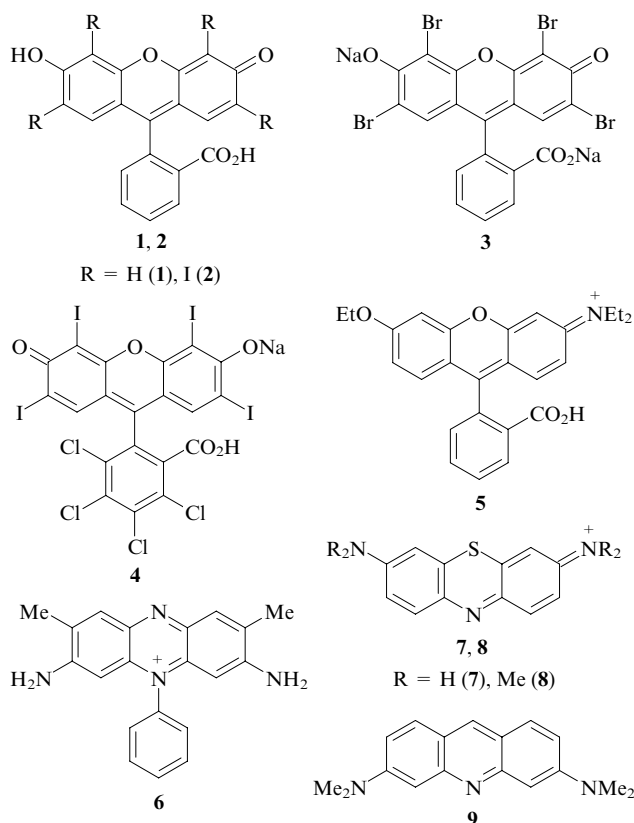
Comprehensive studies of PSCL of chlorophyll and its analogues were carried out by Krasnovsky (Jr) *et al.*^{12–17} In a review,¹⁷ the major experimental approaches to investigations of light-created CL have been outlined and, first of all, the process has been proposed to be divided into photochemical and chemiluminescence stages. Studies of the photochemical stage involve the determination of an action spectrum of the exciting light, the elucidation of the role of oxygen in the photoirradiation and the determination of the nature of the primary photoproduct. The use of thermograms of CL ignition in the course of heating of deeply frozen photoirradiated aerated solutions has been pioneered in studies of the chemiluminescence stage. Thermograms reflect the involvement of various labile photoproducts in CL (*i.e.*, in 'photo-thermochemiluminescence').

The efficiency of chlorophyll PSCL is low, namely, one emitted quantum per 10⁸ absorbed quanta. The general scheme of PSCL of chlorophyll (Chl) can be represented as the following reaction sequence:



Light quanta are radiated by emitters Y₁, Y₂, ..., *i.e.*, the products of chlorophyll oxidation.

PSCL of aerated solutions of fluorescein (1), erythrosine (2), eosin Y (3), Rose Bengal (4), rhodamine B (5), safranin (6), thionine (7), Methylene Blue (8), Acridine Orange (9), anthracene and naphthacene was discovered and studied,^{14,17} as well as of pyrene and benzopyrene.¹⁸

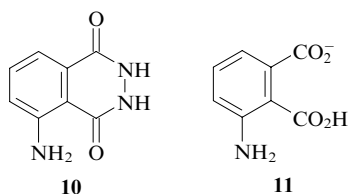


The presence of dissolved oxygen at the moment of illumination is a prerequisite for persistent afterglow of the compounds listed. The PSCL yield for solutions of compounds **2–4** is maximum in aprotic solvents such as acetone, dioxane, DMF, DMSO. The PSCL spectra differ from the fluorescence spectra of the original compounds. Thus the fluorescence peak of compound **8** is at ~ 700 nm, while its PSCL peak is at ~ 560 nm. Based on the studies of the glow decay kinetics and the analysis of photo-thermochemiluminescence curves, it was concluded that PSCL starts with the formation of several types of labile peroxide compounds.

The observed phenomenon was called^{12–17} photochemiluminescence,⁸ its main feature is photooxidation of the starting compounds in the presence of oxygen.

3. Luminol

In 1961, it was discovered¹⁹ that in aerated solutions containing luminol (5-amino-2,3-dihydrophthalazine-1,4-dione, **10**), a dye (eosin, fluorescein) and a base, chemiluminescence occurs upon irradiation in the region of the dye absorption band. The PSCL spectrum coincided with the CL spectrum of luminol in the presence of an oxidant and corresponded to the fluorescence spectrum of 3-aminophthalate (**11**), *i.e.*, the oxidation product and the CL emitter.



Kuschnir and Kuwana¹⁹ assumed luminol to be oxidised by singlet oxygen, which at that time was considered (and for a good reason) as the driving force of many reaction mechanisms. (It should be noted that Foote's study²⁰ in which he attributed the photosensitised oxidation of substrates to the electron transfer rather than the action of singlet oxygen was published much later.)

This mechanism was called into question in a study by Matheson and Lee,²¹ who, based on the kinetic analysis, ruled out the possibility of direct involvement of singlet oxygen in PSCL. Later, in the determination of the rate constant for the luminol reaction with $^1\text{O}_2$ ($\sim 3 \times 10^7$ litre mol⁻¹ s⁻¹), it was shown that the structure of the final product of luminol oxidation with singlet oxygen differed from that of compound **11**. The CL yield in the luminol reaction with singlet oxygen was $< 3 \times 10^{-9}$ per luminol molecule, which is infinitesimally small as compared with the quantum yield of PSCL.²²

A detailed study of PSCL of luminol and other phthalohydrazides was carried out by Emokhonov and co-workers.^{23–27} They used eosin and Methylene Blue as the photosensitisers. The action spectrum of light for PSCL coincided with the absorption spectra of these dyes. In the UV region, which corresponds to the luminol absorption, autosenitisation occurred, *i.e.*, in the UV illumination, luminol itself served as the photosensitiser. Both photochemiluminescence and autosenitised CL of luminol were quenched by superoxide dismutase. Hence, superoxide ions play an important role in PSCL of luminol. This catalytic cycle (see Table 1, type Ib) includes the following stages:

(1) light absorption by the sensitiser and its transition into the triplet state;

(2) electron transfer from a luminol molecule to the triplet sensitiser to form radicals (or radical ions) of the sensitiser and

luminol (under the experimental conditions, *i.e.*, in a phosphate buffer with pH 10–12, luminol, eosin and their radicals exist in the form of anions, while Methylene Blue exists in the form of a cation, and its radical is neutral);

(3) oxidation of the sensitiser radical with dissolved oxygen to afford a superoxide ion and to recover the sensitiser in its original state.

The rate constant for the third stage is 2×10^8 litre mol⁻¹ s⁻¹ for eosin and 5×10^5 litre mol⁻¹ s⁻¹ for Methylene Blue. The reaction of the luminol radical with a superoxide ion is the key stage of the luminescence pathway of luminol reaction, its rate constant is $\sim 7 \times 10^7$ litre mol⁻¹ s⁻¹. It was shown that the reaction of luminol with singlet oxygen afforded an unstable product that quenched PSCL. Its lifetime amounts to minutes and seconds when isoluminol and 4-dimethylaminophthalohydrazide are used. This explains the intricate (with two peaks) kinetic curve of PSCL of these compounds. The formation of a quencher complicates the CL kinetics. The side effect could be avoided if the PSCL experiments employed pulsed illumination rather than stationary.²⁴ Figure 1 *a* shows the kinetics of luminol PSCL initiated by a flash of ~ 10 μs ($\lambda > 610$ nm) from a flash lamp.

PSCL of luminol induced by radiation from a pulsed laser ($\lambda = 530$ nm) and a stationary source was studied.²⁸ Figure 1 *b* shows the PSCL spectrum for the laser stimulation. The marked segments correspond to chemiluminescence caused by the involvement of singlet oxygen (type II) and initiated by the electron transfer (type I). A comparison of curves in Figs 1 *a, b* shows that they substantially differ, first of all, in the time intervals of the

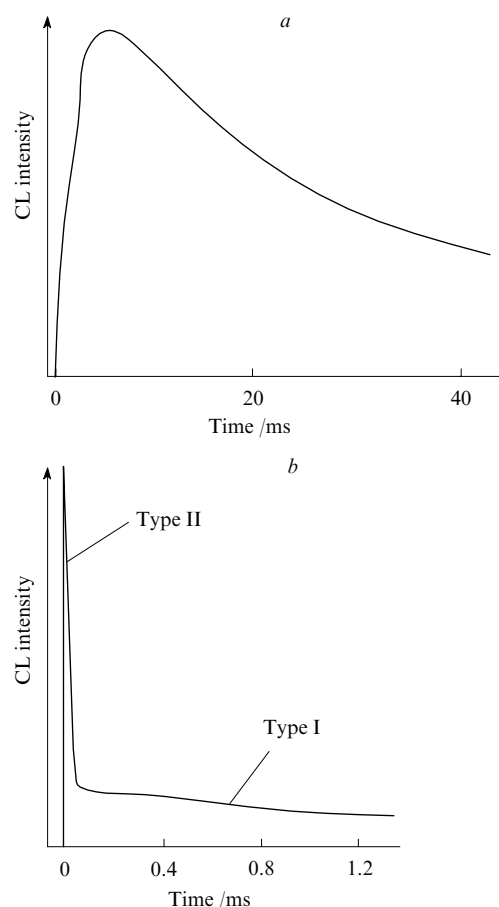


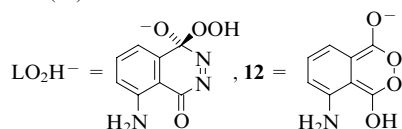
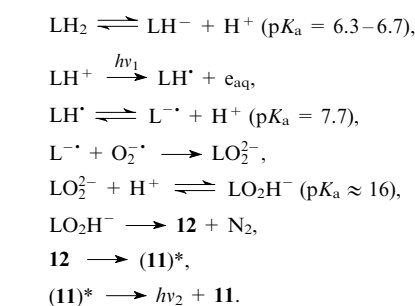
Figure 1. PSCL spectra of luminol with a sensitiser excited by filtered light from a pulse lamp ($\lambda > 610$ nm, CL registration in a band at 380–480 nm) (*a*) and a laser pulse ($\lambda \sim 530$ nm, registration at 420 nm) (*b*).²⁸

§At present, the term 'photochemiluminescence' is understood as a mnemonic code of the sequence of operations with the reaction mixture (or as a protocol of the experiment), *cf.* the use of the term 'photo-thermochemiluminescence' mentioned above.

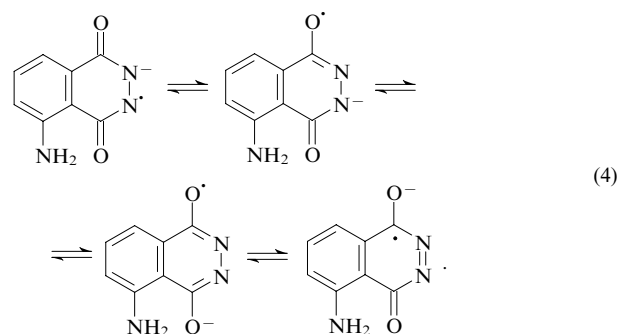
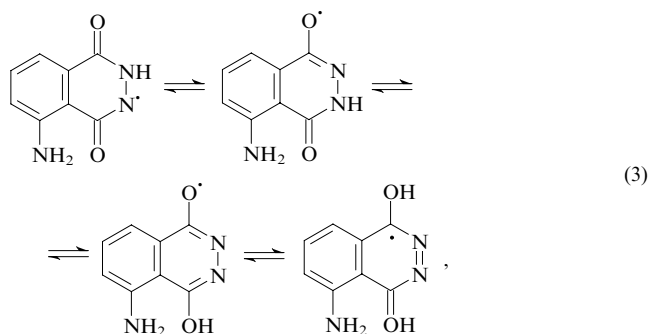
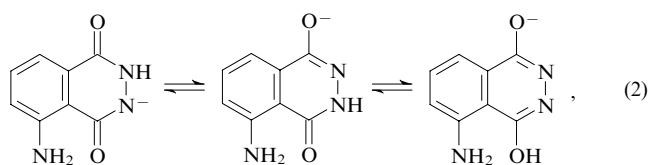
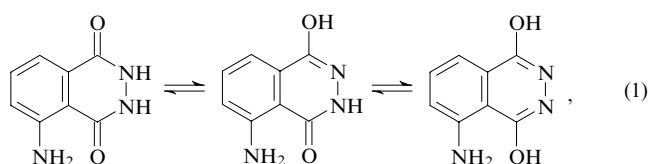
PSCL evolution. The assignment of the initial flash to the chemiluminescence induced by the formation of singlet oxygen has not yet been proved. The role of $^1\text{O}_2$ in the luminol PSCL might be clarified by the detection of emission in two spectral channels, *viz.*, in the blue region of the luminol CL emission band and at 1270 nm in the emission band of singlet oxygen.

The kinetics of autosensitised CL of luminol upon the pulsed-laser UV irradiation ($\lambda = 347$ nm) was studied.²⁷ It was shown that the primary process corresponds to the one-photon ionisation of luminol to afford a luminol radical and a hydrated electron (e_{aq}). The latter is captured by dissolved oxygen to form a superoxide ion. The subsequent reaction of the luminol radical with the superoxide ion is accompanied by chemiluminescence. Scheme 1^{29–31} shows the mechanism of this process and the structures of reactants and intermediates.

Scheme 1



Structures of LH_2 (**10**), LH^- , $\text{LH}^\bullet$ and $\text{L}^{\bullet-}$ can be presented as tautomeric equilibrium forms (1)–(4), respectively,



To explain the PSCL of luminol, a general scheme of photosensitised oxidation according to which luminol is the oxidised substrate was used.³² From our viewpoint, the new name of this phenomenon, 'optically pumped chemiluminescence', offers less information.

Although the nature of luminol PSCL long remained unclear, this phenomenon was already used in the medical and biological studies of antioxidants.^{33–39} Certain progress was achieved in the application of PSCL for the analysis of antioxidant activity of substances; however, the applicability of PSCL for these purposes has recently been questioned because of the absence of any correlation in the activity estimates made using PSCL and other methods.⁴⁰ It is the fact that in luminol PSCL the main targets of antioxidants are luminol radicals and superoxide ions that probably accounts for the lack of correlation.

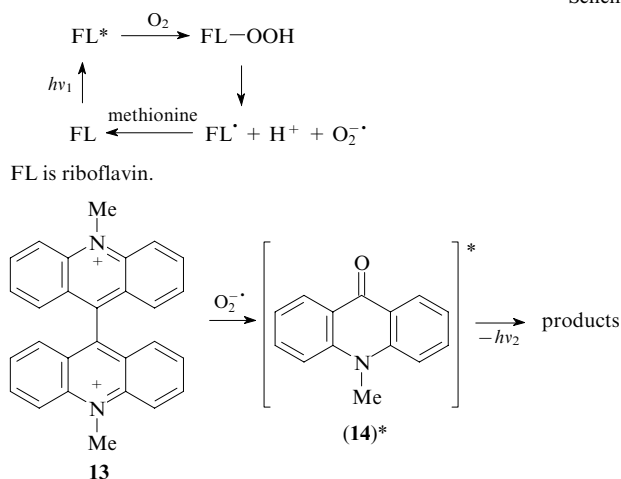
Photosensitised chemiluminescence of luminol was also proposed³² to be used for the detection of antibodies covalently stained with Methylene Blue (up to 16 photosensitiser molecules per antibody); based on this reaction, a method of immunochemical assay of α -fetoprotein has been developed (detection limit 1.7×10^{-11} g).

4. Lucigenin and analogues of luciferin

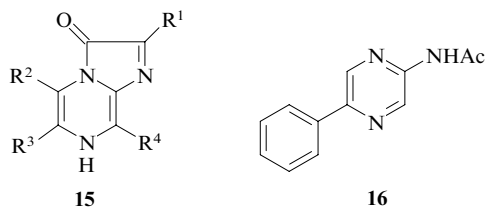
Lucigenin (*N,N'*-dimethylbiacridylum ion, **13**), like luminol, is a widely known chemiluminophore the oxidation of which is accompanied by bright CL.

Riboflavin-photosensitised chemiluminescence of lucigenin was studied.^{41,42} UV irradiation of riboflavin generates superoxide radical ions the reaction of which with lucigenin leads to excited *N*-methylacridone (**14**), which is the chemiluminescence emitter (Scheme 2). This mechanism is confirmed by the fact that the addition of superoxide dismutase into the reaction mixture quenches the glow. The addition of methionine into the reactor is aimed at reduction of riboflavin radicals.

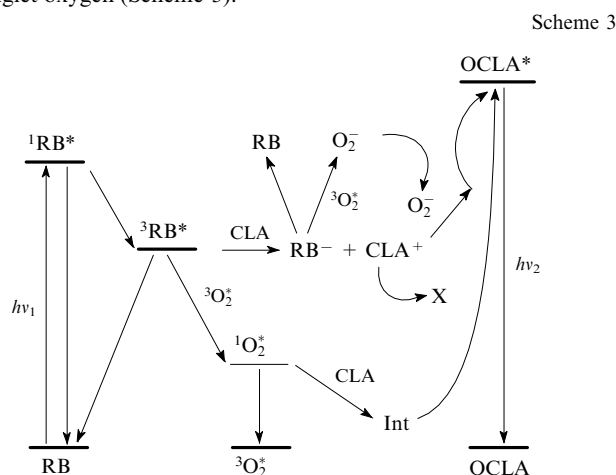
Scheme 2



In the 1980s, chemiluminophores **15**, which represent the analogues of luciferin (coelenterazine) inducing the glow of certain medusas and *Cypridina* hermit crabs, were synthesised (see Ref. 43 and references cited therein).



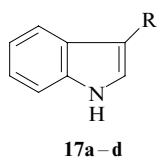
One of the analogues, viz., 2-methyl-6-phenyl-3,7-dihydroimidazo[1,2-a]pyrazinone (**15**, $R^1 = \text{Me}$, $R^2 = R^4 = \text{H}$, $R^3 = \text{Ph}$) was named CLA (Cypridina Luciferin Analogue). The CLA chemiluminescence photosensitised by Rose Bengal (RB) in an aqueous solution with pH 7 was studied.⁴⁴ The reaction proceeds through the formation of excited 2-acetamido-5-phenylpyrazine (OCLA, **16**), which is the CL emitter, and of an unidentified intermediate (Int), which is the reaction product of CLA with singlet oxygen (Scheme 3).



Photosensitised oxidation of CLA includes the same stages as the luminol oxidation; however, the intermediate formed in the CLA reaction with $^1\text{O}_2$ also takes part in the luminescence transformations.

5. Indole derivatives

Photosensitised chemiluminescence of indole (**17a**) derivatives was discovered following observation of persistent afterglow of proteins and amino acids^{45,46} and of solutions of proteins and synthetic polymers irradiated with X-rays⁴⁷ and UV light.⁴⁸



$R = \text{H}$ (**a**), $\text{CH}_2\text{CH}(\text{NH}_2)\text{CO}_2\text{H}$ (**b**),

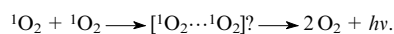
$\text{CH}_2\text{CH}(\text{NHCOCH}_2\text{NH}_2)\text{CO}_2\text{H}$ (**c**), $\text{CH}_2\text{CO}_2\text{H}$ (**d**).

In 1968, Sapezhinskii and Voloshin⁴⁹ reported on chemiluminescence accompanying the photooxidation of tryptophan (**17b**) in aerated solutions. Later, this research group studied the autosensitised CL of glycyltryptophan (**17c**) and its dye-sensitised chemiluminescence.^{50–58} The results of studies of radiation-induced CL in peptides, proteins and synthetic polymers were generalised in a monograph.⁵⁹

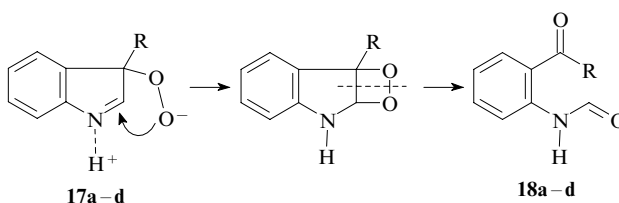
The photoexcitation site of a sensitizer can be fixed by its adsorption on a plate immersed in the substrate solution.⁵⁵ The idea of spatial separation of a sensitizer and a solution exposed to

sensitisation products was forwarded in the studies of photo-sensitised oxidation⁵ and PSCL of glycyltryptophan.⁵⁵ This heterogeneous PSCL offers good prospects in analytical applications and in the development of chemiluminescence sensors.

The phenomenon of autosensitised CL of tryptophan (**17b**) upon its UV irradiation was studied by several optical techniques.⁶⁰ CL in the blue region was attributed to tryptophan photooxidation. Chemiluminescence at 630–705 nm was intensified in heavy water and quenched by 10%–15% upon the addition of NaN_3 and DABCO. This suggests that dimolar luminescence of singlet oxygen made a certain contribution to the total CL



Rose Bengal-photosensitised CL of indol-3-ylacetic acid (**17d**) was studied.⁶¹ Superoxide ions and singlet oxygen were the major photooxidants of indole derivatives. The attachment of superoxide at position 3 of the indole molecule was accompanied by the formation of intermediate dioxetane; cleavage of C–C and O–O bonds in the latter led to formylkynurenine derivatives (**18a–d**).



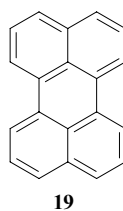
Opening of the dioxetane ring was accompanied by the release of energy $> 270 \text{ kJ mol}^{-1}$, which is quite sufficient for the chemiexcitation of the carbonyl product.⁶⁰ The formation of dioxetane intermediates is probably typical of all indole derivatives.⁶²

The phenomenon of PSCL of glycyltryptophan (**17c**) was used in the determination of the activity of superoxide dismutase in its reaction with riboflavin as the photosensitizer and for studying the photoprotection and antioxidant properties of a series of natural compounds and medicinal drugs.^{63–70}

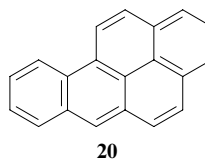
Yet another application field of the PSCL of indole derivatives are the studies of conformational transformations of proteins induced by various effects.^{71–73} Insofar as most proteins contain tryptophan, the intensity of protein PSCL depends on the number of tryptophan residues accessible for photooxidation.

6. Polyaromatic hydrocarbons

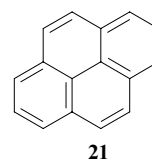
PSCL of aerated solutions of anthracene, naphthalene, pyrene and benzopyrene as well as base-induced enhancement of glow was first reported in the 1970s.^{17,18} Chemiluminescence appeared upon mixing of a solution of an organic base (triethylamine, piperidine) with aerated and irradiated ($\lambda > 320 \text{ nm}$) solutions of polyaromatic hydrocarbons (PAH) in CCl_4 , acetone or benzene.⁷⁴ The highest CL yield was observed in CCl_4 solutions of the following PAH (the series is given in order of decreasing CL quantum yield): perylene (**19**), benzo(*a*)pyrene (**20**), pyrene (**21**), fluoranthene (**22**), chrysene (**23**), 1,2-benzanthracene (**24**), 9,10-diphenylanthracene, anthracene.



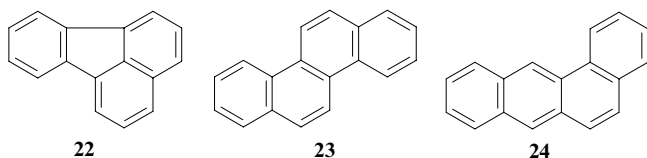
19



20



21



Presumably, UV irradiation of PAH solutions results in the photoionisation of the substrate to form the corresponding radical cation and a photoelectron, which is captured by the solvent.⁷⁴ Subsequent interaction of PAH radical cations with dissolved oxygen leads to the formation of, first, peroxide radicals and, then, peroxides. Chemiluminescence is induced in the reaction of primary and secondary peroxides with hydroxyl anions HO^- or a base. The proposed mechanism brings about many questions. For example, is it possible to distinguish light-generated radical cations from those formed as a result of electron transfer from an excited PAH molecule to oxygen, based on observations of radical cations alone? Apparently, the insight into the mechanism requires additional studies.

PSCL of fluoranthene (**22**)⁷⁴ can be compared with studies⁷⁵ of base-induced CL reactions of this compound. It is reasonable to assume that the chemiluminescence of compound **22** and other PAH, which was observed in Ref. 75, was, in fact, PSCL initiated by the laboratory light.[¶]

7. Chromone-2-carboxylic acid

The primary process of the reaction of a light-excited molecule with oxygen can be not only the transfer of an electron or excitation energy to the oxygen molecule to form $^1\text{O}_2$, but also the addition of oxygen to the substrate molecule (type II c photo-oxidation, see Table 1). Thus in studies^{76,77} devoted to PSCL of aerated solutions of chromone-2-carboxylic acid (**25**), it was shown that its photolysis affords 4-hydroxycoumarin (**26**) as the only product, which corresponds to the formal substitution of oxygen for the carboxyl group in the starting molecule. Com-

pound **26** is not formed in either deoxygenated or aerated solutions in the presence of sensitizers (Methylene Blue and Rose Bengal). It was thus concluded that it is the ground-state oxygen molecule rather than its active form that takes part in the reaction. Moreover, the photolysis of compound **25** was not accompanied by the formation of ketyl radicals, typical products of the abstraction of hydrogen atoms from solvent molecules by excited ketones. The presence of a strong electron-withdrawing group in the molecule of keto acid **25** makes the electron transfer from the excited molecule **25** to the O_2 molecule impossible. Hence, the primary process of photolysis consists of the addition of oxygen to the excited molecule of coumarin **25** the triplet state ($n\pi$ -type) of which has the structure of biradical **27** (Scheme 4).

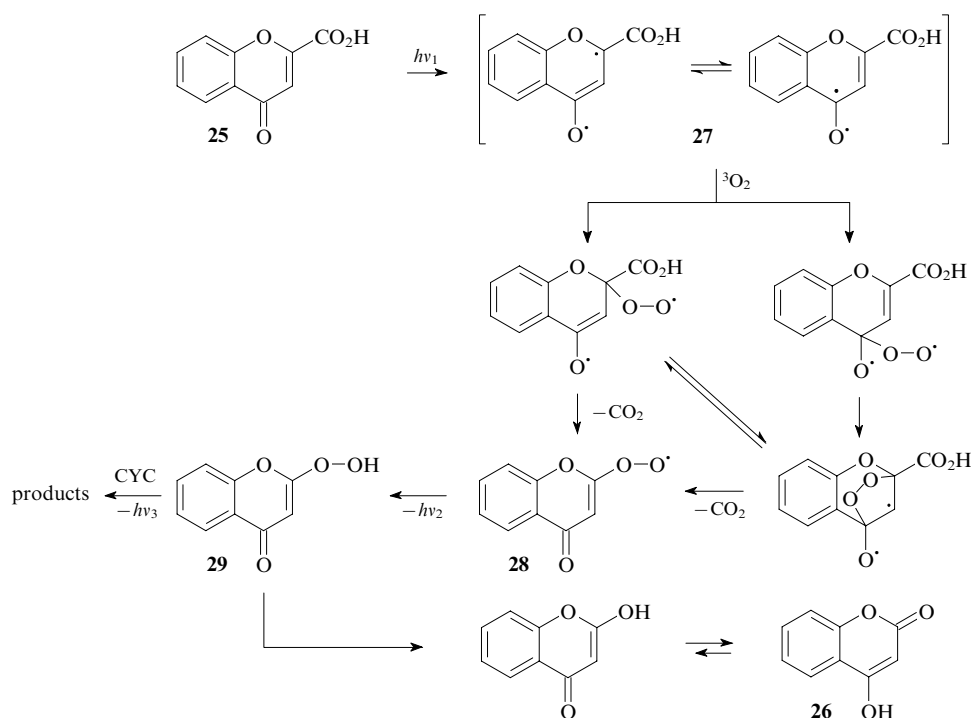
Chemiluminescence ($h\nu_2$) of irradiated solutions of compound **25** arises due to the reactions of peroxide radicals **28**. Exponential decay of CL intensity following the irradiation of solutions was observed with a rate constant of $4.2 \times 10^{-4} \text{ s}^{-1}$. Unfortunately, Scheme 4 does not explain this peculiarity of the kinetics. Moreover, disproportionation of tertiary peroxide radicals does not lead to product **26**, being only the source of hydroxyl radicals, and cannot be assigned to chemiexcitation reactions.^{78–80} It should be noted that the possibility of photoionisation of acid **25** cannot be totally ruled out, because this was observed for certain derivatives of 4-oxoquinoline-3-carboxylic acid.⁸¹

Chemiluminescence ($h\nu_3$) also arises when an iron-containing protein, namely, cytochrome *c*, which catalyses decomposition of hydroperoxides, is added to a photosensitized ethanolic solution of compound **25**.⁷⁷ This enhances the emission intensity 30-fold as compared with the CL intensity observed immediately after the irradiation. This can be considered as evidence for the formation of hydroperoxide **29** in the photolysed solution (see Scheme 4). However, this process calls for further investigations.

8. Organic azides

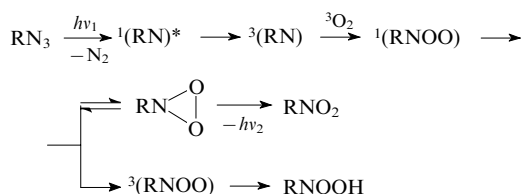
Zelentsov and co-workers^{82,83} observed chemiluminescence in the oxidation of organic azides with molecular oxygen in ethanol under UV irradiation ($\lambda > 280 \text{ nm}$), where the CL spectrum of photooxidation of 4,4'-diazidobiphenyl had two peaks in the blue region. Presumably, the chemiexcitation occurs in the isomer-

Scheme 4



¶ Berger *et al.*⁷⁵ ignored the possibility of phototransformation of reagents at the stage of solution preparation and pretreatment; this is why they assigned this reaction to CL.

isation of dioxaziridine (a dioxirane analogue) to afford a nitro compound with energy release ($> 315 \text{ kJ mol}^{-1}$).



R = Alk, Ar.

Apparently, the nitro compound serves as the emitter.

In 1954, when studying the luminescence of nitro-substituted biphenyl and stilbene, Lippert⁸⁴ observed no fluorescence in the region $< 500 \text{ nm}$. However, the shift of the absorption band of a nitro compound to the long-wave region (by varying solvents or substituents in the nitro compound) gave rise to fluorescence at $\lambda > 500 \text{ nm}$. Thus, nitro compounds with peaks of long-wave absorption bands below 500 nm do not fluoresce (the so-called Lippert rule),⁸⁵ *i.e.*, nitro derivatives do not exhibit blue luminescence.

The question of the nature of the emitter could be solved ultimately using an organic azide the photooxidation product of which exhibited known luminescence properties. Thus for 4-azido-4'-dimethylaminostilbene, the presumed emitter would be 4-dimethylamino-4'-nitrostilbene which emits with the quantum yield of 0.7 luminesces at 590 nm .⁸⁶

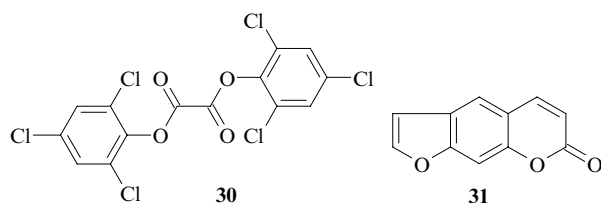
9. Complex systems

In a photolysed solution that originally contained a single substance, a complex mixture of different products and intermediates is gradually formed. Moreover, if the solution to be photolysed originally contained a mixture of substances, the elucidation of the mechanism of phototransformations becomes an extremely difficult task. Nonetheless, the PSCL phenomenon was described for complex systems too.

PSCL of certain high-boiling oil fractions was observed.⁸⁷ Aerated samples (at 77 K) were irradiated in different spectral ranges for different exposure times. Emission was registered in the course of sample heating from 77 to 550 K . Several temperature zones in which light was emitted in a range of 400 – 700 nm with peaks at 520 – 550 nm were revealed.

PSCL of aerated aqueous solutions of humic acids, both natural and synthetic, was studied.^{88,89} A relationship was established between the observed CL and the photooxidation process, CL and fluorescence spectra were recorded and their changes with the photolysis time were revealed. Presumably, the photodecomposition products are the CL emitters in this process; moreover, the energy is transferred from primarily excited species to chromophores in the polymer, which become the emitters of light.

PSCL of bis(2,4,6-trichlorophenyl) oxalate (**30**) observed upon mixing of its photolysed aerated solution in isopropyl alcohol with an unirradiated solution of anthracene (or some other polyaromatic fluorophore) was described.⁹⁰ It should be noted that a mixture of diaryl oxalates with fluorophores enters into the composition of commercial light sources in which the glow is 'triggered' by the addition of H_2O_2 solutions. However, in this case, the PSCL effect is caused by reasons other than the photosynthetic formation of hydrogen peroxide.



Chemiluminescence that arises upon mixing of a UV-photolysed aerated solution of psoralene (**31**) with a solution of FeSO_4 in a Tris buffer (pH 7.4) was described,⁹¹ however, the mechanism of this phenomenon was not considered in detail.

In closing this Section, it should be noted that characteristic feature of photosensitised chemiluminescence is the photooxidation in the presence of molecular oxygen, chemical transformations of the reaction products being accompanied by chemiluminescence.

III. Photochemical synthesis of chemiluminescent reagents

In the definition of light-created chemiluminescence systems given in the Introduction, attention was paid only to the order in which the stages of illumination and CL observation occur. The time factor (*i.e.*, the interval between these stages) was ignored. In the PSCL processes discussed above, the chemiluminophores formed, *viz.*, hydroperoxides and 1,2-dioxetanes, were characterised by relatively short lifetimes. However, sufficiently stable chemiluminophores are known to be formed photochemically. These can be both peroxides (particularly, 1,2-dioxetanes) and other classes of chemical compounds. The photochemical method can also afford reactants that, being added to solutions of chemiluminophores, induce chemiluminescence.

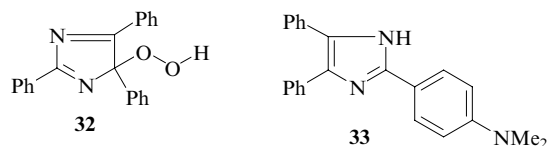
1. Chemiluminophores obtained by photochemical methods

a. Lophine peroxide

Lophine hydroperoxide (4-hydroperoxy-2,4,5-triphenylimidazole, **32**) was synthesised in 1964 upon illumination of a lophine solution in chloroform (18°C) in the presence of Methylene Blue and oxygen in 68% yield.⁹²

It was assumed earlier⁹³ that this compound is an intermediate in the chemiluminescence reaction of lophine with oxygen in an alkaline medium. It was proved that the reaction product is hydroperoxide rather than lophine endoperoxide. Chemiluminescence of peroxide **32** was observed in the thermolysis ($T > 110^\circ\text{C}$) and also under the action of bases in the absence of oxidants.

An unusual effect of light on a chemiluminescence system was observed.⁹⁴ Gradual decay of chemiluminescence during the oxidation of 2-(*p*-dimethylaminophenyl)-4,5-diphenylimidazole (**33**) with molecular oxygen was observed; however, the illumination of the partly reacted mixture restored the glow up to its original level.

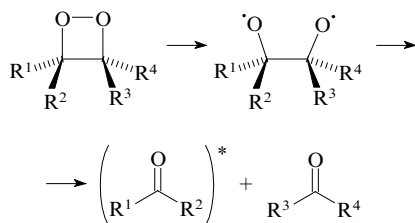


According to one of explanations of this effect, the dark transformation pathway of compound **33** involves the formation of an inactive dimer, which decomposes in the light to the starting imidazole and its peroxide derivative.

b. 1,2-Dioxetanes

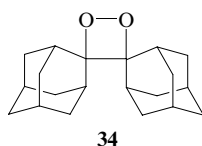
1,2-Dioxetanes are four-membered cyclic peroxides, which attract great interest as chemiluminophores. Chemistry, mechanisms and applications of CL of these compounds are documented in surveys^{43,95,96} and books.^{97,98}

Unimolecular decomposition of 1,2-dioxethane into two carbonyl compounds proceeds *via* a biradical and is accompanied by liberation of energy of about 290 kJ mol^{-1} . This energy (even ignoring the activation energy) is sufficient for the excitation of one of the products.

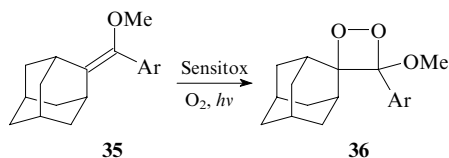


$R^1 - R^4 = \text{Alk.}$

The addition of photochemically generated singlet oxygen to the C=C bond of a precursor molecule is a convenient method for the synthesis of 1,2-dioxethanes.^{99–107} It is this method that was used in the synthesis of the first dioxetane (**34**)^{99,100} stable under normal conditions from adamantylideneadamantane. Its yield depended on the sensitizer and solvent used. Improper combination of the latter resulted in a dramatic increase in the yield of side epoxide.¹⁰¹ Other limitations for the photochemical synthesis of 1,2-dioxethanes are also known.¹⁰⁷



Photooxygenation of alkene **35** in CH_2Cl_2 employed polymer-bound Rose Bengal (Sensitox),¹⁰² which facilitated the separation of the sensitizer from the product. Irradiation of the solution (15–30 min), removal of the sensitizer and evaporation of the solvent afforded the product, dioxetane **36**.



The earlier version of this reaction employed a heterogeneous photogenerator of singlet oxygen.¹⁰³

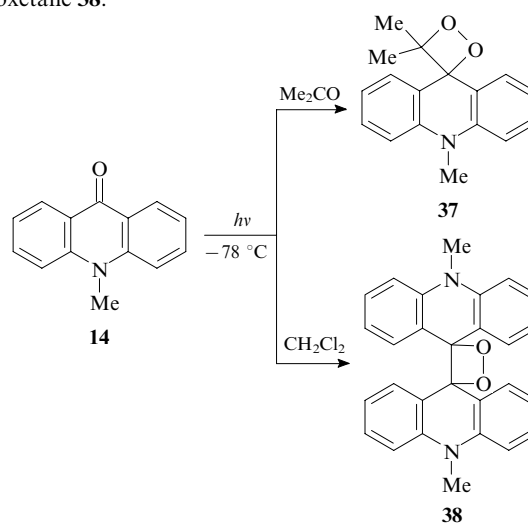
The kinetic stability of dioxetane **36** under normal conditions is due to the high activation barrier to its decomposition. Thermolysis of this compound is accompanied by CL. Chemical excitation of dioxetane **36** is characterised by a high (up to 60%!) yield of triplet carbonyl compounds. The yield of products in the excited singlet state is lower by a factor of 10–1000. Efficient population of the triplet term is attributed to the fact that, according to the Hund rule, this is the lower term in the intermediate biradical (the transition state in the decomposition).⁸⁰

The presence of electron-donating groups in the dioxetane molecule favours partial population of the antibonding π^* -orbital of the O–O bond. This dramatically decreases the activation barrier to decomposition so that this can begin even at ambient

temperature. The decomposition process can be controlled by introducing an electron-withdrawing group into the composition of the aromatic substituent of compound **36**. The interaction of this group with a special reagent (trigger) resulted in the transformation of the starting molecule into *m*-methoxycarbonylphenolate anion, partial electron transfer to the π^* -orbital of the O–O bond and decomposition of the dioxetane (Scheme 5, pathway *a*).

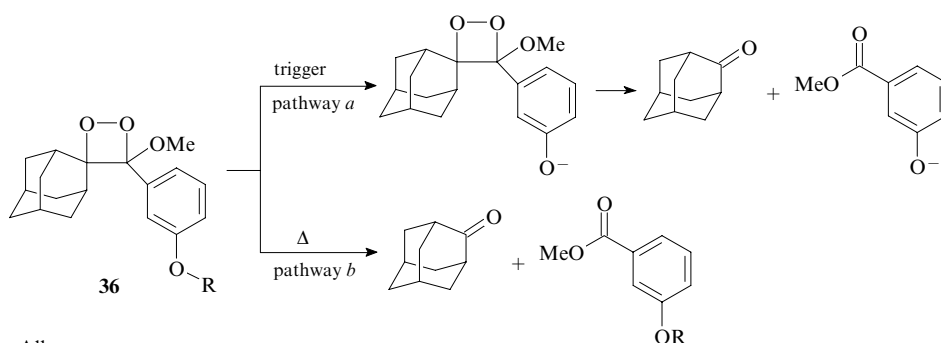
The thermal (pathway *b*) and the electron-transfer-initiated mechanisms of decomposition of compound **36** were studied.^{108,109} It was found that in the thermal process, the triplet states $^3(n\pi^*)$ of adamantan-2-one and $^3(\pi\pi^*)$ of methyl *m*-alkoxybenzoate are excited in similar quantum yields (~ 0.1) and the singlet state $^1(n\pi^*)$ of adamantan-2-one is excited in an insignificant yield. In the electron-transfer-initiated decomposition of dioxetane, only the singlet state $^1(\pi\pi^*)$ of the corresponding phenolate anion is excited. Such a striking difference points to the fundamental difference in the mechanisms of the decomposition and chemical excitation in the thermolysis, on the one hand, and the process initiated by the electron transfer, on the other hand (see Scheme 5).

The photochemical synthesis of 1,2-dioxetane can be carried out by a different route, namely, by the total reversal of the chemical excitation process. Irradiation of an acetone solution of *N*-methylacridone (**14**) with light from a high-pressure mercury lamp in an argon atmosphere at -78°C afforded a cycloaddition product, 1,2-dioxetane **37**,¹¹⁰ while irradiation of a solution of compound **14** in CH_2Cl_2 under the same conditions led to 1,2-dioxetane **38**.



Thermolysis of dioxetane **37** gave rise to CL the spectrum of which coincided with the fluorescence spectrum of compound **14** in acetone ($\lambda_{\text{max}} = 525 \text{ nm}$), the CL quantum yield reached 10^{-6} . Unfortunately, the preliminary communication¹¹⁰ was not followed by more detailed investigations. At the same time, it is

Scheme 5



$R = \text{Alk.}$

known that *N*-methylacridone (**14**) exhibits $\pi\pi^*$ -phosphorescence with a well resolved vibrational structure.⁸⁵ Hence, it would be interesting to obtain its complete CL spectrum.

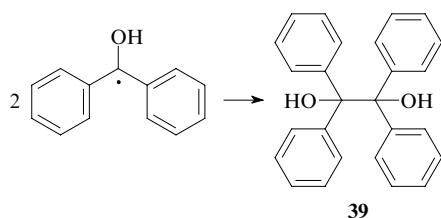
Photochemical synthesis of dioxetanes has found its application not only in preparative chemistry, but also in the on-line kinetic analysis of samples.¹¹¹

c. Pinacols

UV irradiation ($\lambda > 320$ nm) of an acetone solution of acridone **14** in an argon atmosphere at room temperature (*i.e.*, under the conditions where dioxetanes **37** and **38** decompose) affords products that require the combined action of an oxidant (*e.g.*, oxygen) and a strong base for their chemiluminescence to be initiated.⁷⁴ These products are pinacols (1,2-glycols).

The synthesis of different chemiluminophores under UV irradiation of the corresponding carbonyl-containing polyaromatic hydrocarbons was described.⁷⁴ The similarity of conditions of the photochemical treatment of these compounds did not guarantee the formation of the same chemical class of products: the starting substances belong to substantially different spectral-luminescent classes and, hence, possess different photochemical properties.

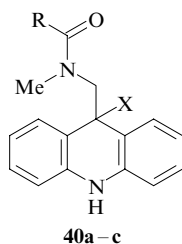
Pinacols are the products of photoreduction of many aromatic carbonyl compounds. For example, dimerisation of radical products of benzophenone photoreduction yields benzopinacol (**39**).



The dimerisation constant of neutral ketyl radicals is 10^{10} – 10^{13} litre mol⁻¹. Just as each dioxetane molecule can be said to 'harbour a photon',⁹⁷ each molecule of certain pinacols can be said to contain two radicals. This is explained by the fact that in strongly alkaline media pinacols lose their stability and undergo dismutation *via* ketyl radicals and radical anions.¹¹² The radical processes are frequently accompanied by chemiluminescence. The acidity of pinacols ($pK_a \approx 14$) is substantially lower as compared with ketyl radicals;¹¹³ hence, initiation of radical reactions involving pinacols requires a strongly alkaline medium. It is assumed that photochemically generated pinacols play the role of important intermediates in the chemiluminescence of photolysed solutions of aromatic carbonyl compounds. In the presence of oxidants, pinacols can become dioxetane precursors.

d. Acridans

The first members of a new family of chemiluminescent reactants, namely, dihydroacridines (acridans) **40a**, were prepared by the photolysis of deaerated solutions of acridine in DMF (for R = H) or dimethylacetamide (for R = Me).¹¹⁴ In solutions of acridans **40a**, the quantum yield of chemiluminescence initiated by strong bases (NaH, Bu^tOK, MeONa) in the presence of O₂ reaches 0.006.



R = H, Me; X = H (**a**), OH (**b**), CH₂Ph (**c**).

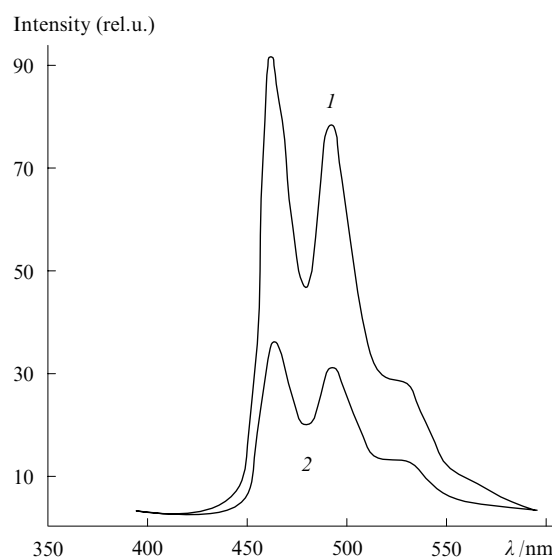
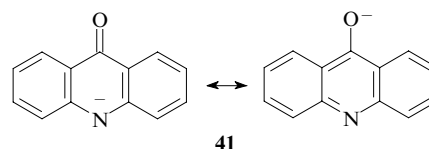


Figure 2. Fluorescence spectrum of anion **41** (1) and CL spectrum of compound **40a** (2).

The acridone anion (**41**) is the emitter of radiation. Figure 2 shows the CL spectrum of compound **40a** (curve 2) and the fluorescence spectrum of anion **41** (curve 1), which have similar patterns.



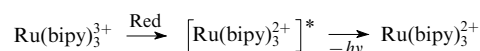
γ -Radiolysis produces¹¹⁵ acridans **40b,c** and their *N*-methyl derivatives. The quantum yield of CL of acridans **40b** (R = H or Me) exceeds 0.01.

It is known that oxidation of 9-methylacridine with molecular oxygen in DMF in the presence of Bu^tOK is accompanied by chemiluminescence.¹¹⁶ Here, acridone anion served as the emitter. This brings up the question: would this be a chemiluminescence reaction if solutions of 9-methylacridine were prepared in darkness thus excluding the possibility of chemiluminophore photogeneration?

e. Ruthenium complexes

The bipyridyl complex of Ru(III) is a bright example of chemiluminophores based on metal complexes.^{117–119}

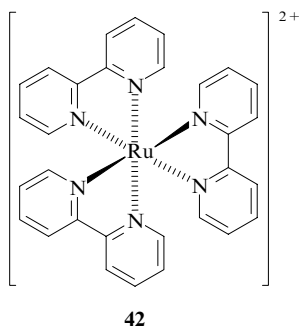
Chemical excitation of ruthenium cation occurs in the reaction of Ru(III) bipyridyl complex with a reducing agent (Red) with the standard redox potential < 0.86 V.



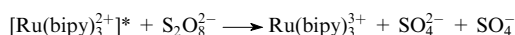
bipy is 2,2'-bipyridyl.

Complex Ru(bipy)₃²⁺ (**42**) is sufficiently stable (it withstands boiling in concentrated HCl or 50% NaOH solutions) and chemically inert, whereas Ru(bipy)₃³⁺ is chemically reactive.¹¹⁹

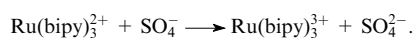
For the chemiluminescence analysis, Ru(bipy)₃³⁺ was synthesised from cation **42** by different methods,¹²⁰ *e.g.*, by the photochemical activation of Ru(bipy)₃²⁺ oxidation with peroxydisulfate ions.¹²¹ Optical absorption of the [Ru(bipy)₃³⁺] complex at the 450 nm band ($\epsilon = 14600$) results in the population, with the quantum yield equal to 1, of the excited state [Ru(bipy)₃²⁺]^{*}



(lifetime $\sim 0.6 \mu\text{s}$). In the excited state, the complex acquires reductive properties and is oxidised by the $\text{S}_2\text{O}_8^{2-}$ ion.



The SO_4^- ion formed oxidises the ground-state $\text{Ru}(\text{bipy})_3^{2+}$ complex.



As a result, the quantum yield of the formation of $\text{Ru}(\text{bipy})_3^{3+}$ complex is equal to 2.

A flow photochemical synthesis of $\text{Ru}(\text{bipy})_3^{3+}$ ions was used for the chemiluminescence detection of certain compounds.^{122–124} In those cases where the compound to be analysed was a weak reducing agent, it was proposed to subject it to photochemical decomposition into the fragments capable of reducing the metal ion in the metal-complex chemiluminophore, thus triggering the CL.¹²⁵

2. Photoactivation of substrates

Illumination of solutions containing chemiluminescent substrates and an oxidant in the spectral region of the oxidant absorption band results in the formation of active forms of the oxidant, which are capable of exciting the CL of an appropriate chemiluminophore. Thus mixing of a UV-irradiated solution of potassium nitrate with an unirradiated solution of luminol induced excitation of chemiluminescence of luminol.¹²⁶ The nitrate ion has two absorption bands in the UV range at 202 ($\epsilon = 9500$) and 304 nm ($\epsilon = 7$). Chemiluminescence of luminol arises only upon irradiation of the nitrate solution in the region of the first absorption band. The luminol oxidation and the excitation of its CL were attributed to the action of peroxyxynitrite (ONOO^-), which is formed from nitrate (NO_3^-) as a result of intramolecular rearrangement upon excitation. In contrast to nitrate, peroxyxynitrite is a strong oxidant capable of initiating the chemiluminescence oxidation of luminol.^{127–130} The resulting photochemically produced peroxyxynitrite is a structural isomer of the original anion. The reverse reaction¹³¹ will be discussed in the next Section.

The chemiluminescence reaction of luminol with a photoactivated reactant was used for the determination of nitrates in water.^{126, 132} Complex chemiluminescence reactions of photoactivated ClO_2 and SO_2 molecules in a mixture of perchloric and sulfuric acids were also described.¹³³

* * *

Coupling the procedures of the photochemical synthesis of chemiluminophores and their observation would provide a 'complete' system in which the external effect of light on the reaction mixture gives rise to chemiluminescence. Hence, the above-described examples of the preparation of lophin peroxide from lophin and of dioxetane from alkene in the presence of sensitizers and dissolved oxygen may be considered in the Section devoted to PSCL. However, this is not true for those cases where either the illumination stage requires the use of deoxygenated solutions or the reactions occur independently of the presence of oxygen. The primary photoprocesses (in addition to photooxidation) can include photoreduction, photoaddition and photoisomerisation,

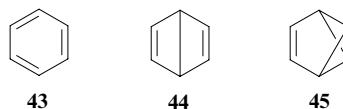
which substantially increase the number of photochemical processes that occur in light-created chemiluminescence systems.

IV. Photoinduced chemiluminescence

In the periods of energy crises, the idea of using solar energy gains a new impetus. Active studies on both the conversion of solar energy into electricity and the storage of solar energy as the internal energy of photochemical reaction products, *i.e.*, H_2O_2 (Ref. 134) or structural isomers of different compounds,¹³⁵ are initiated. Studies in the latter field have also stimulated the investigation of the reverse process, *viz.*, the conversion of the internal energy of photoproducts into electronic excitation and further into light emission.

1. Photoisomers

The structural formula of a C_6H_6 molecule can be represented as three valence (or structural) isomers, namely, benzene (**43**), Dewar benzene (**44**) and benzvalene (**45**). Structures **44** and **45** were detected in the phototransformation products of isomer **43**.

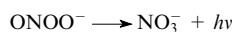


The enthalpy of formation of structure **44** exceeds that of benzene by 251 kJ mol^{-1} . The isomerisation reaction $\text{44} \rightarrow \text{43}$ has an activation energy of $\sim 96 \text{ kJ mol}^{-1}$; hence, $\sim 347 \text{ kJ mol}^{-1}$ is liberated in the elementary act of molecule rearrangement. This is comparable with the energy of the triplet state of structure **43** (355 kJ mol^{-1}) but smaller than the energy of its excited singlet state (481 kJ mol^{-1}). One can expect such isomerisation to be accompanied by chemical excitation of benzene into the triplet state ($^3\text{43}$). This process was studied.¹³⁶ Insofar as under experimental conditions (solution at ambient temperature) state $^3\text{43}$ is non-radiative, its detection involves the use of the triplet–singlet transfer of energy from species $^3\text{43}$ to the singlet fluorophore, namely, 9,10-dibromoanthracene (DBA), with the energy of 310 kJ mol^{-1} . Such a transfer of energy is spin forbidden; however, this prohibition is lifted due to the presence of a heavy atom (Br). The triplet–singlet transfer of energy to DBA is fairly efficient. The reaction $\text{44} \rightarrow \text{43}$, which occurs on heating of a solution in the presence of DBA is accompanied by chemiluminescence with the spectrum typical of DBA fluorescence. The efficiency of chemical excitation in the reaction $\text{44} \rightarrow ^3\text{43}$ is $\sim 2 \times 10^{-4}$; in the case of 1,4-dichlorobenzene, it is equal to $\sim 10^{-3}$.

Thus, it was discovered¹³⁶ that the energy stored in a molecule can be converted into the energy of electronic excitation and, under suitable conditions, into light emission. Later, this was demonstrated by the example of thermal isomerisation of Dewar acetophenone,¹³⁷ 3,3'-bis(cyclopropenyl) and Dewar xylenes.¹³⁸

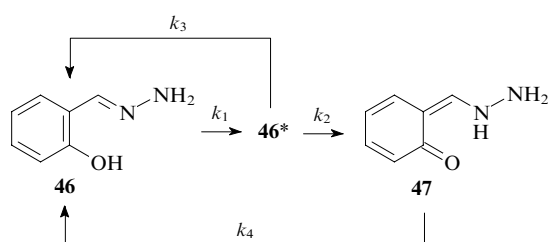
Reaction $\text{45} \rightarrow \text{43}$ is not accompanied by CL,¹³⁹ although its elementary act liberates more energy than the isomerisation $\text{44} \rightarrow \text{43}$ discussed above. In the former case, the total energy is converted into heat. This is caused by the great difference in the configurations of structures $^3\text{43}$ and **45**. In the reaction $\text{45} \rightarrow \text{43}$, the nuclei in the molecular core should travel considerable distances, which is accompanied by excitation of vibrational modes and dissipation of energy. For $\text{44} \rightarrow \text{43}$, the configurations of species **44** and $^3\text{43}$ are virtually identical ('gable roof'), hence, the core restructuring is minimum.

As was already mentioned (see Section III.2), peroxyxynitrite can be considered as a photoisomer of nitrate. It was shown¹³¹ that spontaneous isomerisation of peroxyxynitrite to nitrate is accompanied by CL with a quantum yield of $\sim 10^{-9}$. In this case, the quantum yield of chemical excitation of the emitter (peroxyxynitrite) reaches a very high value (0.2).



Structural isomerisation also occurs upon the intramolecular phototransfer of a proton or a hydrogen atom. In this case, the stored energy is small; however, if the reactivity of the isomer formed substantially exceeds that of the original isomer, the former can undergo reactions hindered for the original reactant.

It was shown¹⁴⁰ that chemiluminescence appears in the reaction of salicylaldehyde hydrazone (**46**) with a base if the aqueous solution of hydrazone **46** was pre-irradiated with visible light (400–540 nm) with an intensity of merely several milliwatt per square metre. The illumination results in isomerisation of inactive benzenoid form **46** into active quinonoid form **47**. The kinetic scheme of photoinduced formation of isomer **47** can be presented as follows:

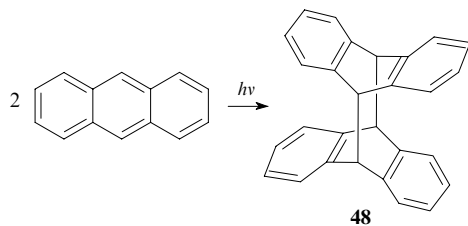


Here, k_1 is the formal constant of photoexcitation of hydrazone **46**, which is proportional to the light intensity (the optical density of solutions is far below 1); k_2 is the rate constant for the transformation of the excited molecule **46*** into the product; k_3 is the rate constant that takes into account all possible processes of degradation of the excited state **46*** that do not lead to compound **47**; k_4 is the rate constant for reaction **47** → **46** [at ambient temperature, $k_4 = (6 \pm 3) \times 10^{-4} \text{ s}^{-1}$]. The height of the energy barrier for the transition **47** → **46** is 18 kJ mol⁻¹. In the stationary illumination, the concentration of isomer **47** gradually reached a steady-state value, which is independent of the light intensity and temperature and increases upon the substitution of D₂O for H₂O.

Reactions of a base with both isomers (**46** and **47**) are exothermic and their final product is, probably, the hydrazone anion. However, the enthalpy of formation of isomer **47** exceeds that of isomer **46** by 130 kJ mol⁻¹; hence, the liberated energy is sufficient for the excitation of the reaction product of the base with the former isomer and too low for the latter isomer. This is why chemiluminescence accompanies only the reaction of the base with compound **47** and is not observed in the reaction with hydrazone **46**.

2. Photodimers

Photodimerisation of anthracene is the first photochemical reaction studied. In 1867, Fritzsche observed the formation of an insoluble substance ‘paraphoten’ (sited according to Ref. 141), *i.e.*, dimer **48**, in a sunlight-exposed benzene solution of anthracene. Its melting produced anthracene.



As was found later,¹³⁵ this reaction involves accumulation of energy.

Synthesis of various cyclodimers of anthracene and benzene, particularly, [4π + 4π] heterodimer **49**, was described and their transformations were studied.^{142, 143}

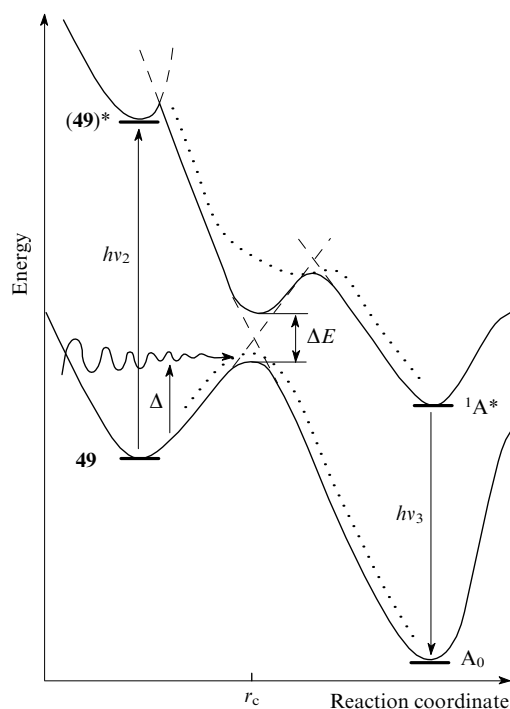
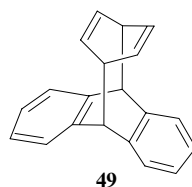
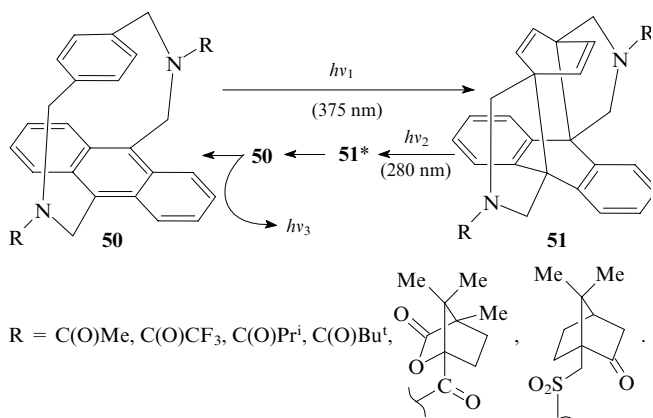


Figure 3. Cross-sections of the potential energy surface along the reaction coordinate at the thermolysis and the light-induced decomposition of heterodimer **49**.^{142, 143} A_0 , $^1A^*$ are ground and excited singlet states of anthracene, r_c is the critical point.

It was shown that the thermal decomposition of heterodimer **49** is a dark reaction, whereas its light-induced decomposition is accompanied by CL with the efficiency of chemical excitation of singlet anthracene of ~0.9! A scheme of energy levels in Fig. 3 shows that in the vicinity of the pericyclic minimum, the greatest part of energy of the absorbed photon is already consumed in reaction,¹⁴⁴ because the formation of a chemiluminescence photon consumes the chemical energy liberated in the decomposition of the heterodimer. Hence, in this case, the reason for the light emission is indeed chemiluminescence.

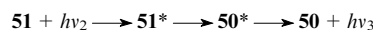


Synthesis of compounds containing photocyclisable aromatic fragments (*e.g.*, benzene and anthracene) linked with bridges,



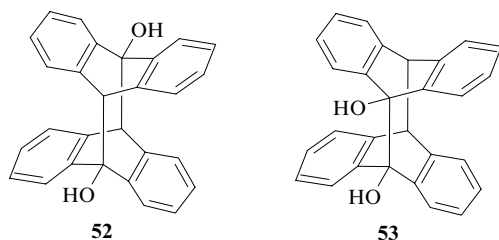
which makes them more flexible, was described.^{145,146} This allowed the whole sequence of transformations, *viz.*, cyclisation under illumination at 375 nm, recyclisation under illumination at 280 nm, chemical excitation and CL of the product, to be observed.

The introduction of substituents R into the bridge changes the distance between the planes of the benzene and anthracene fragments, which makes it possible to control the potential energy surface along the reaction route. The cross-section of the potential energy surface along the reaction route



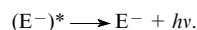
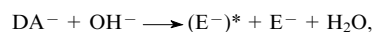
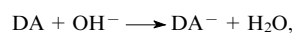
can also be represented by curves similar to those in Fig. 3 (the ground and excited states of molecule **50** correspond to species **49**, while those of molecule **51** correspond to anthracene).

The prohibition for the formation of excited products in the thermal reaction of photodimer decomposition can be substantially reduced (and even eliminated) if the reaction involves ionisation of molecules. It was shown^{147,148} that the base-induced decomposition of anthrol photodimers **52** ('head-to-tail') and **53** ('head-to-head') is accompanied by CL with a spectrum similar to the fluorescence spectrum of the anthrol anion.



Earlier, chemiluminescence of photolysed solutions of anthrol was associated exclusively with CL of its peroxy derivatives.¹⁴⁹ The anthrol photolysis products were isolated by high-performance thin layer chromatography (HPTLC).¹⁴⁸ The R_f value of the substance that exhibits CL activity in the reaction with the base differs from the R_f of the peroxide, which was determined in its colour reaction with iodine. Reversed-phase HPTLC allowed better resolution of these bands. Chemiluminescence was observed for both the photodimer and peroxides, but the CL intensity of the photodimer proved to be more than 10 times higher.

Upon deprotonation, both hydroxyl groups in anthrol photodimers **52** and **53** (DA) decompose to two anthrol anions (E^-). Taking into account that the formation of two anthracene molecules with conjugated bond systems involves liberation of considerable energy, the DA decomposition product can exist in the electronically excited state



In an ethanolic extract of dry *Hypericum perforatum* (St-John's wort), which can produce and accumulate various anthracene derivatives, a compound identical to the anthrol photodimer was detected using HPLC coupled with CL detection.

V. Analytical applications

Chemiluminescence analysis attracts steady interest among biologists and physicians and promises to become a routine test in many biological and medical laboratories.

The advances of nanotechnologies that employ 10–100-nm metal particles with 'extraordinary' properties as the transducers and amplifiers of fluorescence and CL open up new possibilities.^{150,151} In light-created chemiluminescence systems, light plays the role of a cheap, available and convenient reactant.

Photosensitised CL of various chemiluminophores was employed for the assessment of the activity of superoxide dismutase and the antioxidant effect of different substances^{33–39,41,42,59,63–70} and also in the chemiluminescence immunoassay.³² Based on the detection of chemiluminescence that accompanies photooxidation, a new method of assessment of the state of rarities and historical objects and materials was proposed.^{152,153} A method for studying photostability of polymers has been developed.^{154–158}

Photochemical synthesis of dioxethanes and their use in the on-line kinetic analysis of alkenes were described.¹¹¹

A highly selective ozone sensor was obtained by the photochemical modification of 4,5-dihydroxynaphthalene-2,7-disulfonic acid (chromotropic acid).¹⁵⁹

Light-induced chemiluminescence systems were proposed for analysis of polyaromatic hydrocarbons,⁷⁴ pharmaceuticals^{125,160,161} and pesticides.¹²³

VI. Conclusion

Based on the material presented in this review, it follows that the problem of classification of light-created chemiluminescence systems is solved as soon as the mechanism of the light effect becomes clear.

Classification of 'parental' photochemical mechanisms already exists. Nowadays, in light-created chemiluminescence systems, the 'parental' mechanisms are represented by various kinds and types of photooxidation, structural photoisomerisation, phototransfer of protons (hydrogen atoms) and photodimerisation.

Any other classification unrelated to the mechanism of the chemical effect of light would be arbitrary, *e.g.*, a classification based on the differences in the CL kinetics. The authors who proposed a new term 'photostorage CL',¹¹⁴ distinguished this phenomenon from the others by the fact that the former does not exhibit any afterglow decay upon the effect of light but requires to be initiated by a base. We assume this difference insignificant. Indeed, if we change the experimental conditions, namely, add the base to solution beforehand and use pulse light, then the CL kinetics will take the form of afterglow decay.

One cannot but state the similarity in the response of different scientists to their first encounter with light-created chemiluminescence systems. First, this is bewilderment caused by the lack of understanding of the reasons for the scatter of experimental results on CL reactions, then, astonishment when one becomes aware that solutions prepared or stored for a long time in darkness do not provide a chemiluminescence reaction. Moreover, the efficiency of common laboratory illumination seems strange.

However, photochemical activity of ordinary illumination should not surprise. In the ordinary illumination, more than 10^{13} photons pass through an area of 1 cm² per second, which is 10^9 times greater than the detection limit of laboratory chemiluminometers; hence, the formed gap can be occupied by numerous chemical systems for which the multiplied efficiencies of absorption, photochemical transformation and chemiluminescence of the product are no less than 10^{-9} .

After the discovery of the key role of oxygen in luminescence and photochemical reactions, the scientists became very much aware of the presence of dissolved oxygen. Now that a sufficiently large number of chemiluminescence systems have been studied, it is time to become aware of the role of illumination conditions during the preparation of solutions and reaction mixtures.

This work has been written with the financial support from the Russian Foundation for Basic Research (Project No. 05-03-32730) and the Division of Chemistry and Materials Sciences of the Russian Academy of Sciences (Programme No. 1, 2004–2006).

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^a — *Dokl. Chem. (Engl. Transl.)*

^b — *Mol. Biol. (Engl. Transl.)*

^c — *Biophysics (Engl. Transl.)*

^d — *Chem. Phys. Rep. (Engl. Transl.)*

^e — *Russ. Chem. Bull., Int. Ed. (Engl. Transl.)*

^f — *High Energ. Chem. (Engl. Transl.)*

^g — *Russ. J. Phys. Chem. (Engl. Transl.)*

^h — *Biochemistry (Moscow) (Engl. Transl.)*

ⁱ — *Kinet. Catal. (Engl. Transl.)*

^j — *J. Anal. Chem. (Engl. Transl.)*

Application of metal – carbon catalysts in conversions of lower aliphatic alcohols[†]

M A Ryashentseva, E V Egorova, A I Trusov, E R Nougmanov, S N Antonyuk

Contents

I. Introduction	1003
II. Carbon materials and their application in heterogeneous catalysis	1004
III. Conversions of lower alcohols on metal – carbon catalysts	1007
IV. Conclusion	1012

Abstract. Various carbon materials including carbon nanotubes and graphitised nanofibres used as supports in heterogeneous catalysis are considered. The methods for modification of catalysts and the results obtained as applied to three important processes of organic synthesis, viz., conversions of methanol into methyl formate, of ethanol into acetaldehyde and of isopropyl alcohol into acetone, are analysed. The bibliography includes 117 references.

I. Introduction

Design of syntheses of various classes of organic compounds from non-oil raw materials is one of the major trends in the progress in chemical industry. The use of the so-called one-carbon compounds, such as carbon monoxide, carbon dioxide, methanol and methane, in organic synthesis is becoming increasingly topical. The production of essential organic compounds from coal is a reasonable alternative to their manufacture from oil and natural gas.

In 2000, the world production of methanol amounted to 39 752 000 tons;¹ in the first quarter of 2004, methanol production in Russia was 798 000 tons. Methanol is used as starting material in the synthesis of many chemical compounds, *e.g.*, formaldehyde, acetic acid, ethylene glycol, *etc.* Synthesis of methyl formate, an important intermediate in many processes of the industrial organic synthesis, is yet another promising route of methanol conversion. The greater part of methyl formate (its annual world production amounts to ~160 000 tons)² is utilised for the manufacture of formic acid,^{3,4} which is used as a preservative in agriculture. Methyl formate is also processed into formamides⁵ and *N*-formylmorpholine; it is used as a solvent for fats, fatty acids, acetylcellulose and as an insecticide.⁶ Besides, it can be used in the production of high-purity carbon monoxide, dimethyl

carbonate, diphosgene and methyl glycolate⁷ and employed instead of synthesis gas in carbonylation and alkoxycarbonylation of alkenes.

Traditionally, methyl formate is prepared by carbonylation of methanol in the presence of alkali metal alcoxides.^{2,8} However, purification of starting materials demands considerable investment and is efficient only in the case of large-scale production. However, methyl formate conversion products are mostly utilised in low-tonnage chemistry; therefore, establishing small-scale plants in close proximity of potential consumers is currently rather topical. Dehydrogenation of methanol,⁹ which does not require the use of high pressures and is rather insensitive to impurities present in the feed stock, is underway on a large scale. Ethanol, yet another industrial intermediate for organic synthesis, has recently become very popular. There are environmentally safe technologies for its production from organic wastes and biomass which are based on the use of microbial enzymes.¹⁰ At present, the world production of ethanol amounts to 40 milliard litres per year and, according to prognoses, will increase in future.¹¹ Catalytic dehydrogenation of ethanol into acetaldehyde, a valuable intermediate in the synthesis of a broad range of compounds, is one of directions of ethanol processing. This method has a number of advantages, *e.g.*, lack of toxic waste products, relatively mild reaction conditions and production of hydrogen in addition to acetaldehyde, which can further be utilised in other processes.

Isopropyl alcohol, another representative of low-molecular-mass alcohols, is used in production of acetone without formation of side products.

As is known, organisation of a profitable chemical production is only possible with highly active and highly selective catalysts. A search for novel supports, which have a great influence on the structure and properties of catalysts, is an essential step in the development of efficient catalytic systems. The use of novel carbon materials with fibrous-tubular structure and carbon – carbon composites holds great promise.

This review deals with various aspects of the development of efficient low-percentage (with respect to a metal) metal – carbon catalysts, including the methods used for their preparation, modification and activation and choice of optimum conditions for dehydrogenation of lower aliphatic alcohols (C₁ – C₃) leading to the corresponding ester, aldehyde and ketone.

M A Ryashentseva N D Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky prosp. 47, 119991 Moscow, Russian Federation. Fax (7-495) 135 53 28, tel. (7-495) 137 65 18, e-mail: ryashentseva@comail.ru

E V Egorova, A I Trusov, E R Nougmanov, S N Antonyuk
M V Lomonosov State Academy of Fine Chemical Technology, prosp. Vernadskogo 86, 117571 Moscow, Russian Federation. Fax (7-495) 434 87 11, tel. (7-495) 246 48 23, e-mail: nhsigt@mitht.ru (E V Egorova, A I Trusov, E R Nougmanov), antonyuk@mitht.ru (S N Antonyuk)

Received 30 August 2006

Uspekhi Khimii 75 (11) 1119–1132 (2006); translated by R L Birnova

[†] Dedicated to Academician O M Nefedov on occasion of his 75th birthday.

II. Carbon materials and their application in heterogeneous catalysis

1. Preparation and properties of various carbon materials

Carbon materials have long been used in heterogeneous catalysis as both catalysts themselves and supports for active components. These materials possess a number of valuable properties, *e.g.*, controlled specific surface and adsorption capacity, high thermal and chemical stability, high mechanical strength, long service life, *etc.*¹² In 1998, about 70 industrial chemical catalytic processes were run on carbon supports.¹³

At present, a vast array of novel carbon materials¹⁴ [carbon fibres,^{15–17} graphite intercalates, fullerenes, carbyne-like compounds (carbolites), nanocarbon structures, pyrocarbons, carbon–carbon composites, *etc.*] are employed along with traditional carbon supports (activated carbons, graphite and soot).^{13, 14, 17, 18} These novel materials differ from the traditional supports in low content of mineral admixtures, which is especially important for the preparation of catalytic systems. Their advantages include high resistance to acidic and basic media and high temperatures, controllable porosity. The production technologies of many novel carbon materials enable the preparation of diverse forms, *e.g.*, granules, tissues, honeycomb structures, *etc.*, which significantly facilitates the design and optimisation of reaction units employed in production of many valuable components of organic synthesis. The use of carbon supports allows regeneration of active components of catalysts, which is especially important if the active component is a precious metal.^{13, 15} However, the range of commercial porous carbon materials as candidate supports for catalysts is rather narrow. Commercial catalysts are still manufactured on the basis of activated carbons prepared from coal or vegetal stuff.

a. Activated carbons

Activated carbons (AC) are prepared by pyrolysis of carbon-containing materials, *e.g.*, wood, peat, coal and petroleum products. These materials possess a well-developed porous structure, but their microporous structure is not always optimum for the support of catalysts. Besides, the shape and size of activated carbon granules do not always meet the requirements of catalytic processes. Other disadvantages include high content of mineral impurities and sulfur as well as low mechanical strength.¹⁷ Modern catalytic techniques demand carbon materials with large controllable pores and a definite combination of specific properties. These properties are manifested by a novel type of supports based on synthetic carbon–carbon composite materials.¹⁷

b. Carbon–carbon composite materials

Technical carbon is used as a starting material in the synthesis of porous carbon–carbon composites, which combine the advantages of activated carbons and graphite. Several methods for their preparation are known. For instance, technical carbon is mixed with a hydrocarbon binder; the resulting mass is compacted or granulated to obtain grains of definite shapes. The grains are then subject to thermal treatment in an inert or reducing medium, which results in carbonisation of the hydrocarbon component and formation of porous carbon, which binds technical carbon globules.¹⁷ An alternative approach, which was developed at the Institute of Catalysis of the Siberian Branch of the Russian Academy of Sciences, consists of several successive steps. The first of them includes preparation of matrices, which represent granules of spherical or more complicated shape, from technical carbon. This is followed by compaction of the matrices and deposition of carbon formed by pyrolysis of gaseous hydrocarbons.^{19–21} The porous carbon material thus prepared represents a globular system the primary morphological units of technical carbon in which are bound by pyrolytic carbon. Meso- and macroporous composites with low specific surfaces ($2–10 \text{ m}^2 \text{ g}^{-1}$) are formed in this step. The next step includes their activation by partial selective gasification. The texture and

other characteristics of porous materials are controlled by varying the nature and properties of technical carbon, degree of compaction of the matrix by pyrocarbon, degree of scorching of the composite mass in the course of its activation, the nature of the gasifying agent and activation conditions.^{22, 23} It is this approach that has been used in the preparation of a novel class of porous carbon–carbon composite materials for adsorption and catalysis, known under the name 'sibunit'.

The porous structures of such materials contain macro-, meso- and micropores. The volumes and sizes of meso- and macropores are controlled by varying the sizes of primary technical carbon globules, their reciprocal positions and the ratio of technical and pyrolytic carbons. The sizes of micropores and fine mesopores can be increased by steaming and oxygen treatment, which does not influence essentially the sizes of large pores.²⁴ Some characteristics of sibunit and activated carbons are given in Table 1.

Table 1. Some properties of porous carbon materials of the sibunit and activated carbon type.¹⁷

Parameter	Sibunits	Activated carbons
Specific surface area / $\text{m}^2 \text{ g}^{-1}$	2–800	600–1800
Total pore volume / $\text{cm}^3 \text{ g}^{-1}$	0.2–1.2	0.2–1.2
Micropore volume / $\text{cm}^3 \text{ g}^{-1}$	0.01–0.15	0.2–0.6
Mesopore volume / $\text{cm}^3 \text{ g}^{-1}$	0.2–0.8	0.1–0.3
Macropore volume / $\text{cm}^3 \text{ g}^{-1}$	0.1–0.7	0.1–1.0
Mean pore radius /nm	4–200	from < 1.5 to > 100
Ash content (mass %)	< 1	> 3
Crush strength / kg cm^{-2}	40–200	5–60

The technology of sibunit synthesis allows directed modification of its textural characteristics in the whole range required for the solution of specific problems of catalysis and adsorption.²⁵ Other advantages of these composites include reproducibility of their porous structure, high chemical purity, high mechanical strength, high activity and long operating life of catalysts based on them. These materials manifest high thermal stability; their chemical stability in oxidative media is much higher than that of activated carbons prepared from plants and coal.

Traditional carbon supports and sorbents are available only in the form of tablets, spherical granules or grains with diameter not exceeding 3–5 mm. At the same time, in some chemical processes the most efficient supports for catalysts have intricate geometrical shapes, *e.g.*, rings, straw, petals, microassemblies and honeycomb structures.²⁶ The use of sibunit as a support makes it possible to solve this problem.

c. Carbon fibre materials

A great number of recent publications and patents are devoted to carbon materials with fibrous-tubular structure. Carbon fibrous materials (*e.g.*, fibres, cords, felts, fabrics, yarns, cotton wool) are usually prepared by pyrolysis of polymeric fibres and fibrous articles with subsequent high-temperature treatment. After preliminary activation, these materials can be used as sorbents, ion-exchangers and supports for catalysts.^{27–29} Activated fibrous carbon materials not only possess large specific surface and high porosity, but also manifest high thermal and chemical stability. Modern technologies allow preparation of materials of various shapes, which significantly extends the possibilities of hardware implementation of technological processes.

Polyvinylchloride fibres, phenolic polymers, polyvinyl alcohol, polyacrylonitrile, hydrated cellulose, *etc.* are used as raw materials for the preparation of carbon fibres. Their properties including chemical stability depend largely on the choice of the starting polymer, conditions for its carbonisation and thermal treatment (activation) as well as by different additives.³⁰ For example, carbon fibres prepared from hydrated cellulose manifest

Table 2. Characteristics of carbon fibres prepared from polyacrylonitrile.³⁰

Parameter	Fibre	
	carbonised	graphitised
Density /g cm ⁻³	1.3–1.65	1.3–1.9
Specific surface area /m ² g ⁻¹	0.3–1000	0.15–3.0
Temperature coefficient of linear expansion, 10 ⁶ α /K ⁻¹	4	2
Specific heat capacity /kJ m ⁻¹ K ⁻¹	0.66	0.66
Thermal conductivity coefficient /W m ⁻¹ K ⁻¹	0.837–20.934	83.74–125.6
Electric resistance, 10 ⁵ ρ /Ω m	0.4–70	0.003–0.6
Sublimation temperature /°C	—	3600
Hygroscopicity (%)	0.1–10	1
Tensile strength /MPa	350–700	1200–3100
Modulus of elasticity /GPa	30–200	300–700

higher chemical stability than fibres prepared from polyacrylonitrile (PAN) under identical conditions. The main characteristics of carbon fibres prepared from PAN are listed in Table 2.³⁰

Carbon fibres based on hydrated cellulose are prepared in several steps:³¹ (1) processing of raw materials (fibres, fabrics or felts) to make them more resistant to oxygen; (2) drying at 25–150 °C to remove water, carbon oxides and carbonyl compounds from the surface of fibres; (3) heating and partial oxidation at 200–300 °C; (4) high-temperature treatment of fibres (depending on the temperature regime, this step results in carbonisation or graphitisation of fibres); (5) activation and dressing of the fibre surface.

The first step consists of removal of bound water. Dehydration in the second step yields fragments containing carbonyl groups and C=C bonds. The third step includes thermal cleavage of the C–C and C–O bonds, which yields H₂O and gaseous decomposition products (CO₂, CO, etc.). Carbonisation, which occurs in the fourth step, begins at 375–450 °C and is complete at 1200 °C. In the course of gasification, all atoms of the organic polymer (with the exception of carbon) are eliminated from carbon fibres which acquire a ribbon-like structure. Graphitisation requires higher temperatures and is complete at 2200–2800 °C. This step includes final thermolysis of the polymer and accumulation of aromatic fragments and is accompanied by an increase in the ordering of ribbon-like structures, elasticity modulus and electroconductivity of carbon fibres. And, finally, the fifth (activation) step is carried out in the presence of an oxidising agent (e.g., atmospheric oxygen, water steam, carbon dioxide) for 30–60 min at 600–900 °C to increase the specific surface of carbon fibres.

The activation of carbon fibres and carbon–carbon composites (sibunits), is accompanied by burnout of their amorphous components and formation of microporous structures.³² Further oxidation results in partial burnout of more ordered structures and formation of macropores. The chemical activity of carbon fibres depends on their structure, which is largely determined by conditions employed in this step and, to a lesser degree, by the nature of the starting polymer.³⁰ At present, about 90% of all carbon fibres based on polymers are used for the production of composite materials.³³ Carbon fibres are also used as components in heat-insulating materials and in medicine.^{34,35}

d. Carbon nanofibres and nanotubes

Carbon nanofibres (CNF) formed upon decomposition of gaseous hydrocarbons on the surface of metal components of catalysts are becoming increasingly popular nowadays. The process of their preparation begins with the formation of hydrogen-containing carbon deposits on the surface of metal particles. These deposits are dissolved in the metal and diffuse through it to

form a thin graphite layer on the opposite side of the metal particles.¹⁶ The catalysts used for the preparation of CNF usually contain iron, cobalt, nickel, chromium, vanadium, molybdenum or their alloys. The ability to dissolve carbon and/or to form carbides is the major requirement for such catalysts. This reaction is carried out at 700–1200 K; methane, CO, synthesis gas, acetylene and ethylene are used as the starting materials.^{16,36}

Considerable attention is given to elucidation of mechanisms of formation and morphological characteristics of carbon nanofibres.³⁷ It was established³⁸ that carbon fibres prepared from a mixture of carbon oxides with methane on a nickel catalyst consist of single fibres with a diameter 2000–3000 nm which contain nickel microinclusions. These experiments were carried out in the temperature range 500–650 °C; the ratios of the reactants varied from 0.5 to 2.0 (CO₂:CH₄) and from 0.5 to 3.5 (CO:CH₄). The length of the fibres exceeded their diameters by several orders of magnitude and depended on the contact time of the catalyst with the reaction mixture. According to the suggested scheme,³⁸ the formation of carbon fibres proceeded *via* a metastable carbide-like nickel–carbon complex. In the case of a CO₂–CH₄ mixture, this complex is formed as a result of methane dissociation, whereas in the case of a CO–CH₄ mixture, its formation was due to dissociation of methane and disproportionation of carbon monoxide.

The regularities of formation of carbon with fibrous-tubular structure by disproportionation of CO were studied.³⁹ This reaction occurred in three successive steps. The first step included formation of catalytically active phases, which are represented by carbides with various compositions. In the second step, superficial carbon was formed as a result of disproportionation of CO on catalytically active surfaces. And, finally, the third step consisted of bulk spatial transformation of superficial carbon in a fibrous-tubular structure containing catalyst microinclusions.

The structure of carbon fibres strongly depends on the conditions of synthesis.³⁷ Morphological characteristics of carbon fibres are determined by the chemical nature of the catalyst and conditions for their preparation. Besides, the sizes of nanofibres depend linearly on the sizes of the catalyst particles.

A classification of fibrous-tubular carbon-containing nanomaterials according to their structures and properties has been suggested.¹⁵ These materials are divided into carbon nanotubes (CNT) and graphitised nanofibres. The main difference between them is the lack of hollow cavities in the latter. The diameter of graphitised nanofibres is larger than that of nanotubes and can reach 500 nm. Nanotubes in turn are subdivided into two main categories, *viz.*, single-wall and multi-wall nanotubes. Ideal single-wall carbon nanotubes are made of a perfect graphene sheet rolled up into a cylinder and closed by two caps. Their internal diameter varies from 0.4 to 2.5 nm, while their length varies from several microns to several millimetres. Multi-wall nanotubes can be regarded as a set of coaxial single-wall tubes of increasing diameters.¹⁵ The number of walls in a multi-wall nanotube varies from two to several tens, and the distance between the walls of two neighbouring tubes is equal to 0.34 nm. Depending on the arrangement of the layers, graphitised nanofibres are subdivided into three main types, *viz.*, platelet, ribbon-like and herringbone structures.

The USA and Japan are the major manufacturers of fibrous-tubular carbon nanomaterials and, to a lesser extent, Europe and Korea. These materials are used, along with traditional fibres based on polymers (polyacrylonitrile, viscose, etc.), in the production of composite materials.³⁷ Nanofibres and nanotubes are also employed in the production of electrodes,⁴⁰ they proved to be efficient adsorbents and hydrogen storages.^{16,37}

2. Oxidative modification of carbon supports

As is known,¹³ carbon does not virtually interact with active components of metal–carbon catalysts. Fixation of a precursor of the active component on the carbon surface is an important step in the preparation of supported catalysts. This is achieved, in

particular, by oxidation of the carbon surface. In the oxidative treatment, surface functional groups (acidic, basic or neutral) are formed.⁴¹ Acidic groups include carboxylic, anhydride and lactone groups; weakly acidic and neutral groups are represented by phenolic, carbonyl, quinone and ester groups, while pyrone and chromene are regarded as the main basic groups. The determination of the amount, thermal stability and nature of surface oxygen-containing groups is carried out by temperature-programmed desorption (TPD).⁴¹ These groups are destroyed during TPD to yield carbon dioxide from carboxylic, anhydride and lactone groups and carbon monoxide from phenolic, carbonyl, quinone and pyrone groups. The structures of surface oxygen-containing groups and gaseous decomposition products formed in the TPD as well as the decomposition temperatures have been studied.⁴² The interaction of free active centres of the carbon surface with oxygen is usually accompanied by conversions of one kind of oxygen-containing groups into another.

The possibility of incorporation of oxygen into carbon supports is determined by their structural features. The boundaries of the basal planes of the graphite structure contain carbon atoms with unsaturated valences. High concentration of unpaired electrons in these regions has a strong impact on the chemisorption. Graphite weakly chemisorbs oxygen, because the boundary zone in graphite crystallites is small in comparison with the basal plane. At the same time, microcrystalline carbon materials, such as activated carbons, have less ordered structures and a much larger boundary zone, which favours oxygen chemisorption.¹³ In contrast to graphite, the basal planes of activated carbon crystallites contain multiple defects, which play the role of chemisorption sites for the oxidant.⁴³ And, finally, activated carbons are highly porous and possess large specific surfaces; consequently, the number of potential active sites for the oxidant chemisorption is large enough.

It is noteworthy that the susceptibility of carbon materials to oxidation and, as a consequence, the number of oxygen-containing surface groups formed upon chemisorption of the oxidant depend on the degree of their graphitisation. Interactions of carbon materials with oxidants also depend on oxidation conditions, *e.g.*, reaction temperature. Treatment of carbon materials with oxygen may result in physical (reversible) and chemical (irreversible) adsorption of the oxidant gas. The former takes place at low temperatures, but the role of chemisorption increases with an increase in temperature. Chemisorbed oxygen molecules dissociate into atoms, which interact with surface carbon to form superficial complexes.⁴⁴

Oxygen-containing complexes can be formed on the carbon surface upon interaction not only with oxygen, but also with many other gaseous oxidants, *e.g.*, ozone, nitrogen oxides or carbon dioxide.^{13, 30, 45} Nitric acid, sodium hypochlorite, potassium permanganate and hydrogen peroxide can be used as liquid oxidants. Electrochemical oxidation of carbon materials is also possible.³⁰

Impregnation of a carbon support and ion exchange with a solution containing a precursor of the active component are the most popular approaches to prepare the catalysts. The mode of interaction of metal salts with supports strongly depends on the nature and number of functional groups formed on the support surface under the action of the oxidant.¹³ The major portion of the metal is applied onto the carbon surface, if the maximum surface of the support is chemically accessible, *i.e.*, if the largest electrostatic forces arise between the positively charged surface and negatively charged anions of a salt of the active component precursor, or, *vice versa*, between the negatively charged surface and the salt cations.^{46, 47} Thus the adsorption capacity of granular activated carbon with respect to copper ions increases upon modification with citric acid due to introduction of carboxyl groups.⁴⁵

The nature of the solvent used for impregnation is a factor determining the distribution of a metal (*e.g.*, platinum) on the surface of carbon supports.⁴⁸ Since carbon materials are, as a rule, hydrophobic, they possess very low affinity for polar solvents and

high affinity for non-polar solvents.¹³ Accordingly, impregnation of granular activated carbon with a solution of a platinum salt in acetone results in more uniform distribution of the salt over the surface of grains of the support than in the case of aqueous solutions.⁴⁸ The presence of oxygen-containing groups on the surface of carbon materials decreases their hydrophobicity, *i.e.*, increases the hydrophilicity, and favours impregnation of the support with aqueous solutions.⁴⁹

The effects of surface groups on the dispersity and sintering of metal–carbon catalysts were studied.^{50, 51} Preliminary modification of the surface significantly affects the interaction of the active phase with the support in the formation of a catalyst and the dispersity of the metal. The latter can be controlled by thermal and chemical modification of the porous structure of the support ensuring the formation of surface oxygen-containing groups.⁴¹ Thus oxidative treatment of activated carbon favours more uniform distribution of nickel over the support granules in a nickel–carbon catalyst. Probably, this is due to more intense diffusion of nickel into pores of the support. Preliminary oxidative treatment of carbon supports also has a beneficial effect on the stability of catalysts. Presumably,³⁰ the oxidation favours the formation of acid ion-exchange groups that form chelates with metal-containing compounds, which prevents the migration of the metal over the carbon surface. The surface oxygen-containing groups play the role of binding sites for the active metal component on the carbon surface.⁴⁹ The strongest ‘anchoring’ effect is manifested by weakly acid and neutral oxygen-containing groups, probably, due to stability of such groups at temperatures used for pretreatment of catalysts, whereas the acid groups decompose with liberation of carbon dioxide.

The ever-increasing number of publications devoted to effects of oxygen-containing surface groups on the properties of carbon supports and ultimately on the properties of catalysts prepared points to high prospects of this line of research.

3. Metal–carbon systems in catalysis

Catalytic systems based on activated carbons compete favourably with catalysts based on oxide supports. Thus the activities of In- and Sn-doped palladium catalysts supported on activated carbons that are used for denitrification of water are comparable with those on metal oxides.⁵² Catalysts with activated carbon as a support are used for methanol conversion into synthesis gas.⁵³ In the presence of copper–chromium catalysts, the degree of methanol conversion exceeds 90%, and side products including methane are formed in only trace amounts.

Despite the relatively high cost of commercial fibrous carbon materials, they are becoming more popular as supports for active components of heterogeneous catalysts.^{54, 55} The use of catalysts supported onto fibrous carbon nanomaterials in hydrogenation, hydroformylation, decomposition and oxidation of methanol is documented.^{14, 15, 37, 56} Catalysts supported onto carbon fibres doped with Co, Ni, Cr and Mn were tested in various conversion reactions of secondary alcohols.^{57, 58} Owing to well-developed porous structure and high thermal stability, novel fibrous carbon materials can be used as catalysts in oxidative dehydrogenation of organic compounds, in particular, of cumene.^{59, 60} Comparative studies have shown that the yield of styrene on carbon nanotubes is 1.5 times higher than on graphite.⁶⁰ It is noteworthy that no loss of CNT due to carbon oxidation took place, which was the case with soot as a catalyst.

Ruthenium catalysts on CNT and oxide supports (MgO, Al₂O₃, TiO₂) accelerate decomposition of NH₃ with the formation of CO-free hydrogen.⁶¹ The highest activity was observed for Ru/CNT, which is explained by high degree of dispersity of its active component and chemical purity of the support. These conclusions were confirmed by the results of TPD studies and high-resolution tunneling microscopy.

A nickel catalyst supported on carbon nanotubes manifested much higher activity in the hydrogenation of benzene than an analogous catalyst on γ -Al₂O₃.⁶² This was attributed to higher

dispersity of the active component on CNT and weaker interaction of Ni with the support. Ni/CNT manifested higher thermal stability than Ni/ γ -Al₂O₃, since the unique porous structure of CNT prevents agglomeration of Ni particles.

Carbon nanofibres can be used as supports for a nickel catalyst applied for the decomposition of ethylene to produce CO-free hydrogen.⁶³ The maximum yield of hydrogen on Ni/CNF is 2.5 times higher than on Ni/SiO₂.

A comparison of iron–copper catalysts supported onto carbon nanofibres, activated carbon and γ -Al₂O₃ revealed⁶⁴ that the degree of ethylene hydrogenation on Fe–Cu/CNF exceeded that on Fe–Cu/activated carbon and Fe–Cu/ γ -Al₂O₃ more than fourfold. The size of particles of the active component in the Fe–Cu/CNF catalyst was 12–16 nm, whereas that in Fe–Cu/activated carbon and Fe–Cu/ γ -Al₂O₃ catalytic systems varied from 6–10 to 2–8 nm, respectively. These results are consistent with the concept⁶³ according to which it is the porous structure and chemical composition of the support rather than the dispersity of the active component that play the crucial role in the activity of catalysts. It was suggested⁶⁴ that the surface layer of carbon fibres in bimetallic catalytic systems can be enriched with one of elements of the active component giving rise to strong metal–support interactions. Such an interaction is hardly possible for a carbon support with a less ordered structures.

Copper-containing catalysts supported onto carbon fibres were used in the dehydrogenation of cyclohexanol.⁶⁵ The yield of the target product at 350 °C was 93%. The dehydrogenation of isopropyl alcohol on this catalyst gave acetone (yield 95%–96% with 100% selectivity). The same system modified with Ti, TiO₂ and TiC was used for catalytic purification of hydrogen and decomposition of H₂S. The use of titanium as an additive resulted in virtually complete dissociation of hydrogen sulfide into hydrogen and sulfur.

Studies on denitrification in water using Pd–Cu-catalysts supported onto activated carbon cloth (ACC), Al₂O₃ and SnO₂ revealed⁶⁶ that Pd–Cu/ACC manifested 2.7–3 times higher activity than Pd–Cu/Al₂O₃ or Pd–Cu/SnO₂. The rate of denitrification on Pd–Cu/ACC was 33 mmol (g Cat)^{–1} h^{–1} (Cat is catalyst), whereas that on Pd–Cu/Al₂O₃ and Pd–Cu/SnO₂ did not exceed 12 and 15 mmol (g Cat)^{–1} h^{–1}, respectively.

A comparative study of Co–Mo-containing catalysts supported onto nanoporous carbon (NC) and traditional supports, *e.g.*, activated carbon and Al₂O₃, has been studied⁶⁷ in hydrodesulfurisation of dibenzothiophene and 4,6-dimethyldibenzothiophene. The overall activities of the catalysts increased in the following order: Co–Mo/Al₂O₃ < Co–Mo/activated carbon < Co–Mo/NC. The mesoporous structure of NC and its large surface area favoured higher dispersity of the catalyst. The metal loading lowered the surface area of activated carbon, but did not virtually affected the other supports.

A whole family of sibunit-based palladium catalysts have been developed. These include catalysts for hydrogenation of aromatic nitro compounds and vegetable oils, hydrorefining of terephthalic acid from *p*-carboxybenzaldehyde, hydrogenation and disproportionation of colophony, *etc.*^{24,68} Sibunit is also used for the preparation of sulfide Ni–Mo-catalysts, which are used for hydrorefining⁶⁹ and hydrodemetallisation,⁷⁰ and of rhenium catalysts for dehydrogenation of cyclohexane⁷¹ and isopropyl alcohol,⁷² hydrogenation of ethyl acetate⁷³ and some other organic reactions.⁷⁴

III. Conversions of lower alcohols on metal–carbon catalysts

1. Synthesis of methyl formate by dehydrogenation of methanol

In-depth thermodynamic studies of dehydrogenation of methanol into methyl formate (MF)⁷⁵ with consideration of side reactions (*e.g.*, dissociation of methanol into carbon monoxide and hydrogen; decarbonylation of methyl formate; dehydration and steam

conversion of methanol), revealed that the equilibrium constants of side reactions significantly exceed that of dehydrogenation of methanol so that the equilibrium concentration of MF in the reaction products is low. Thus, synthesis of methyl formate by this method is expedient only if highly selective catalysts are available. The properties of these catalysts determine the optimum temperature of the process. The concentration of methyl formate in the equilibrium mixture increases with an increase in temperature, but this is accompanied by increase in its decomposition rate. High concentrations of methanol and/or methyl formate suppress the decomposition of MF.⁷⁶ High temperature (240 °C) and properly selected partial pressure of methanol allows virtually complete prevention of MF decomposition.

The degree of methanol conversion can also be increased by removal of hydrogen from the reaction zone using advanced membrane technologies.^{76,77} Membranes of palladium–ruthenium alloys can be used to this end. However, they undergo deactivation by CO formed in a side reaction, *viz.*, decomposition of methyl formate. This problem was successfully overcome through the use of a specially designed reactor⁷⁶ where the membrane was not deactivated even at high (~20%) concentrations of CO in the gas mixture, whereas the permeability of this membrane with respect to hydrogen significantly decreased after passage of hydrogen containing admixture of CO in the absence of the catalytic mixture.

Copper-containing catalysts are especially active in the dehydrogenation of methanol.⁷⁸ The key role in this process is ascribed to the interaction of the support with components of the catalytic system. In metal–carbon catalysts, the lack of strong interaction of the active component with the support facilitates the reduction of the metal on the surface.^{79,80} For this reason, a series of well-known carbon materials that have not previously been employed in the process under consideration were tested as potential supports for copper catalysts.

The following supports were used:^{81–84} (1) activated carbon AC₁ prepared from peat; (2) activated carbon AC₂ prepared from coconut shells (grain diameter 1.7–3.35 mm, moisture content 2.80 mass %, ash content 0.60 mass %, packed density 0.510 g cm^{–3}, abrasion resistance 95%–99%, pH 7.5); (3) fibrous-tubular carbons (FTC) prepared by decomposition of gaseous hydrocarbons on an iron catalyst with subsequent removal of iron with a large excess of 37% hydrochloric acid, washing off chloride ions and drying at room temperature for 24 h and at 105 °C for 3 h (the size of graphite crystallites was 53 Å, density 3.862 g cm^{–3}); (4) non-woven carbon material (NCM) prepared from hydrated cellulose fibres (total pore volume > 0.8 cm³ g^{–1}, surface density 120 g m^{–2}, carbon content > 99 mass %, layer thickness > 0.8 mm); (5) woven carbon material (WCM) prepared from PAN fibres (carbon content 98%–99%, abrasion resistance 700–800 N); (6) sibunit P-232 obtained by deposition of pyrocarbon on a technical carbon support with subsequent activation (total pore volume with respect to H₂O 0.57 cm³ g^{–1}, apparent density 0.597 g cm^{–3}).

Catalysts containing 5 mass % of copper were prepared by impregnation of the aforementioned supports with a solution of a copper salt (nitrate, acetate or tetraammine nitrate) with subsequent drying at 100 °C and reduction of samples in a hydrogen flow at 400 °C.

Analysis of the reaction mixture in a flow-through reactor at a volumetric flow rate of methanol of 3.0 h^{–1} and temperature of 200–400 °C revealed^{84,85} that it was only Cu/sibunit that provided a sufficiently high degree of methanol conversion in the given temperature range. Presumably, the formation of catalytic sites on carbon supports requires higher concentrations of the metal than on oxide supports.⁸⁶ The highest degree of methanol conversion (63.3%) was observed at 350 °C; however, this parameter decreased with further increase in temperature. On other catalysts, the degree of methanol conversion was 12%.^{87,88}

In addition to methyl formate, the liquid phase contained non-consumed methanol and water present in the alcohol. The gas

phase contained hydrogen and carbon monoxide. At temperatures above 250 °C, CO₂ was found in the gas phase, whereas at 300 °C methane was additionally formed. The highest selectivity of MF formation (88.9% at 200 °C) was observed on Cu/AC₂; however, the activity of this catalyst was low. Moreover, its selectivity dropped with an increase in temperature. At temperatures above 300 °C, the highest selectivity was manifested by Cu/WCM.

The reduction of catalytic activity at elevated temperatures can be caused by several factors.

First, agglomeration of metal particles on the surface of the support can occur as a result of their migration or sintering.⁸⁹ Sintering is possible even in the preparation and pretreatment of the catalyst. The migration of active component (metal) particles over the surface of the support and the formation of large agglomerates can be explained by thermodynamic instability of smaller particles.

Second, deactivation can be caused by fouling of the surfaces of the active component and the support itself by carbon deposits of different origin.⁸⁹

It was shown that virtually no changes in specific surface of copper-containing catalysts occurred following methanol dehydrogenation in the temperature range from 200 to 400 °C. This confirms the assumption that the reduction of activity results from sintering of active component particles. Specific surface of a specimen based on sibunit somewhat increased after several runs. Probably, sintering of copper is accompanied by its partial removal from the granulated support with a flow of the reaction mixture. This is rationalised as the virtual lack of interaction between the active component and the carbon support.¹³

Data from X-ray photoelectron spectroscopy (XPS) suggest that, after reduction, the active component of the catalyst 5% Cu/sibunit is predominantly localised on the surface of the granulated support. Its content in the dead catalyst is markedly reduced suggesting that the copper particles migrate over the surface of sibunit granules rather than in their interior in the course of methanol conversion. Analysis of powdered grains of the dead catalyst revealed that the amount of copper particles inside pores of sibunit is much smaller than in the surface layer.⁸⁵ It may thus be concluded that the preparation and preactivation procedures favour the formation of catalysts of the shell type, and the decrease in the catalyst activity can be attributed to the migration of copper particles over the surface of the support.

As mentioned above, Cu/sibunit is the most efficient catalyst for dehydrogenation of methanol into MF, the yield of MF being 28.4% at 275 °C and 45% methanol conversion. However, low thermal stability is a serious drawback of sibunit-based catalysts. Their activity drops drastically at temperatures above 275 °C.

The oxidative modification of the carbon support described above, which decreases its hydrophobicity and provides a more uniform distribution of the active component, is one of the ways to increase stability of supported catalyst.⁴⁹ To this end, sibunit was

oxidised by treatment with 10% and 20% H₂O₂ or HNO₃, or by passing air at 400–500 °C (Refs 85 and 90). Copper was applied onto the modified support washed with distilled water and dried at 100 °C. Copper-containing catalysts usually manifest much higher selectivity and thermal stability on such supports. The highest yield of MF (36.8% at 325 °C) was obtained in the presence of sibunit pretreated with 20% HNO₃. This specimen contained 2.8% of oxygen incorporated upon oxidation. The maximum yields of MF on catalysts based on supports premodified with 20% H₂O₂ or air at 500 °C were 32.9% at 300 °C or 29.7% at 275 °C, respectively. It is noteworthy that the maximum yield of MF after liquid-phase oxidation of sibunit was achieved at higher temperatures than on non-modified specimens.^{91,92}

Introduction of high-melting modifying agents (promoters) might be an alternative approach to increase the catalyst stability. It was supposed^{85,90} that the use of zinc oxide to this end would favour retention of the optimum dispersity of copper in the catalyst 5% Cu/sibunit and ensure stronger interaction between the active component and the carbon support. However, the addition of 0.25 mass %–3.75 mass % of zinc oxide significantly decreased the selectivity together with the obvious increase in the thermal stability of the catalyst.

The ability to selectively accelerate the target reactions is yet another important feature of modifying additives. Considering that rhenium-containing catalysts possess good dehydrogenating properties,^{71,93} copper- and rhenium-containing mono- and bimetallic sibunit catalysts were tested in methanol decomposition at 200–400 °C.⁸³

Synthesis of methyl formate from methanol on copper-containing oxide catalysts is accompanied by decomposition of MF into carbon monoxide and hydrogen or into carbon dioxide and methane.^{77,94} Decarbonylation of MF^{75,95} and steam conversion of carbon monoxide⁹⁶ and methanol^{97,98} also took place under these conditions. The selectivity of MF formation at high degrees of conversion rapidly decreased as a result of decomposition of MF. The kinetics and mechanism of MF conversion on copper-containing oxide catalysts were studied in detail.^{77,94,99,100}

In the presence of monometallic copper- and rhenium-containing sibunit catalysts, methanol conversion into MF increased at first with an increase in temperature from 200 to 250 °C and then decreased gradually. With an increase in the rhenium concentration from 1% to 2%, the selectivity of the reaction at 250 °C increased from 33.3% to 42.9%. The same increase in the content of copper on a monometallic catalyst increased the selectivity from 46.5% to 59.1%. However, the decomposition of MF on 1% Cu/sibunit proceeded much faster than on 1% Re/sibunit. For instance, the yield of methanol at 200 °C on the former was three times larger than on the latter. It is noteworthy that the ratio CO:H₂ is equal to 1:1 on 1% Re/sibunit, which corresponded to the stoichiometry of MF decomposition, while that for the copper-sibunit catalyst was equal to 2:1. This suggests that the selectivity of MF formation changed oppositely to methanol

Table 3. Effect of rhenium additives to copper-sibunit catalysts on the conversion of methanol and selectivity of formation of methyl formate (pressure 0.1 MPa, volumetric flow rate 7.5 h⁻¹).⁸³

Parameter	Addition of Re (mass %)									
	2% Cu/sibunit					4% Cu/sibunit				
	0	0.25	0.5	1.0	2.0	0	0.25	0.5	1.0	
Total conversion (%) at										
200 °C	1.6	1.5	1.4	1.3	1.1	1.3	1.5	2.7	2.3	
250 °C	4.3	4.1	3.7	3.5	3.4	2.2	5.8	5.2	4.7	
300 °C	5.9	6.2	6.4	6.9	7.1	3.1	8.7	8.4	8.6	
Selectivity (%) at										
200 °C	69.0	66.4	62.5	60.0	59.2	65.8	63.5	62.3	53.5	
250 °C	59.1	52.5	49.9	42.4	35.1	55.6	52.6	52.5	44.3	
300 °C	42.1	36.0	28.4	17.1	12.5	20.0	28.2	25.5	20.8	

conversion. At high degrees of conversion, the selectivity of formation of the target product decreased rapidly as a result of decomposition of MF into CO₂ and CH₄.

The dehydrogenation activity of bimetallic Cu–Re/sibunit catalysts containing 2% and 4% of copper changed insignificantly with an increase in temperature from 200 to 300 °C (Table 3).⁸³ The addition of 0.25%–1% rhenium to 4% Cu/sibunit resulted in a threefold increase in the total conversion of methanol at 300 °C with a slight increase in selectivity. A catalyst containing 4% of Cu and 0.25% of Re on sibunit manifested the highest dehydrogenation activity. Such a noticeable increase in the catalyst activity implies that sintering of copper at high temperatures proceeds more strongly in the absence of this additive. The addition of 0.25% rhenium to 4% Cu/sibunit increased not only its activity and selectivity, but also its stability.⁸³

Thus, modification with rhenium provides an efficient copper-sibunit catalyst for dehydrogenation of methanol into methyl formate.

2. Synthesis of acetaldehyde by dehydrogenation of ethanol

Copper-containing catalysts are most active in dehydrogenation of alcohols.^{12, 101} As a rule, copper is supported onto silica gel.¹⁰² It was suggested that acetaldehyde is formed on the surface of metallic copper, since the UV spectrum of Cu/SiO₂ contains a single peak at 560 nm, which is assigned to Cu⁰ (Ref. 103). Activated carbon, which is basic by nature, also catalyses the dehydrogenation of ethanol.¹⁰⁴ On oxidised carbons, ethanol undergoes dehydrogenation and dehydration, the latter yielding diethyl ether and ethylene. Dehydration usually occurs on surface Brønsted acid centres and increases with an increase in the total surface acidity. However, oxidation of carbon promotes acetaldehyde formation, since dehydrogenation is catalysed by Lewis acid centres. Most probably, the dehydrogenation takes place on both basic and acidic surface centres, not necessarily simultaneously on both types of centres. In addition, the increase in the intensity of formation of acetaldehyde with an increase in specific surface suggests that the dehydrogenation is catalysed not only by external, but also by some internal surface groups.¹⁰⁴

The main drawback of copper-containing catalysts is their short service life. In connection with the problem of enhancement of stability of catalysts for ethanol dehydrogenation, studies into properties of various supports, their interactions with active components of catalytic systems and choice of modifying agents and pretreatment conditions become of special importance.

The search for the best support for a catalyst of acetaldehyde synthesis was carried out by performing conversion of ethanol on supports devoid of an active component, *viz.*, galumin (calcium aluminum cement), silica gel and sibunit.^{105–107} On galumin, which contains alumina, in addition to acetaldehyde, C₄ compounds (butan-1-ol, diethyl ether and ethyl methyl ketone) were identified in liquid products; these are formed on acid centres. Dehydration with formation of large amount of ethylene was the

main reaction on silica gel over the whole range of temperatures studied (200–500 °C). Acetaldehyde and, at temperatures above 250 °C, diethyl ether formed in insignificant amounts. No ethanol decomposition took place on sibunit at temperatures below 250 °C. At higher temperatures, CO, CO₂ and H₂ were formed in trace amounts. At temperatures above 400 °C, the reaction products contained acetaldehyde. On sibunit, the conversion of ethanol was as low as 2% at 500 °C, whereas on oxide supports (galumin and silica gel) it reached 80% and 70%, respectively. Among copper-containing catalysts based on these supports, the Cu/sibunit system manifested the highest activity in the dehydrogenation: the yield of acetaldehyde was 43% at 400 °C. Due to lower selectivities of systems based on the oxide supports, the yields of acetaldehyde were by 11%–13% lower.

Thus, side reactions accompanying acetaldehyde synthesis from ethanol are much less pronounced on sibunit than on the oxide supports.

It was shown^{91, 92} that ethanol conversion on copper-sibunit catalysts increases with an increase in the copper concentration from 0.3 mass % to 10 mass %. This is accompanied by a decrease in the selectivity of acetaldehyde synthesis and by formation of side products, *viz.*, buta-1,3-diene, ethyl acetate, butan-1-ol and acetone. The increase in the copper content in the catalyst from 3 to 5 mass % decreases the selectivity by 22%. The maximum yield of acetaldehyde (54%) was obtained on 3% Cu/sibunit. At the copper content of 5%, the yield of acetaldehyde decreased to 43%, but it did not change with a further increase in the copper content. Presumably, these catalysts are of the shell type where copper is predominantly localised in the surface layer, which makes the porous cavity of sibunits inaccessible for the reaction. This is corroborated by a decrease in the specific surfaces of catalysts with an increase in the copper content. Higher copper content in the surface layer of 5% Cu/sibunit (2.9 at %) in comparison with 3% Cu/sibunit (2.2 at %) was confirmed by XPES.

The temperature-dependent changes in the compositions of ethanol conversion products on the most efficient catalyst (3% Cu/sibunit) are given in Table 4.

By selecting conditions of pretreatment of a copper-sibunit catalyst (3% Cu/sibunit), one can significantly increase the yield of the target product.¹⁰¹ The catalyst calcined in argon and subsequently reduced in hydrogen at 400 °C afforded the highest yield of acetaldehyde (69.2%) at 375 °C. Preliminary calcination has a great impact on the selectivity of the process. An increase in the calcination temperature from 200 to 400 °C increases the selectivity of acetaldehyde formation. Reduction of the catalyst with hydrogen increases the conversion of ethanol and the yield of acetaldehyde (by 10%–14%). The difference between the yields of acetaldehyde in the presence of non-reduced and reduced catalysts can be explained by different states of copper on the surface of the support. XPES studies showed that 64% of copper atoms in the reduced sample are in the Cu⁰ or in the Cu⁺ state, while the rest 36% are in the Cu²⁺ state. The corresponding values

Table 4. Composition of ethanol conversion products on a 3% Cu/sibunit catalyst at different temperatures.¹⁰¹

$T/^{\circ}\text{C}$	Product content (mol.%) (see ^a)															
	E	AA	Et	DEE	H ₂ O	EA	EMK	BT	Ac	C ₂ H ₄	H ₂	CO	CO ₂	CH ₄	BD	
200	—	3.68	77.01	—	16.21	—	—	—	—	—	3.10	—	0.01	—	—	
250	—	11.67	58.14	—	14.48	0.31	0.09	—	—	0.03	15.27	—	0.01	—	—	
300	—	18.97	34.83	0.16	12.89	0.54	0.25	0.09	tr.	0.09	30.52	—	0.04	—	1.62	
350	—	23.05	16.07	0.14	11.38	0.51	0.32	0.06	0.12	0.08	43.01	0.07	0.08	0.06	5.05	
400	tr.	27.86	12.05	0.16	12.11	0.26	0.32	0.04	0.20	0.05	42.08	0.21	0.06	0.16	4.44	
450	0.02	13.65	56.95	—	15.70	0.16	—	0.18	0.10	0.05	12.30	0.25	0.04	0.21	0.39	
500	0.10	8.74	61.63	—	15.49	0.05	—	—	—	0.09	12.16	0.63	0.06	0.57	0.62	

^a E is ethane; AA is acetaldehyde; Et is ethanol; DEE is diethyl ether; EA is ethyl acetate; EMK is ethyl methyl ketone; BT is butan-1-ol; Ac is acetone; BD is buta-1,3-diene; tr. is traces.

for a calcined non-reduced sample are 51% and 49%, respectively; the copper ions exist, most probably, only in Cu^+ and Cu^{2+} states. Presumably, higher concentration of Cu^{2+} in the calcined sample is the reason for inferior reaction parameters in the presence of non-reduced catalysts.

Stability is an extremely important characteristics of catalysts, especially of those intended for industrial use. However, the activity of 3% Cu/sibunit is lost dramatically at temperatures above 400 °C. According to XPES data, under the action of the reaction medium, copper passes into a Cu^{2+} state, which is less active as regards ethanol conversion, in the temperature range 200–500 °C. The period of stable active operation of the catalyst under conditions ensuring the maximum yield of the target product (375 °C, volumetric flow rate 0.3 h⁻¹) is 30 h after which its activity decreases.¹⁰⁸ Analysis of the XPE spectrum of the dead catalyst revealed an insignificant increase in Cu^{2+} content in comparison with the initial specimen. This suggests that the decrease in the catalytic activity of Cu/sibunit during its continuous operation is due to agglomeration of copper particles.

The agglomeration of copper particles into larger crystallites can be prevented and enhancement of the interaction of copper with the support surface can be reached if the catalyst is supplemented with magnesium oxide and chromium oxide. Magnesium oxide is known to decrease both the activity and the selectivity of Cu/sibunit catalysts, while chromium oxide causes significant increase in their activity at temperatures above 400 °C. However, a twofold (in comparison with the non-modified catalyst) increase in the degree of ethanol conversion was accompanied by a decrease in its selectivity. The best results were obtained at the copper : chromium oxide ratio 20 : 1 (the yield of acetaldehyde was 63.3% at 375 °C). Moreover, the addition of chromium oxide prolonged the operation life of the catalyst. Under conditions ensuring the maximum yield of acetaldehyde, the system can steady operate for at least 80 h.

Thus, the use of a carbon-containing material (sibunit) as a support allowed the development of an efficient catalyst for acetaldehyde synthesis. The parameters of this process can be improved through optimisation of conditions for pretreatment of copper–sibunit catalysts. Their stability can be increased by promotion with chromium oxide. The yield of acetaldehyde attained markedly exceeds the yields on the known industrial catalysts.¹⁰¹

3. Synthesis of acetone from isopropyl alcohol

Isopropyl alcohol undergoes easy (in comparison with other aliphatic alcohols) dehydrogenation to give acetone and dehydration to give propene.

Traditional copper-containing catalysts for dehydrogenation of alcohols into aldehydes usually contain significant amounts of a metal. Thus the commercial catalyst SNM-1 ($\text{CuO} - \text{ZnO} - \text{Al}_2\text{O}_3$) manufactured in Russia contains 64% of CuO. A 30% rhenium catalyst on activated carbon manifests high dehydrogenating properties, but rapidly loses its activity.

Modification of metal catalysts used for the conversion of isopropyl alcohol can be achieved by replacement of activated carbons by sibunit.⁷² In a series of monometallic 1% Cu-, Re-, Ni- and Pd/sibunit catalysts, the highest activity was manifested by 1% Re/sibunit (Table 5). At 250 °C, the yield of acetone on this catalyst was commensurate with that obtained on 30% rhenium/activated carbon at 195 °C.¹⁰⁸

On bimetallic catalysts containing 1% Re and Cu, Re and Ni or Re and Pd, the degree of conversion of isopropyl alcohol into acetone markedly exceeds that on monometallic 1% Cu/sibunit, Ni/sibunit and Pd/sibunit catalysts. Thus the introduction of rhenium to a palladium-containing catalyst increases its activity 35-fold and its stability, nearly twofold. Bimetallic catalysts retain their activities and high selectivity (77%–90%) even after 6–9 h of operation.

The obvious advantage of bimetallic catalysts over monometallic ones is that rhenium favours the reduction of the second

Table 5. Dehydrogenation of isopropyl alcohol on mono- and bimetallic catalysts supported onto sibunit (volumetric flow rate 1.1 h⁻¹, reaction in a flow of hydrogen).⁷²

Metal content	Reaction conditions		Degree of alcohol conversion (%)		Selectivity of acetone formation (%)
	<i>T</i> / °C	time / h	total	into acetone	
1% Re	200	1	34.2	26.5	77.0
	250	2	66.6	54.7	82.0
1% Re + 1% Cu	200	1	27.7	21.0	75.8
	250	2	61.7	49.0	79.4
1% Cu	200	1	20.5	15.3	74.6
	250	2	52.5	43.7	83.2
1% Re + 1% Ni	200	1	61.5	53.0	86.0
	250	2	79.7	64.0	80.3
1% Ni	200	1	15.1	12.1	80.1
	250	2	43.1	33.3	77.3
1% Re + 1% Pd	200	1	76.1	55.5	82.7
	250	2	93.0	77.2	83.0
1% Pd	200	1	1.6	1.6	100.0

metal (Cu, Ni or Pd). In the alcohol dehydrogenation, the activities of the above-mentioned bimetallic catalysts increase in the following order: Re–Cu < Re–Ni < Re–Pd.

No rhenium crystalline phase could be detected by X-ray phase analysis in a bimetallic catalyst containing 2% Re and 2% Ni on sibunit, which suggests a highly dispersed state of rhenium. The data listed in Table 6 illustrate the effects of added rhenium on the activity of 2% Cu/sibunit in the conversion of isopropyl alcohol at 200–270 °C.¹⁰⁹ Liquid products formed on a monometallic (*i.e.*, containing no rhenium) catalyst contain acetone and water (along with the non-consumed alcohol), while the gas phase contains propene and hydrogen. At 200 °C, the dehydrogenation and dehydration occur in parallel. Thirty minutes after the beginning of the reaction, the total conversion of the alcohol on 2% Cu/sibunit is ~15.3%, while the ratio of yields of acetone and water is 3.3. With an increase in temperature from 200 to 270 °C, the dehydrogenating activity of the monometallic catalyst increases 3.2-fold. The selectivity of acetone formation increases from 76.6% to 86.7%. If after 2 h-operation of 2% Cu/sibunit at 270 °C the temperature is decreased to 200 °C, the initial dehydrogenating activity of the catalyst is recovered virtually completely.

Rhenium, which has a high melting temperature (3170 °C), is not subject to recrystallisation in the course of the catalytic process; therefore its addition can increase the stability of catalytic systems.⁸⁵ As can be seen from Table 6, the addition of 0.25% rhenium improves the dehydrogenating properties of 2% Cu/sibunit in the conversion of isopropyl alcohol. The lack of a strong metal–support interaction on a carbon support facilitates the reduction of the metal on the catalyst surface, which takes place even at 200 °C.¹⁰⁹

Glow discharge plasma treatment in oxygen is a way to control properties of copper and copper-rhenium catalysts.¹¹⁰ The effect of plasma treatment was assessed by measuring the degree of conversion of isopropyl alcohol into acetone in the temperature range 177–327 °C. The catalysts were processed in the following regimes: (1) hydrogen treatment; (2) hydrogen treatment with subsequent catalysis and repeated hydrogen treatment; (3) plasma treatment with subsequent hydrogen treatment; (4) plasma treatment; (5) plasma treatment with subsequent catalysis and final hydrogen treatment.

The yield of acetone after treatment of a copper-sibunit catalyst in regime (3) decreased, while that of Cu–Re/sibunit increased. Manifold increase in the activity was observed after treatment of the catalyst in regime (5). In order to elucidate the reasons for the change in activity of the catalyst depending on the

Table 6. Conversions of isopropyl alcohol on 2% Cu/sibunit catalysts containing different concentrations of rhenium (flow systems, atmospheric pressure, reaction in H₂ flow, volumetric flow rate 1.0 h⁻¹, reaction time 30 min).¹⁰⁹

Re content (%)	<i>T</i> /°C	Composition of liquid phase (%)			Conversion (%)			Selectivity (%)	
		acetone	H ₂ O	alcohol	total	into acetone	into H ₂ O	acetone	H ₂ O
0	200	11.6	1.1	87.3	15.3	11.7	3.6	76.6	23.4
	235	28.6	1.8	69.6	33.8	28.1	5.7	83.1	16.9
	250	33.6	1.7	64.7	38.4	33.0	5.4	86.0	14.0
	270	37.7	1.8	60.5	42.7	37.0	5.7	86.7	13.3
0.25	200	18.2	1.0	80.8	21.5	18.3	3.2	85.0	15.0
	235	39.2	1.7	59.1	43.9	38.6	5.3	87.8	12.2
	250	45.1	2.4	52.5	51.1	43.6	7.5	85.4	14.6
	270	56.4	2.8	40.8	62.4	53.8	8.6	86.3	13.7
0.5	200	23.9	2.0	75.1	29.4	23.1	6.3	78.6	21.4
	235	46.8	2.4	50.8	52.6	45.2	7.4	85.9	14.1
	250	49.7	2.2	48.1	54.8	47.9	6.9	87.4	12.6
	270	57.3	2.4	40.3	62.6	55.2	7.4	88.1	11.9
1.0	200	23.0	2.6	74.4	30.4	22.3	8.1	73.3	26.7
	235	37.3	3.6	59.1	46.1	35.2	10.9	76.0	24.0
	250	45.1	3.6	51.3	51.5	39.5	12.0	76.0	24.0
	270	53.6	4.1	42.3	62.0	49.8	12.2	80.3	19.7
2.0	200	35.1	3.1	61.8	43.3	33.9	9.4	78.3	21.7
	235	51.0	7.2	41.8	64.8	44.5	20.3	68.7	31.3
	250	59.2	8.9	31.9	71.8	50.0	24.2	67.5	32.3
	270	65.4	9.7	24.9	80.1	54.2	25.9	67.6	32.4

Table 7. Activation energies and preexponential factors for dehydrogenation of isopropyl alcohol on 2% Cu/sibunit catalysts containing different amounts of rhenium before and after plasma treatment in regime (4) (see the text).¹¹⁰

Re content (%)	Before treatment		After treatment	
	<i>E_a</i> /kJ mol ⁻¹	ln <i>A</i> ₀	<i>E_a</i> /kJ mol ⁻¹	ln <i>A</i> ₀
0	38.7	14.1	—	—
0.25	34.9	12.3	38.7	14.1
0.5	48.4	16.5	13.4	9.2
1.0	51.7	16.3	38.1	13.4
2.0	57.5	17.7	46.5	16.2

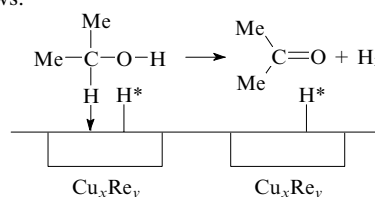
mode of treatment were elucidated by studying the temperature dependences of the yield of acetone (*Y*) at low degrees of conversion in the Arrhenius coordinates (ln *Y* vs. *T*⁻¹). As can be seen from Table 7, the values of activation energies (*E_a*) and the preexponential coefficients (*A*₀) for the dehydrogenation of isopropyl alcohol on 2% Cu/sibunit and 2% Cu + 0.25% Re/sibunit are very similar. Much higher *E_a* values (48.4, 51.7 and 57.5 kJ mol⁻¹, respectively) were obtained for samples with a higher rhenium content (0.5%, 1.0% and 2.0%).

Treatment of the catalyst 2% Cu + 0.25% Re/sibunit in regime (4) slightly increases its activity, which can be attributed to the larger number of active centres rather than to structural changes, as can be evidenced from a significant increase in ln *A*₀ with a small change in *E_a*. A decrease in the activation energy of the reaction on 2% Cu + 0.5% Re/sibunit under identical conditions is due to the substantial changes in the structures of the active centres. However, the effect of this factor is compensated by a significant decrease in the number of these active centres (factor *A*₀); therefore, the yield of acetone on this catalyst is only slightly higher than on 2% Cu + 0.25% Re/sibunit processed in a similar regime. The increase in the yield of acetone on 2% Cu + 1% Re/sibunit can be explained exclusively by a decrease of the activation energy, since the value of *A*₀ after treatment in regime (4)

decreased. On 2% Cu + 2% Re/sibunit, the changes in the *E_a* and ln *A*₀ are insignificant.

Treatment in regimes (1–5) has different effects on the activities of copper and copper–rhenium catalysts on sibunit. This suggests that active centres of copper–rhenium catalysts based on sibunit represent bimetallic clusters Cu_{*x*}Re_{*y*} with Cu–Re bonds. Presumably, the active centre of the catalyst contains a hydrogen atom, since the highest activity was manifested after plasma treatment followed by a series of catalytic runs and final hydrogen treatment (regime 5). If plasma treatment was not followed by hydrogen treatment, the activity changed only insignificantly and showed a tendency to decrease, apparently due to partial removal of hydrogen from the active centres.

Apparently, the role of rhenium atoms in the active centres consists, first, of stabilisation of the structure of these centres.^{72, 108} This follows from the fact that copper–rhenium catalysts maintain their activity on sibunit for longer periods of time than catalysts containing no rhenium. Second, the interaction of Re atoms with Cu atoms results in positive polarisation of the latter, which favours the displacement of an electron from the carbon atom of the CH group of isopropyl alcohol first to the copper atom and then to the hydrogen atom in the active centre. This, in turn, favours the interaction of the hydrogen atom in the active centre with a positively polarised hydrogen atom of the hydroxy group. It is noteworthy that the work function of electron is equal to 5.0 eV for rhenium and 4.4 eV for copper. Hence, the dehydrogenation process can schematically be presented as follows:



Ab initio quantum-chemical calculations (GAUSSIAN-98) confirmed the suggested structure of the active centre.¹¹¹ The lower activity of 2% Cu + 2% Re/sibunit as compared with that

Table 8. Conversion of isopropyl alcohol in samples obtained by passage of volcanic gas through sibunit.¹¹⁶

Gas temperature /°C	Total metal content (mass %)	Reaction conditions			Yield of liquid products (%)	Degree of alcohol conversion (%)	
		<i>T</i> /°C	time /min	volumetric flow rate /h ⁻¹		total	into acetone
339	0.056	400	30	3.14	98.0	23.0	21.1
		400	60	0.98	96.7	22.4	19.4
		400	90	2.20	96.6	18.7	15.6
610	0.025	400	30	2.20	89.0	33.0	23.0
		400	60	3.14	97.6	23.9	22.0
		450	90	3.14	91.1	49.6	42.1
		450	120	3.14	100	40.3	40.3
		500	30	3.14	84.6	47.3	33.0
		450	60	3.14	100	12.0	11.9
610	3.13	400	30	3.14	100	20.0	20.0
		450	60	3.14	96.7	38.6	37.7
See ^a	see ^a	400	30	3.41	97.7	10.3	5.3

^a The original sample non-treated with the volcanic gas.

of 2% Cu + 0.5% Re/sibunit is probably due to formation, in the former case, of rhenium structures outside the active centres.

Thus, 2% copper/sibunit catalysts containing 0.25%–0.5% of rhenium selectively dehydrogenate isopropyl alcohol into acetone. Glow discharge plasma treatment of Cu/sibunit catalysts in oxygen decreases the yield of acetone, while similar treatment of Cu–Re catalysts increases it. The activity of catalysts can be increased manifold by plasmochemical treatment followed by a series of catalytic conversions of isopropyl alcohol and, finally, reduction with hydrogen.

4. Catalytic properties of natural volcanic rock from the Isle of Iturup

High concentrations of compounds containing rhenium, copper and other metals were found in the gases leaking from fumaroles (small holes and clefts through which eruptive gas emerges from the Earth's interior) of the volcano Kudryavy (the Isle of Iturup in the Kuriles).^{112–114} Volcanic rock represents a solid silicate mass with ingrain sulfide sublimate crystals of pyrite (FeS₂), galenite (PbS) and rhenium sulfide (ReS₂). Sulfide sublimates form small (as a rule, less than 40 μm) isolated excretions on the boundaries of volcanic rock grains and in the pores of other minerals. Volcanic rock contains the following metals (mass %): Re (0.005), Cu (0.005), Ag (0.0002), Zn (0.070), Cd (0.040), Ga (0.0015), In (0.020), Tl (0.0004), Co (0.0005), Ni (0.003), Ge (0.001), Sn (0.030), Pb (0.020), As (0.010), Sb (0.005), Bi (0.030), V (0.015), Mo (0.004). Rock samples manifest high dehydrogenating activity, although the content of metal sulfides (including rhenium sulfide) is an order of magnitude lower than in ordinary dehydrogenation catalysts.¹¹⁵

Synthetic samples prepared by passage of volcanic gas through quartz tubes filled with a support for 14–17-days manifested catalytic activity in the dehydrogenation and dehydration of isopropyl alcohol. The samples were prepared on zeolite, alumina and sibunit. On zeolite and on γ-Al₂O₃, the dehydration of isopropyl alcohol was complete at 400 °C and at 300 °C, respectively; no dehydrogenation was observed on these catalysts. On sibunit non-treated with volcanic gases, both dehydrogenation and dehydration took place at 400 °C, the total degree of isopropyl alcohol conversion being ~10%. The catalytic properties of sibunit samples are summarised in Table 8. The major contribution to the dehydrogenating activity of volcanic rock samples and artificial samples is made by magnesium, molybdenum and rhenium sulfides.

Rhenium and other rare elements of volcanic gas are best adsorbed on zeolite. A method for isolation of rhenium from zeolite is developed, which can be useful for the design of novel efficient catalysts for different organic chemical and petrochemical processes.^{74, 115–117}

IV. Conclusion

The data presented above suggest high potential of modern carbon materials having globular and fibrous-tubular structure and carbon–carbon composite materials (*e.g.*, sibunit) as supports for catalysts. The use of metal-containing catalysts based on sibunit significantly increases the efficiency of formation of methyl formate, acetaldehyde and acetone by dehydrogenation of the corresponding aliphatic alcohols. Catalysts have been developed that enable significant increase in the yields of target products despite the lower (by an order of magnitude) content of copper in comparison with commercial copper-containing oxide catalysts used for dehydrogenation of alcohols. Rhenium-sibunit catalysts manifest high activity in the dehydrogenation of isopropyl alcohol. Bimetallic catalysts Re–Pd, Re–Ni and Re–Cu on sibunit are much more stable than monometallic systems. Substitution of sibunit for the activated carbon as a support makes it possible to reduce rhenium content from 30% to 1%–2% without any loss of catalytic activity in the dehydrogenation of isopropyl alcohol. The activity of the catalyst can also be increased using glow discharge plasma treatment in oxygen. The excretions from the volcano Kudryavy (Isle of Iturup, Archipelago Kurile Islands) contain oxides of Si, Al, Fe, *etc.*, and some metal sulfides (including Re and Cu sulfides) and manifests dehydrating and dehydrogenating properties in the conversion of isopropyl alcohol. Synthetic samples prepared by condensation of high-temperature volcanic gases on sibunit manifest only dehydrogenating activity. The excretions from the volcano Kudryavy can be regarded as a source of rhenium (in the form of ReS₂) for novel efficient catalysts.

Development of novel metal-containing catalysts for dehydrogenation of aliphatic alcohols in which sibunit is used as a support instead of metal oxides is a basis for the design of efficient catalytic procedures for the synthesis of valuable organic intermediates alternative to the existing techniques. Taking into account the growing tendency towards a departure from the use of crude oil, the use of lower aliphatic alcohols as a raw material seems to be a promising trend in chemical industry.

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Thiophene 1,1-dioxides as unique building blocks in modern organic synthesis and materials chemistry

A M Moiseev, E S Balenkova, V G Nenajdenko

Contents

I. Introduction	1015
II. Synthesis of thiophene 1,1-dioxides	1015
III. Reactions of thiophene 1,1-dioxides	1020
IV. The applications of thiophene 1,1-dioxides	1037
V. Theoretical calculations	1042
VI. Conclusion	1045

Abstract. Data on the synthesis, reactivity features and the key chemical transformations of thiophene 1,1-dioxides are summarised and described systematically. The attention is focused on recent achievements in the chemistry of thiophene dioxides concerning both their practical use and theoretical studies. The bibliography includes 205 references.

I. Introduction

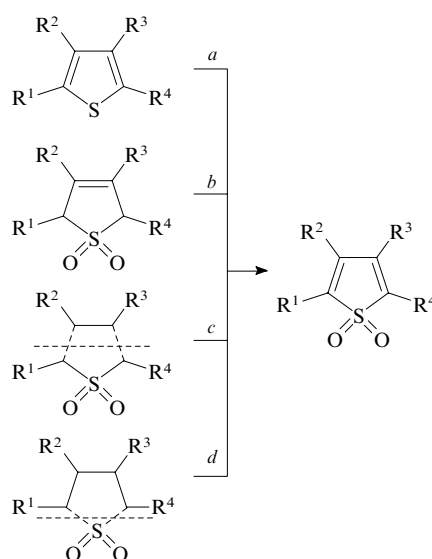
Thiophene 1,1-dioxides are non-aromatic heterocyclic compounds possessing properties of conjugated electron-acceptor dienes. Although the first representatives of thiophene dioxides were obtained back in the early 20th century, the interest in these compounds persists. Owing to the unique structure combined with high reactivity, they can be used to prepare various carbo- and heterocyclic systems; therefore, these compounds are convenient 'building blocks' in organic synthesis.

Extensive information on the synthesis and chemical transformations of thiophene 1,1-dioxides has been accumulated by now. Several published reviews^{1–8} largely cover the research period from the moment the first compounds were obtained (1915) to the mid-1990s. The reference book *Science of Synthesis (Houben-Weyl)*⁸ published in 2004 briefly describes the methods of synthesis and some chemical transformations of thiophene dioxides discovered in recent years. The most comprehensive review on this topic was written by Nakayama³ and published in 1999 in *Topics in Current Chemistry*. However, the number of publications dealing with the chemistry of thiophene dioxide-based new materials, namely, semiconductor organic transistors and light diodes first designed about 15 years ago, started to increase in 1997. In recent years, new data on the biological activity of some thiophene 1,1-dioxide derivatives were obtained. These facts and also the fact that the above-noted publications are not readily available in Russia were the driving forces for writing this review. In addition, the results of our recent studies of

thiophene dioxides with electron-withdrawing substituents together with the fundamental works in this field will provide a holistic view of the synthetic potential of this class of compound.

II. Synthesis of thiophene 1,1-dioxides

The information presented in this Section is classified according to the type of reaction (Scheme 1). The key methods for the synthesis of thiophene dioxides include four types of transformations: oxidation of thiophenes (path *a*), addition–elimination reactions in the series of substituted sulfolenes (path *b*), and various intra- and intermolecular cyclisations (paths *c* and *d*). The oxidation of thiophenes is a well-studied and the most general route to thiophene dioxides. Earlier reviews^{2,3,6–8} describe the methods of oxidation of substituted thiophenes; therefore, for reactions using traditional oxidants we present only a summary Table for the obtained compounds with references to original works. The use of oxidants and reagents discovered in recent years is considered in detail. For more comprehensive presentation of the information concerning this type of reaction, paths *b–d* are considered both in the classical variant and according to the latest achievements in the synthesis of thiophene dioxides. For specific



Scheme 1

$R^1 - R^4 = \text{H, Hal, Alk, Ar, etc.}$

A M Moiseev, E S Balenkova, V G Nenajdenko 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 22 76, e-mail: andmo@petrol.chem.msu.ru (A M Moiseev), balenkova@mail.ru (E S Balenkova), nen@acylium.chem.msu.ru (V G Nenajdenko)

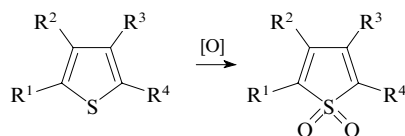
Received 21 July 2006

Uspekhi Khimii 75 (12) 1139–1174 (2006); translated by Z P Bobkova

synthetic routes, only bibliographic data are given due to their limited use.

1. Oxidation of thiophenes

Organic peroxy acids are well-known reagents for thiophene oxidation. Most often, thiophene 1,1-dioxides have been prepared using peracetic, perbenzoic and *m*-chloroperoxybenzoic (MCPBA) acids (Table 1).

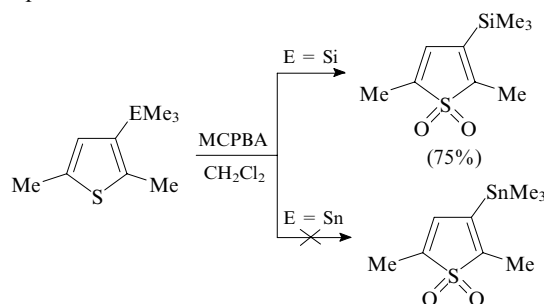


m-Chloroperoxybenzoic acid is most reactive in this series of oxidants. For example, a number of sterically hindered di-*tert*-butyl, dineopentyl and diadamantylthiophene dioxides have been prepared using this reagent.^{18–22, 25} It should be noted that under the action of MCPBA, perhalogenated thiophenes (Cl- or Br-containing) form thiophene dioxides in moderate yields,²⁸ whereas 2,5- or 2,4-dihalo thiophenes are not oxidised by this reagent (see Table 1).

Benzo[*b*]thiophene 1,1-dioxides, important building blocks for the synthesis of various biologically active compounds, are also easily prepared by oxidation of benzothiophenes. Despite the fact that a large number of oxidants are currently known, peracetic acid and MCPBA are still used most often in these reactions.^{29–32}

Recently, this method was used to prepare^{33–35} trimethylsilyl and trimethylgermyl derivatives of thiophene 1,1-dioxides, convenient starting compounds for organic synthesis (see Sections III

and IV). For example, 2,5-dimethyl-3-(trimethylsilyl)thiophene was converted, on treatment with MCPBA, into the corresponding thiophene dioxide in good yield; however, for its stannyl analogue, cleavage of the tin–carbon bond rather than oxidation took place under these conditions.³⁴



A recent alternative to MCPBA is trifluoroperoxyacetic acid usually prepared from a 30% solution of hydrogen peroxide and trifluoroacetic acid or its anhydride. Using this reagent, the yields of halogen-containing thiophene 1,1-dioxides have been markedly increased as compared with the yields with other oxidants^{36, 37} and some benzo-³⁸ and dibenzothiophene 1,1-dioxides have been prepared.^{39, 40}

The use of trifluoroperoxyacetic acid under nonaqueous conditions (prepared from 100% H₂O₂ and trifluoroacetic anhydride) opened up the way to thiophene dioxides containing strong electron-withdrawing substituents.⁴¹ A versatile method for the preparation of sulfones **1a–x** by the reaction with CF₃CO₃H in various solvents has been reported⁴² (Table 2). It was shown that the course of the reaction depends on the structure of the initial

Table 1. Preparation of thiophene 1,1-dioxides using classical peroxy acids.

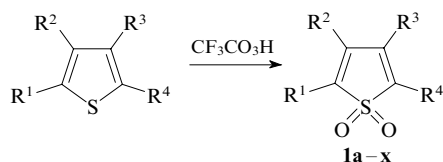
Oxidant	R ¹	R ²	R ³	R ⁴	Yield (%)	Ref.
MeCO ₃ H	Me	Cl	Cl	Me	38	9
	Me	Br	Br	Me	68	10
	Ph ₂ CH	H	H	PhCH ₂	—	11
	Ph	Ph	Ph	Ph	65–100	12, 13
	4-FC ₆ H ₄	Ph	Ph	4-FC ₆ H ₄	93	14
PhCO ₃ H	H	Me	Me	H	62.5	10
	Me	H	H	Me	14	10
	H	Ph	Ph	H	40	15
	H	4-MeC ₆ H ₄	4-MeC ₆ H ₄	H	34	16
	H	4-ClC ₆ H ₄	4-ClC ₆ H ₄	H	18	17
	Ph	H	H	Ph	31	10
	Br	Ph	Ph	H	11	10
	Ac	Ph	Ph	H	72	10
	COPh	Ph	Ph	H	48.5	10
	COPh	Ph	Ph	Ac	60	10
3-ClC ₆ H ₄ CO ₃ H	H	Bu ^t	Bu ^t	H	67	18
	Me	H	H	Me	52	19
	Me	Bu ^t	Bu ^t	Me	67	20
	Me	<i>neo</i> -C ₅ H ₁₁	<i>neo</i> -C ₅ H ₁₁	Me	87	21
	Me	1-Ad ^a	1-Ad	Me	61	22
	Et	H	H	Me	69	23, 24
	Bu ^t	H	H	Bu ^t	70	19
	Bu ^t	H	Bu ^t	H	56	19
	Bu ^t	Bu ^t	H	H	79	25
	Bu ^t	Bu ^t	Bu ^t	Bu ^t	75	26
	C _n H _{2n+1} ^b	H	H	C _n H _{2n+1}	35–51	27
	Ph	H	H	Ph	74	19
	Cl	Cl	Cl	Cl	50	28
	Br	Br	Br	Br	66	28

^a Ad is adamantyl, ^b *n* = 6–11.

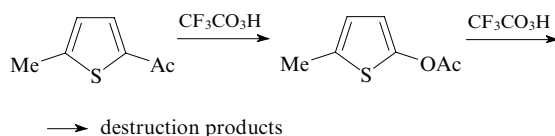
Table 2. Oxidation of substituted thiophenes with trifluoroperoxyacetic acid.⁴²

Compound 1	R ¹	R ²	R ³	R ⁴	Solvent	Reaction time /h	Yield (%)
a	Me	H	H	Me	CH ₂ Cl ₂ , MeCN	0.15	51
b	Ph	H	Ph	H	CH ₂ Cl ₂ , MeCN	0.2	98
c	Br	H	Br	H	MeCN	2	42
d	Br	H	Br	Br	MeCN	3	85
e	Cl	Cl	Cl	Cl	MeCN	2.5	92
f	Br	Br	Br	Br	MeCN	2.5	84
g	Cl	H	Br	Cl	MeCN	3	81
h	Cl	H	H	Cl	MeCN	4	76
i	Br	H	H	Br	MeCN	4	82
j	Me	H	H	SO ₂ Me	CF ₃ CO ₂ H	4	85
k	Cl	H	H	CO ₂ Me	CF ₃ CO ₂ H	5	77
l	Br	H	H	CO ₂ Me	CF ₃ CO ₂ H	5	80
m	Cl	H	H	SO ₂ Me	CF ₃ CO ₂ H	6	66
n	Br	H	H	SO ₂ Me	CF ₃ CO ₂ H	6	77
o	Cl	H	CO ₂ H	Cl	CF ₃ CO ₂ H	4	80
p	SO ₂ Me	H	H	SO ₂ Me	CF ₃ CO ₂ H	48	85
q	H	SO ₂ Me	H	SO ₂ Me	CF ₃ CO ₂ H	48	28
r	CO ₂ Et	H	H	SO ₂ Me	CF ₃ CO ₂ H	24	51
s	SO ₂ Ph	H	H	SO ₂ Me	CF ₃ CO ₂ H	48	88
t	Me	H	H	NO ₂	CF ₃ CO ₂ H	48	41
u	Cl	H	H	NO ₂	CF ₃ CO ₂ H	72	28
v	Me	H	H	CN	CF ₃ CO ₂ H	120	69
w	H	CN	H	CN	CF ₃ CO ₂ H	120	45
x	H	NO ₂	H	NO ₂	CF ₃ CO ₂ H	120	30

thiophene and the nature of the solvent. This method can be used to oxidise thiophenes with both electron-donating and electron-withdrawing groups.

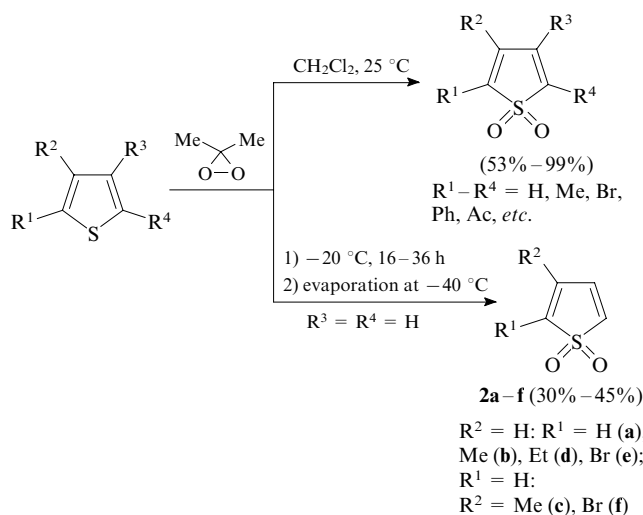


The above-described method has some limitations. Thus thiophenes containing an acetyl group in the position 2 or 3 undergo the Baeyer–Villiger oxidation under these conditions. Further oxidation of the resulting acetoxythiophene with excess trifluoroperoxyacetic acid gives destruction products, which is apparently due to high electrophilicity of the reagent. In addition, by using CF₃CO₃H, it is impossible to obtain mono- or 2,3-disubstituted thiophene dioxides.



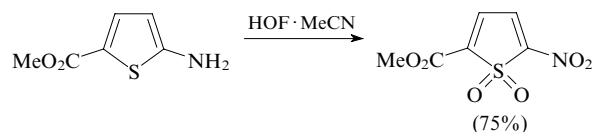
In 1990, Miyahara and Inazu⁴³ introduced, to the synthetic practice, dimethyldioxirane (DMD), a cyclic peroxide, which allows one to oxidise substituted thiophenes under mild conditions to obtain products in high yields. This protocol was employed to prepare thiophene 1,1-dioxides containing not only halogen atoms but also an acetyl group. Nevertheless, monosubstituted 2-ethylthiophene could not be converted into sulfone under these conditions.⁴³ More recently, Nakayama and co-workers^{44,45} have shown that the use of DMD at low temperature can serve as a convenient method for the preparation of unsubstituted (**2a**) and monosubstituted thiophene dioxides **2b–f**.⁴⁶

Due to their exceptional lability, these compounds were isolated by evaporating the solvent *in vacuo* and recrystallised at –40 °C. The degree of conversion of thiophene in these reactions was ≤45%. Note that DMD is the only reagent capable of selective oxidation of thiophenes unsubstituted in C(3)–C(4) positions, since the use of peroxy acids or other oxidants may induce easy epoxidation of the double bond and subsequent overoxidation.



Rozen and co-workers, who investigated the synthetic potential of the HOF·MeCN complex (see, for example, Ref. 47), proposed a method for oxidation of substituted thiophenes.⁴⁸ This reagent, prepared by bubbling elemental fluorine into aqueous acetonitrile, reacts with substituted thiophenes under mild conditions to give target thiophene dioxides in high yields. As a result, sulfones from 2,5-dichloro-, 2,4- and 2,5-dibromothiophenes and from methoxycarbonyl and acetyl derivatives have been prepared. Being a very strong electrophilic oxidant, the

HOF·MeCN complex transformed 2-amino-5-methoxycarbonylthiophene into the corresponding nitrothiophene dioxide.⁴⁷



In the last decade, the search for new catalysed processes for thiophene oxidation with readily available reagents became a topical task. This is due to the necessity of increasing the quality of oil stock. A decrease in the organic sulfur content in oil fractions and engine fuels can be attained by oxidation reactions. The oxidative properties of various catalytic systems were studied using mainly benzo- and dibenzothiophene derivatives that occur in crude oil. Transition metal complexes (W, Mo, Mn, Cr, Fe) in the presence of various oxidants were studied (Table 3). The amount of the catalyst was varied from 0.1 mol.% to 20 mol.%. The turnover numbers (TON) of the catalysts were reported only in one publication.⁵³ The yields in these reactions approach 100%; however, in some cases, the corresponding 1-oxides are formed as admixtures.

Table 3. Catalytic methods of oxidation of benzo[*b*]- and dibenzothiophenes.

Catalyst, solvent	Oxidant	Amount of the catalyst (mol.%)	Ref.
[Mn ^{IV} Mn ^{IV} (μ-O) ₃ L ₂](PF ₆) ₂ , ^a Py	H ₅ IO ₆	0.3–1.8	49
MeReO ₃ , MeCN, HClO ₄	H ₂ O ₂	3–10	50
Na ₂ WO ₄ , PhPO ₃ H ₂	H ₂ O ₂	0.1	51
[Me(<i>n</i> -C ₈ H ₁₇) ₃ N]HSO ₄			
MeReO(mtp)PPh ₃ ^b	Bu ^t OOH	1–3	52
[(R ₃ Sn) ₂ MoO ₄]· <i>n</i> H ₂ O ^c	H ₂ O ₂	1	53
CrO ₃ , MeCN	H ₅ IO ₆	10	54
MPcS ^d	KHSO ₅	10–20	55

^a L is 1,4,7-trimethyl-1,4,7-triazacyclononane; ^b mtp is 2-(mercapto-methyl)thiophenol; ^c R = Me, Bu, Ph, Bn, Cy (cyclohexyl); ^d M = Fe, Co, Ru; PcS is sulfophthalocyanine.

Recently, an efficient heterogeneous catalytic system based on Co-containing aluminophosphates (or MoO₃·Al₂O₃) and Bu^tOOH as the oxidant has been proposed.⁵⁶ High oxidation rates of 2,5-dimethyl-, benzo- and dibenzothiophenes were observed at 80 °C. Low cost of these catalysts is a benefit as regards solving the problem of desulfurisation of engine fuels.

Other inorganic reagents have also been used successfully for thiophene oxidation. A method for the synthesis of thiophene dioxides and their benzo derivatives containing various substituents (55 examples) has been patented.⁵⁷ Thiophenes were oxidised with a 30% solution of hydrogen peroxide in the presence of vanadium and molybdenum oxides generated *in situ* on treatment of the metals with H₂O₂.

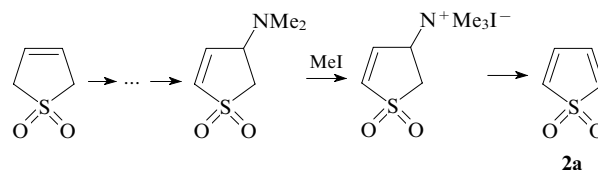
Commercially available reagents such as NaBO₃·4 H₂O in acetic acid⁵⁸ and the H₂O₂·[CO(NH₂)₂] complex in formic acid,⁵⁹ were employed for the oxidation of alkyl-substituted thiophenes and their benzo and dibenzo analogues. Under the action of these oxidants, the corresponding thiophene dioxides were formed in high yields; however, thiophenes containing functional groups and halogen atoms did not undergo oxidation.

Analysis of the above methods for the synthesis of thiophene 1,1-dioxides and their fused derivatives shows that the current

level of synthetic organic chemistry allows one to oxidise thiophenes with diverse substituents. Functionalised thiophene dioxides are prepared only using strong electrophilic oxidants such as CF₃CO₃H, HOF·MeCN and DMD, whereas compounds with electron-donating alkyl, silyl and germly groups are readily oxidised under the action of MCPBA. In recent years, attention has been focused on the development of all-purpose oxidants capable of converting any, including monosubstituted, thiophenes to the corresponding sulfones.

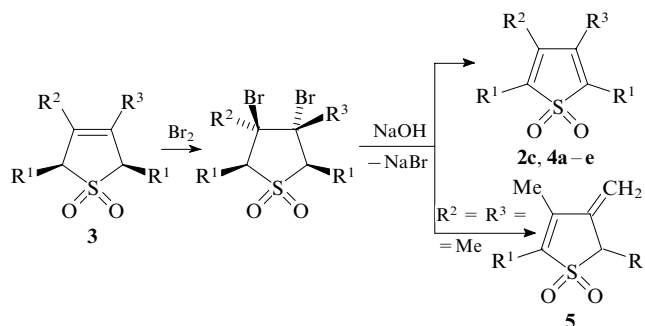
2. Elimination of substituents from sulfolane and sulfolene derivatives

Unsubstituted thiophene 1,1-dioxide (**2a**) was first synthesised by a six-stage sequence of transformations including Hofmann elimination.⁶⁰



Due to the tendency for fast di- and trimerisation, compound **2a** was prepared only as a solution in CHCl₃.

Later, this approach was simplified: bromination of readily available 3-sulfolenes **3** and elimination of HBr with NaOH powder resulted in target thiophene dioxides **4** in two steps.^{61,62} However, this method is inapplicable if there is an alternative way of hydrogen halide elimination to give an exocyclic double bond or if the product is capable of isomerisation. For example, the reaction of 3,4-dibromo-3,4-dimethylsulfolane with NaOH gives compound **5** containing an *exo*-methylene group. This reaction route takes place also for 2,3,4,5-tetramethyl-3,4-dibromosulfolane.

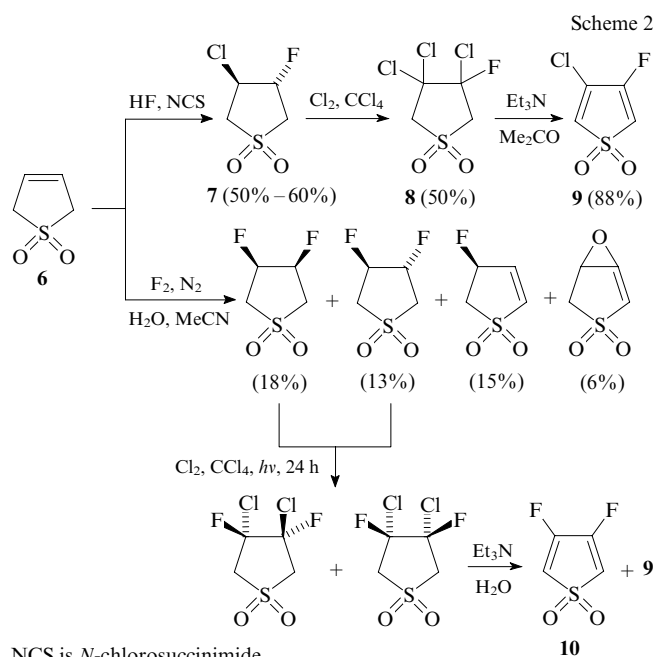


R¹ = R³ = H; R² = Me (**2c**), Et (**4a**), Cl (**4b**);

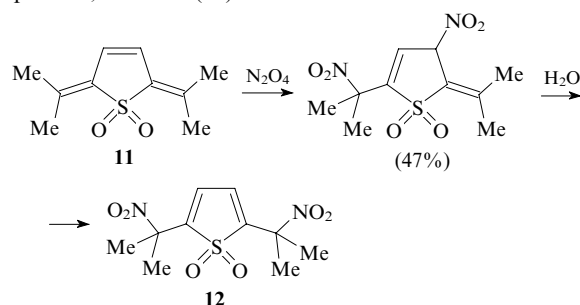
R¹ = H; R² = R³ = Cl (**4c**), Ph (**4d**); R¹ = R² = R³ = Me (**4e**).

The halogenation–elimination strategy was also used for the synthesis of fluorine-containing thiophene dioxides. Heating of 3-sulfolene (**6**) with anhydrous HF and *N*-chlorosuccinimide in an autoclave resulted in 4-chloro-3-fluorosulfolane (**7**), which undergoes radical chlorination to 3,3,4-trichloro-4-fluorosulfolane (**8**). Treatment of this product with triethylamine in acetone gives 4-chloro-3-fluorothiophene 1,1-dioxide (**9**) (Scheme 2).⁶³

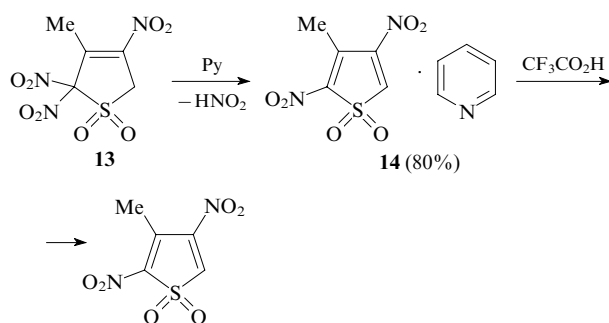
Diffuoro derivative **10** was prepared in a similar way. The addition of elemental fluorine to compound **6** gives a product mixture. The *cis*- and *trans*-difluoro derivatives isolated from this mixture by column chromatography were subjected to radical chlorination, which gave *trans*- and *cis*-isomers (ratio 5 : 1) in 68% yield. The subsequent elimination of HCl resulted in difluorothiophene dioxide **10**.⁶⁴ The last step may give compound **9** as a by-product through alternative elimination of HF. This fact was detected by ¹H NMR spectroscopy. The yield of thiophene dioxide **10** after purification by vacuum sublimation was 53%.



The addition of nitrogen(IV) oxide to 2,5-diisopropylidene-3-sulfolene (**11**), prepared by condensation of 3-sulfolene (**6**) with acetone, gives, after hydrolysis, 2,5-bis(1-methyl-1-nitroethyl)-thiophene 1,1-dioxide (**12**).⁶⁵



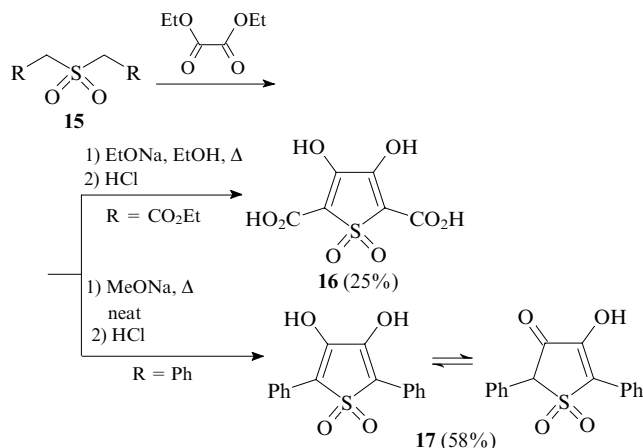
Easy elimination of nitrous acid from trinitro-3-sulfolene **13** under the action of bases (*e.g.*, pyridine) was used to prepare the corresponding 2,4-dinitro derivative.^{66,67} The final product of this transformation was isolated as pyridine complex **14**. Similar complexes of dinitrothiophene 1,1-dioxide with pyridine-d₅ (yield 84%), 4-picoline and quinoline (yields 75%) were also isolated. Treatment of complexes of type **14** with trifluoroacetic acid gave free thiophene 1,1-dioxides.



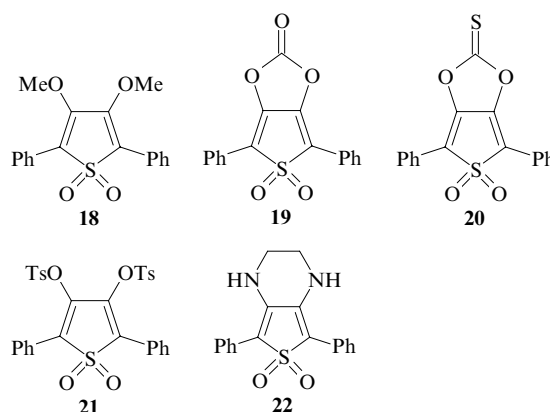
It is noteworthy that all the transformations described above based on the addition–elimination reactions in the sulfolene series and related structures are mostly multistep processes having low chemo- and regioselectivity, which substantially restricts the scope of applicability of this method for synthetic purposes.

3. Methods including ring formation

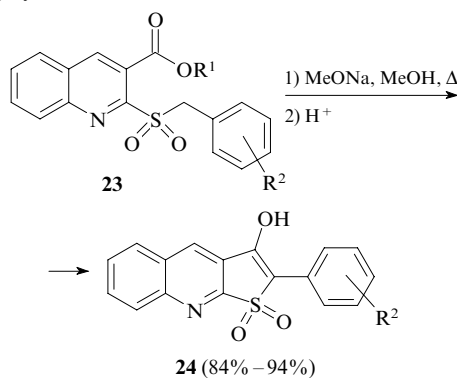
A number of thiophene 1,1-dioxides containing electron-donating substituents (amino, alkoxy or acyloxy groups) can be prepared by intra- and intermolecular cyclisations. The classical condensation of sulfones **15** with diethyl oxalate yields 3,4-dihydroxy derivatives **16** and **17**.⁶⁸ It was shown⁶⁹ that compound **17** is an equilibrium mixture of tautomers.



The reaction of compound **17** with diazomethane, phosgene, thiophosgene, *p*-toluenesulfonyl chloride and ethylenediamine affords derivatives **18–22**, which are true thiophene dioxides.^{69–71}



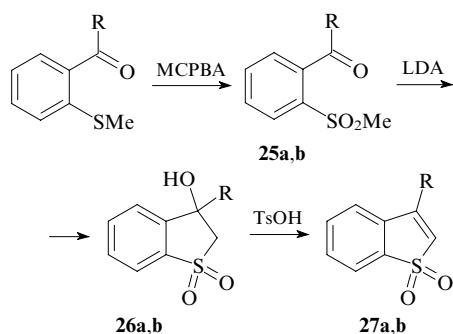
Using the strategy including intramolecular condensation of 3-carboxyquinolines **23**, tricyclic compounds **24** were obtained in high yields.⁷²



R¹ = H, Me; R² = H, 4-Cl, 3-F, 4-F, 4-MeO.

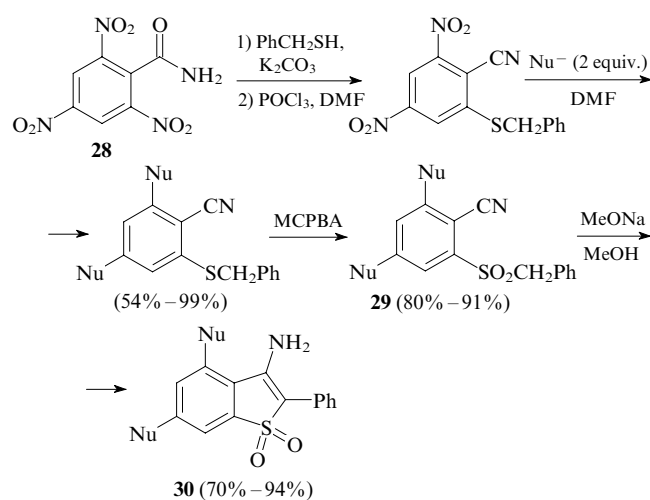
A similar approach has been utilised to obtain 3-substituted benzo[*b*]thiophene 1,1-dioxides.⁷³ For example, on treatment with lithium diisopropylamide (LDA), *o*-methylsulfonyl-substituted aceto- (**25a**) and benzophenones (**25b**) cyclise into dioxides **26a,b**.

The subsequent elimination of water induced by *p*-toluenesulfonic acid (TsOH) gives 3-methyl- (**27a**) and 3-phenylbenzo[*b*]thiophene 1,1-dioxides (**27b**) in high yields.



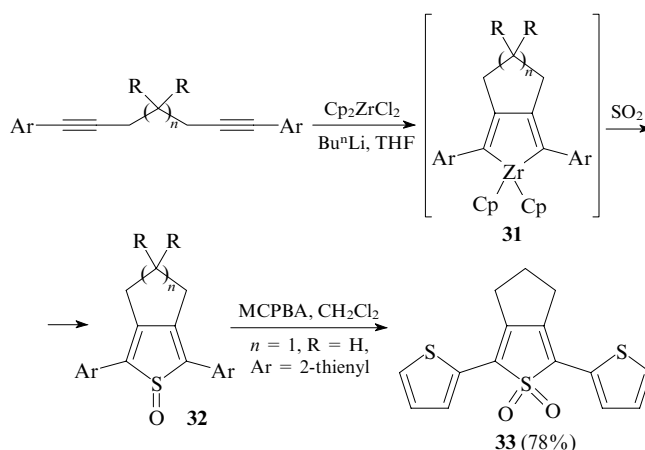
Compound	R	Yield (%)		
		25	26	27
a	Me	76	68	81
b	Ph	78	73	88

Intramolecular condensation has also been used⁷⁴ to prepare functionally substituted 3-aminobenzo[*b*]thiophene dioxides. The nitrile group acts as the 'carbonyl component' for the cyclisation. The whole sequence of transformations is based on modification of available 2,4,6-trinitrobenzamide (**28**) by successive replacement of the nitro groups by various O-, S- and N-nucleophiles. In the key step of the synthesis, the corresponding benzylsulfonylbenzonitrile **29** cyclises under the action of sodium methoxide to give compounds **30**.



Nu = OMe, OPh, OCH₂CF₃, N₃.

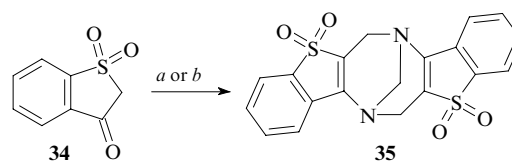
A method comprising the reaction of diaryl- α,ω -diacetylenes with zirconocene generated *in situ* from dicyclopentadienylzirconium chloride and *n*-butyllithium in THF has been proposed for the synthesis of oligomeric derivatives containing thiophene and thiophene 1,1-dioxide fragments. The subsequent treatment of organozirconium intermediates **31** with sulfur dioxide resulted in the corresponding thiophene 1-oxides **32** in nearly quantitative yields. Oxidation of oxide **32** ($n = 1$, R = H, Ar = 2-thienyl) with MCPBA gave oligomer **33** with a central thiophene dioxide fragment.⁷⁵ This approach was also used to prepare more complicated oligomeric structures employed currently in materials chemistry (see Section IV).



$n = 1, 2$; R = H, *n*-C₆H₁₁; Ar = 4-BrC₆H₄, 2-thienyl, 5-bromo-2-thienyl, 2,2'-bithienyl-5-yl.

4. Special methods of synthesis

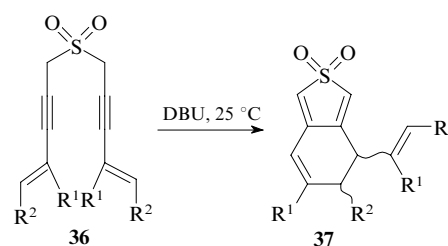
A number of procedures are known in which thiophene 1,1-dioxides and their benzo and dibenzo derivatives are formed as intermediates or as components of complex mixtures.^{3–6} Most often, these transformations are of no synthetic utility; therefore, we will cite only two examples of these reactions discovered in recent years. For example, oxo sulfone **34** is unexpectedly condensed under the action of urotropine or paraformaldehyde in acidic medium in the presence of ammonium acetate to give heterocycle **35** containing two benzo[*b*]thiophene 1,1-dioxide fragments.⁷⁶



(a) (CH₂)₆N₄, AcONH₄, AcOH or CF₃CO₂H;

(b) (CH₂O)_{*n*}, AcONH₄, AcOH, PhMe.

The tandem isomerisation–cyclisation of bis(alkenylpropargyl) sulfone **36** furnishes benzo[*c*]thiophene 1,1-dioxide derivative **37**.⁷⁷



R¹ = R² = (CH=CH)₂; R¹ = Me, R² = H; R¹ = R² = (CH₂)₄; DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene.

III. Reactions of thiophene 1,1-dioxides

The nonaromatic nature of thiophene 1,1-dioxides is responsible for their unique properties. The cyclic diene system bound to the SO₂ group exhibits high activity in both cycloaddition reactions and reactions with nucleophiles. In addition, the presence of the vinylsulfone fragment in the structure of thiophene dioxides makes it possible to carry out CH-deprotonation, oxidation and hydroxylation at the double bond, ring opening with SO₂ elimination and other nucleophilic and electrophilic transformations. All these reactions clearly demonstrate the great synthetic poten-

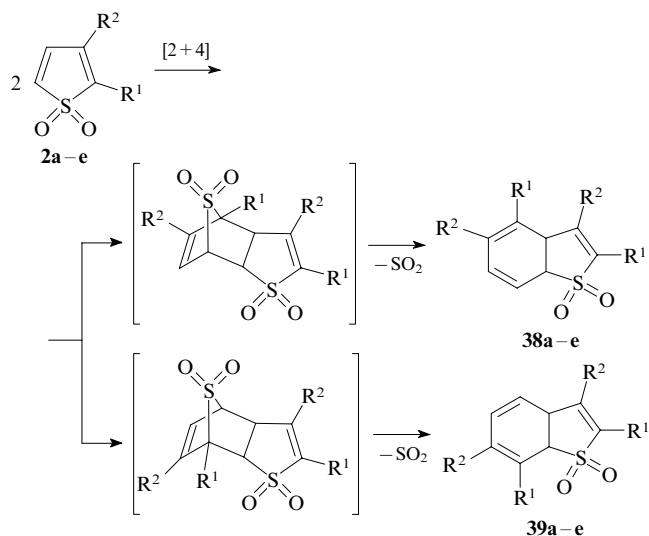
tial of this class of compounds and make thiophene dioxides convenient synthons for the formation of various carbo- and heterocyclic structures.

1. Cycloaddition reactions

a. The formation of dimers and trimers

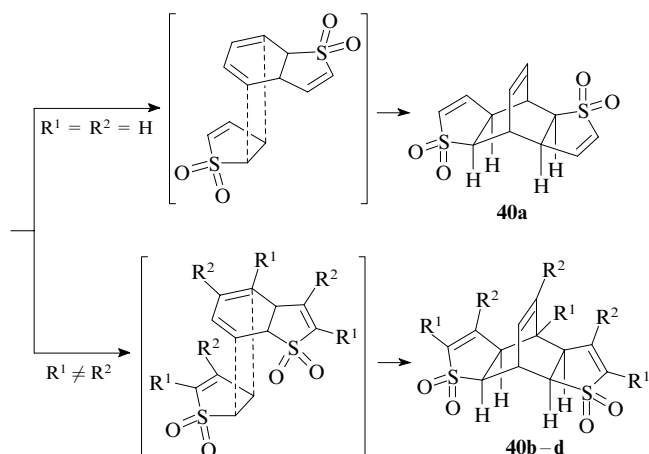
Thiophene 1,1-dioxides are able to undergo [2 + 4] dimerisation in which one molecule acts as a dienophile and the other one, as a diene. Unsubstituted and monosubstituted thiophene dioxides undergo spontaneous dimerisation even at low temperatures; this is why, for a long period these compounds have not been isolated but have been obtained only as dilute solutions. Thermally more stable 3,4- and 2,5-disubstituted and tetrasubstituted thiophene dioxides and their benzo and dibenzo analogues form [2 + 4] dimers at high temperatures. Dimerisation according to the [2 + 2] pattern typically occurs for benzo[*b*]thiophene dioxides on exposure to visible or UV light.

Unsubstituted thiophene dioxide (**2a**) slowly dimerises at temperatures above -25°C .⁴⁴ Spontaneous elimination of SO_2 from the resulting adduct gives rise to the formal dimer, dihydrobenzo[*b*]thiophene 1,1-dioxide (**38a**).^{44–46} Studies of various monosubstituted thiophene dioxides **2b–e** (R^1 or $\text{R}^2 = \text{H}$) have shown⁴⁶ that of the four possible regioisomers, only dimers **38** and **39** are formed, the former being the major reaction product. The authors attributed the regiochemical features of the reaction to steric factors: close proximity of the R^1 , R^2 and SO_2 groups in the transition state are energetically unfavourable; hence, the formation of isomer **38** is preferred.



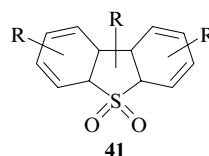
$\text{R}^2 = \text{H}$; $\text{R}^1 = \text{H}(\text{a})$, Me (**b**), Et (**d**), Br (**e**); $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Me}(\text{c})$.

38a–d + **2a–d** $\longrightarrow$

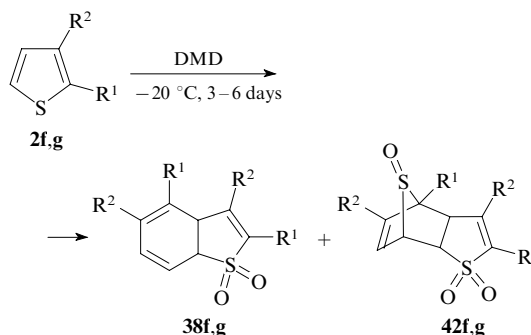


Heating of thiophene dioxide **2** to $25–30^{\circ}\text{C}$ in CDCl_3 gives rise to not only dimers (major products) but also minor trimers. It was shown that the product ratio changes toward trimer formation with an increase in the substrate concentration in solution. It is of note that in the case of unsubstituted thiophene dioxide (**2a**), the ‘head-to-tail’ trimer (**40a**) is produced, whereas sulfones **2b–d** give ‘head-to-head’ isomers (**40b–d**) as the only trimerisation products.

One more theoretically possible product **41** resulting from the reaction of compound **38** as a dienophile with the starting thiophene dioxide **2** as the diene was detected in none of the cases.



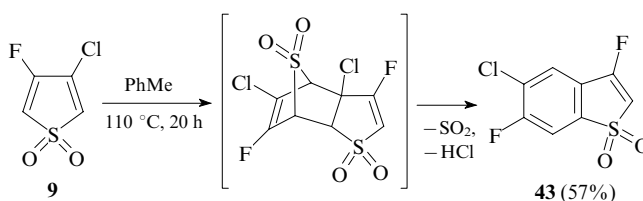
A study of the oxidation of monohalo-substituted thiophene 1,1-dioxides has shown that dimers **38f,g** and **42f,g** can be isolated from the reaction mixture in relatively low yields. Compounds **42** are formed upon cycloaddition of the corresponding thiophene 1-oxide and thiophene 1,1-dioxide, the latter acting as a dienophile.⁴⁶



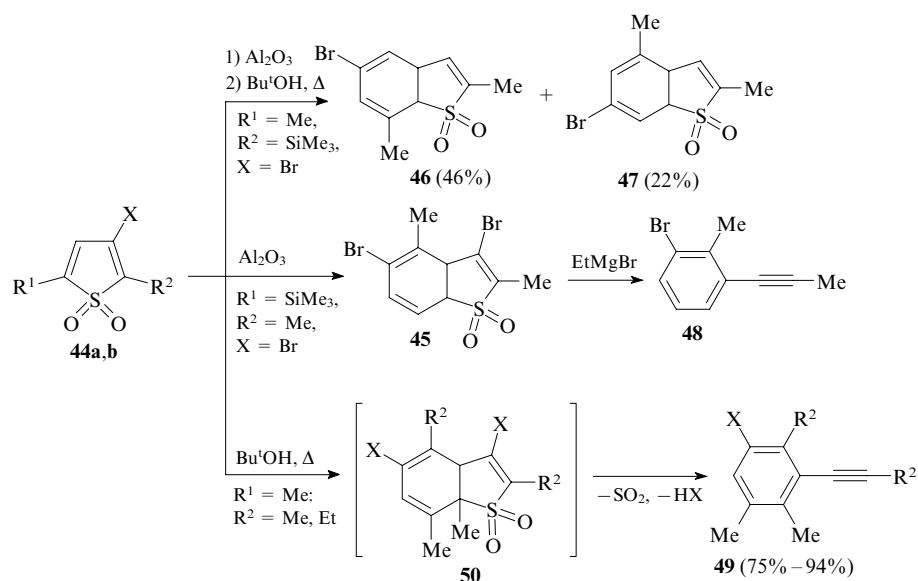
Sulfone	R^1	R^2	Yield (%)	
			38	42
f	H	Br	8	6
g	Cl	H	3	2

The structures of the dimers and trimers formed in this way were determined unambiguously by ^1H NMR spectroscopy,^{44–46} high-resolution mass spectrometry and X-ray diffraction.⁴⁶ The use of advanced spectroscopic techniques made it possible to determine the half conversion period of thiophene dioxides **2** and to propose the thermal stability series for these compounds. The susceptibility for dimerisation was found to decrease in the series: 2-ethyl- > 2-methyl- > 3-methyl- > unsubstituted thiophene dioxide.

The thermal stability of thiophene 1,1-dioxides increases with an increase in the number of substituents in the thiophene ring. For example, 4-chloro-3-fluorothiophene 1,1-dioxide (**9**) dimerises only upon long-term refluxing in toluene giving rise to benzo[*b*]thiophene 1,1-dioxide **43**.⁶³ In this case, the reaction does not stop after the formation of the cyclohexadiene adduct due to the possible easy elimination of both SO_2 and HCl from the bridged intermediate.



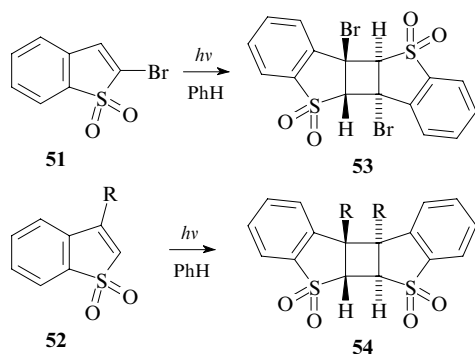
Scheme 3



44a: $R^1 = \text{Me}$, $R^2 = \text{SiMe}_3$; **44b:** $R^1 = \text{SiMe}_3$, $R^2 = \text{Me}$; **44b:** $R^1 = \text{Me}$, $R^2 = \text{Me}$, Et ; $\text{X} = \text{Cl}$, Br .

Trimethylsilyl-containing thiophene dioxides (**44a**) are desilylated on Al_2O_3 . This is accompanied by spontaneous formation of dimer **45**,⁷⁸ while heating of the intermediate thiophene dioxide in *tert*-butyl alcohol affords regioisomers **46** and **47**.⁷⁹ Adduct **45** was treated with EtMgBr to be converted into the corresponding substituted benzene **48** containing an acetylene fragment. Penta-substituted benzenes **49** were prepared by refluxing thiophene dioxide **44b** in Bu^tOH .⁸⁰ In the last-mentioned case, cycloaddition with SO_2 , gehydrohalogenation and subsequent isomerisation apparently occur *via* intermediate adduct **50** (Scheme 3).

Photocyclisation of benzo[*b*]thiophene 1,1-dioxides **51** and **52** affords ‘head-to-tail’ (**53**) and ‘head-to-head’ (**54**) dimers, respectively.^{81–83} The structures of these products were proved by ^1H NMR spectroscopy.⁸²

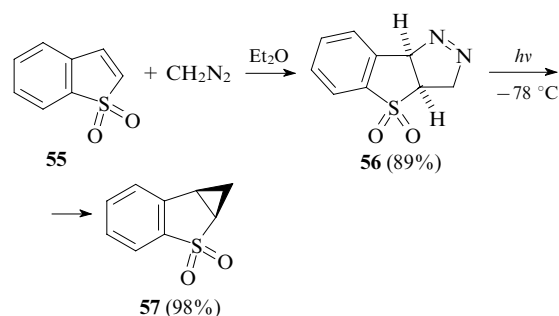


$\text{R} = \text{Me}$, Ph , CO_2H , CO_2Me .

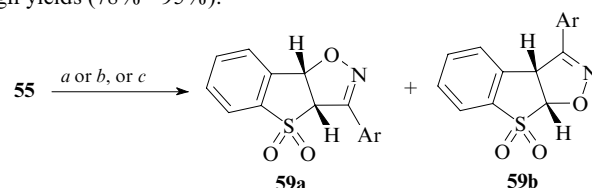
b. Thiophene dioxides as dipolarophiles in 1,3-dipolar cycloaddition

Thiophene 1,1-dioxides react with diverse 1,3-dipoles. In many cases, the process occurs regioselectively. Unsubstituted thiophene dioxide (**2a**) may give bisadducts, *i.e.* the products of dipole addition to two activated double bonds, depending on the amount of the dipole.

The reaction of benzo[*b*]thiophene 1,1-dioxide (**55**) with diazomethane affords adduct **56**, which is then photolysed to give tricyclic compound **57**.⁸⁴



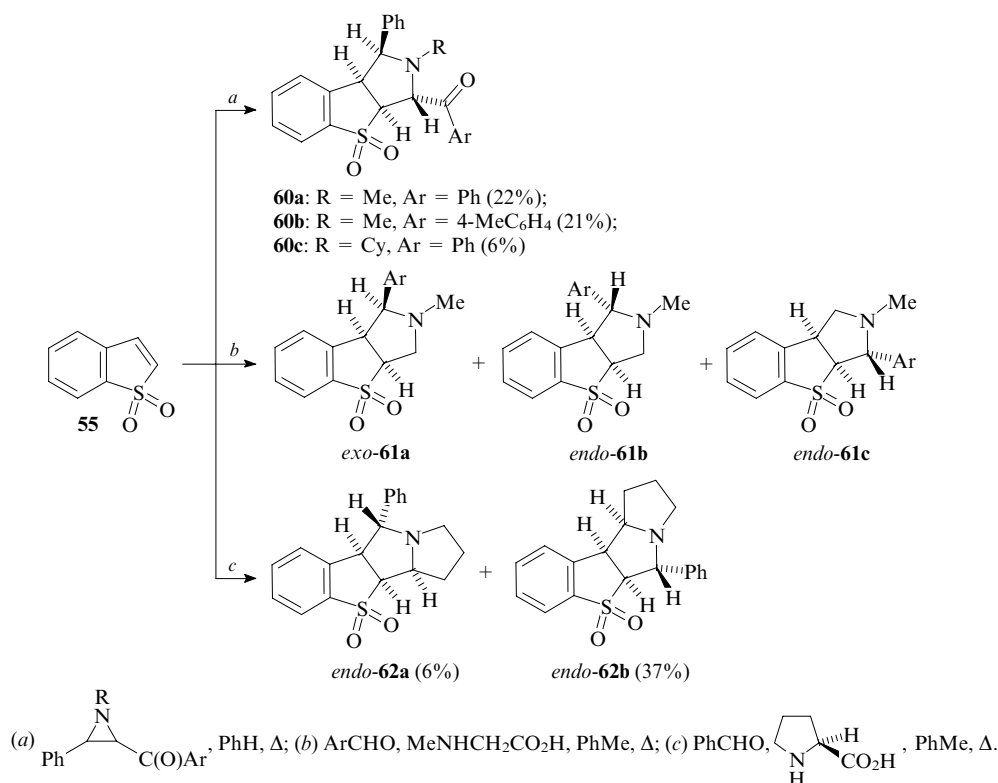
The addition of nitrile oxides $\text{ArC}\equiv\text{N}\rightarrow\text{O}$ (**58**) to sulfone **55** gives isomeric dihydroisoxazoles **59a,b** with high regioselectivity. The reaction is carried out under sonication (conditions *a*)⁸⁵ or microwave (MW)⁸⁶ irradiation (conditions *b* or *c*) to generate nitrile oxide **58** *in situ* from the corresponding aldoxime. Under conditions *a* and *c*, the adduct is formed as a single isomer **59a** in high yields (78%–95%).



(*a*) $\text{ArCH}=\text{NOH}$, $\text{Ca}(\text{OCl})_2$ or NaOCl , $\text{H}_2\text{O}-\text{CH}_2\text{Cl}_2$, sonication;
 (*b*) $\text{ArCCl}=\text{NOH}$, Al_2O_3 , MW irradiation; (*c*) $\text{ArCH}=\text{NOH}$, NCS , Al_2O_3 , MW irradiation;
 $\text{Ar} = \text{Ph}$, $4\text{-MeC}_6\text{H}_4$, $4\text{-MeOC}_6\text{H}_4$, $4\text{-NO}_2\text{C}_6\text{H}_4$, $2\text{-ClC}_6\text{H}_4$, $2,4,6\text{-(MeO)}_3\text{C}_6\text{H}_2$, $3,4\text{-(OCH}_2\text{O)}_2\text{C}_6\text{H}_3$.

Recently, 1,3-dipolar cycloaddition of dioxide **55** to various azomethine ylides has been studied.⁸⁷ The generation of these ylides *in situ* by thermal cleavage of the aziridine ring in the presence of benzothiophene dioxide results regio- and stereospecifically in adducts **60a–c**. From either *cis*- or *trans*-aziridines (Scheme 4, conditions *a*), only one isomer is formed in low yield.

Scheme 4

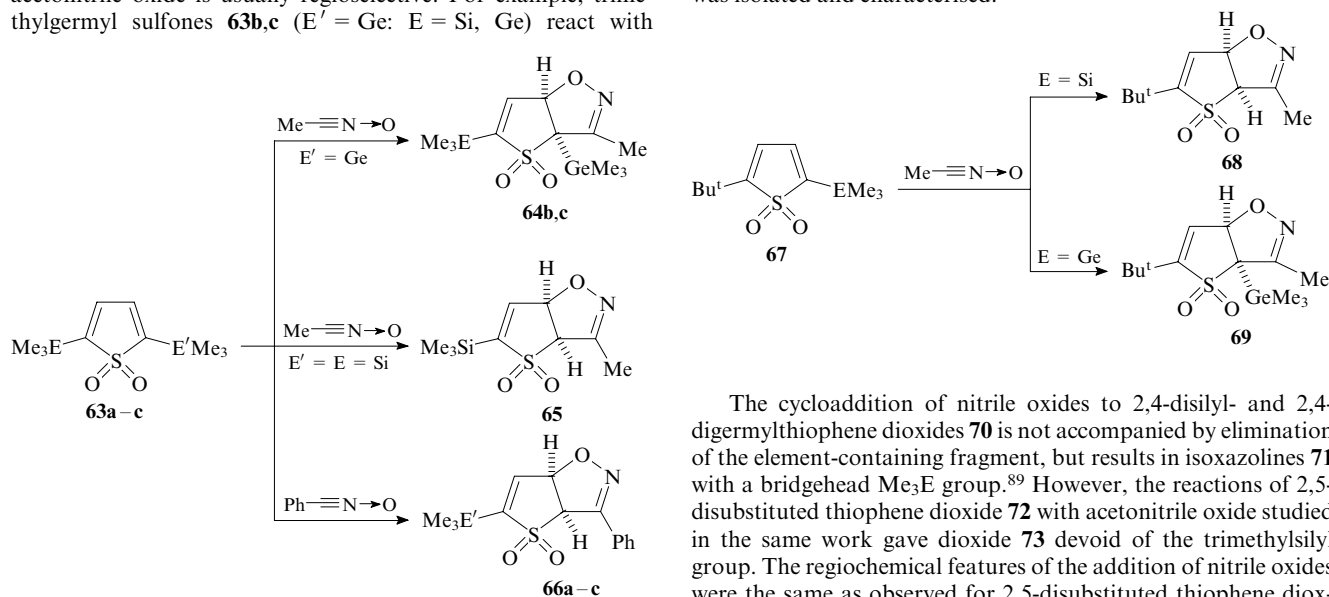


In order to increase the yields in this reaction, alternative attempts to generate the ylide have been undertaken. Thus cycloaddition of dioxide **55** to reactive azomethine ylides generated *in situ* from an aldehyde and an amino acid (sarcosine or proline) with decarboxylation (refluxing in toluene) gives compounds **61a–c** (yields 60%–99%) (conditions *b*) or **62a,b** (conditions *c*). In the latter case, *exo*-adducts are formed (yield 10%), the structure of which has not been unambiguously proven. Thus, the researchers cited were able to increase the overall yield of the products, but this method showed low regio- and stereoselectivities.

In studies of dipolar cycloaddition of acetonitrile oxide and benzonitrile oxide to thiophene dioxides containing silyl- and/or germyl-substituents in positions 2,5 or 2,4, the regiochemical features of these reactions were elucidated.^{88–90} The addition of acetonitrile oxide is usually regioselective. For example, trimethylgermyl sulfones **63b,c** ($\text{E}' = \text{Ge}$; $\text{E} = \text{Si}$, Ge) react with

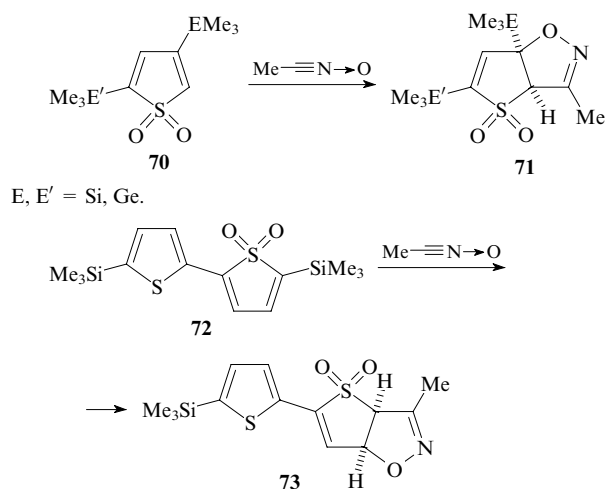
acetonitrile oxide to give only the addition products to the element-containing vinyl fragment, *i.e.* compound **64b,c**. In the case of silyl derivative **63a** ($\text{E} = \text{E}' = \text{Si}$), the addition process is accompanied by parallel elimination of the trimethylsilyl group to give heterocycle **65**. The reaction of 2,5-disubstituted thiophene dioxides **63a–c** with benzonitrile oxide gives adducts **66a–c** with desilylation or degermylation of one Me_3E group ($\text{E} = \text{Si}$ or Ge) from the side of dipole addition. As in the reaction with acetonitrile oxide, the trimethylgermylvinyl fragment of the molecule is most reactive, which accounts for the regioselective formation of only one product.⁸⁸

Similarly, MeCNO is added to 2-*tert*-butyl-5-(trimethylsilyl)thiophene 1,1-dioxide (**67**) to the vinylsilyl fragment of the molecule, resulting in desilylated product **68**. In the case of germyl derivative, the corresponding GeMe_3 -containing heterocycle **69** was isolated and characterised.



The cycloaddition of nitrile oxides to 2,4-disilyl- and 2,4-digermylthiophene dioxides **70** is not accompanied by elimination of the element-containing fragment, but results in isoxazolines **71** with a bridgehead Me_3E group.⁸⁹ However, the reactions of 2,5-disubstituted thiophene dioxide **72** with acetonitrile oxide studied in the same work gave dioxide **73** devoid of the trimethylsilyl group. The regiochemical features of the addition of nitrile oxides were the same as observed for 2,5-disubstituted thiophene dioxides. The exceptional regioselectivity of the dipole addition to the

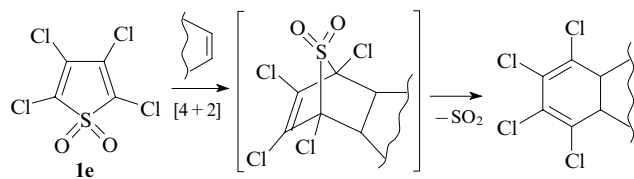
C(4)=C(5) double bond was interpreted resorting to quantum-chemical calculations (see Section V).



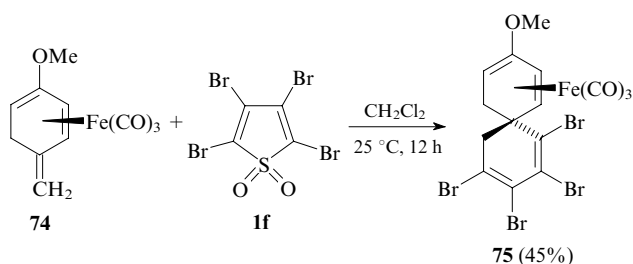
c. Thiophene dioxides as dienes in [4 + 2] cycloaddition reactions

Thiophene 1,1-dioxides react as the 4π -diene component with many compounds containing an unsaturated bond. The tetrachloro (**1e**) and tetrabromo derivatives (**1f**)^{1–3} and sulfones containing *tert*-butyl, neopentyl and 1-adamantyl substituents have been best studied in such transformations.^{3,7} The thermal stability of these compounds allows one to perform cycloaddition at high temperatures, which markedly extends the range of dienophiles used. The presence in the molecule of the SO_2 group capable of being eliminated from the reaction products makes this type of transformations especially attractive from the synthetic standpoint. Moreover, [4 + 2] cycloaddition is usually associated with reverse electronic demand to dienophiles; hence, a broad range of alkenes and alkynes and dehydrobenzene derivatives can be involved in the reaction.

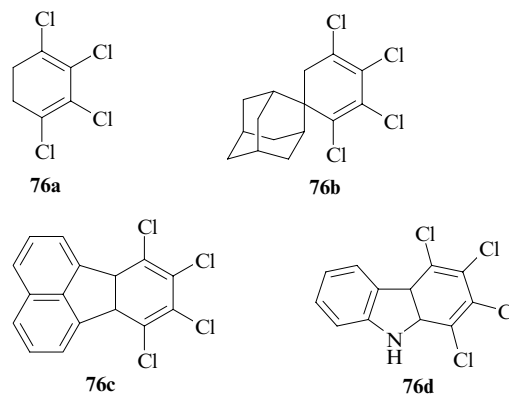
The cycloaddition results in adducts containing a bridging SO_2 group. They often cannot be isolated in a pure state, but undergo spontaneous elimination of sulfur dioxide to give halogenated cyclohexadiene derivatives.



When alkenes contain an *exo*-methylene double bond, the formation of spiro compounds is possible. The recently reported reaction of thiophene dioxide **1f** with complex **74** is a good example of such transformation.⁹¹ Spiro[5.5]undecane complex **75** is formed stereoselectively in several hours. According to X-ray diffraction data for this compound, the tetrabromocyclohexadiene fragment is formed upon *exo*-addition of dienophile **74** to the methylene group, which is due to steric factors.

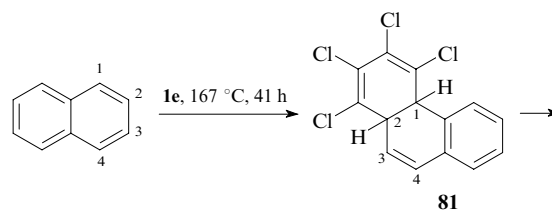


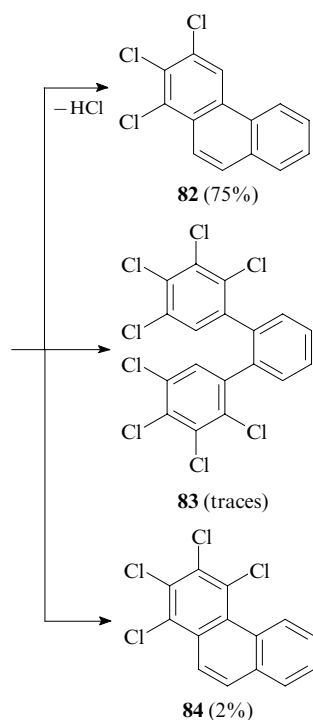
Raasch^{1,28} comprehensively studied the reactivity of thiophene dioxides **1e,f** with respect to various dienophiles. It was shown that sulfone **1e** can form adducts with ethylene, cyclic and acyclic alkenes and with heterocycles. Given below are examples of cycloadducts formed from thiophene 1,1-dioxide **1e**, namely, compounds **76a–d**, where ethylene, 2-methyleneadamantane, acenaphthylene and indole, respectively, acted as the annulation substrates.



If the substrate contains more than one dienophile centre, double addition products or mixtures of mono- and bis-adducts are formed in the reaction. In the studies published after Raasch's works, this approach was used to introduce a tetrachlorocyclohexadiene fragment into various molecules. For example, cycloaddition of sulfone **1e** to substrates having a cage-type carbon skeleton containing one or two $\text{C}=\text{C}$ bonds has been studied.^{92–96} These compounds usually have an inert double bond and do not react with dienes such as cyclopentadiene, furan or 2,3-dimethylbuta-1,3-diene. Nevertheless, under relatively drastic conditions (long-term heating to 115–160 °C), cage alkenes are annulated by thiophene 1,1-dioxide **1e** to give the corresponding adducts.^{92–96} Examples of such reactions are given in Scheme 5.

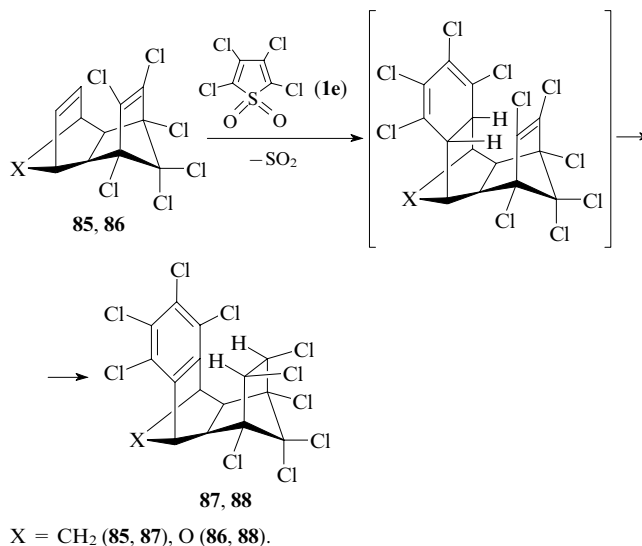
The high reactivity of thiophene 1,1-dioxides is perfectly illustrated by the cycloaddition of sulfone **1e** to naphthalene.⁹⁷ First, the reaction gives intermediate adduct **81** through addition to the C(1)=C(2) double bond. Then three reaction routes develop simultaneously, resulting in a product mixture: 1,5-hydride shift followed by elimination of HCl and aromatisation gives phenanthrene **82**; the addition of a second molecule of sulfone **1e** to the C(3)=C(4) bond of intermediate **81** followed by dehydrogenation and C–C bond cleavage with aromatisation leads to compound **83**; and dehydrogenation of the intermediate adduct **81** gives phenanthrene derivative **84**. The first route predominates: the yield of adduct **82** is 75%.⁹⁷ The authors do not give detailed explanation for the regioselectivity observed or assumptions about the predominant contribution of the route including double bond migration.





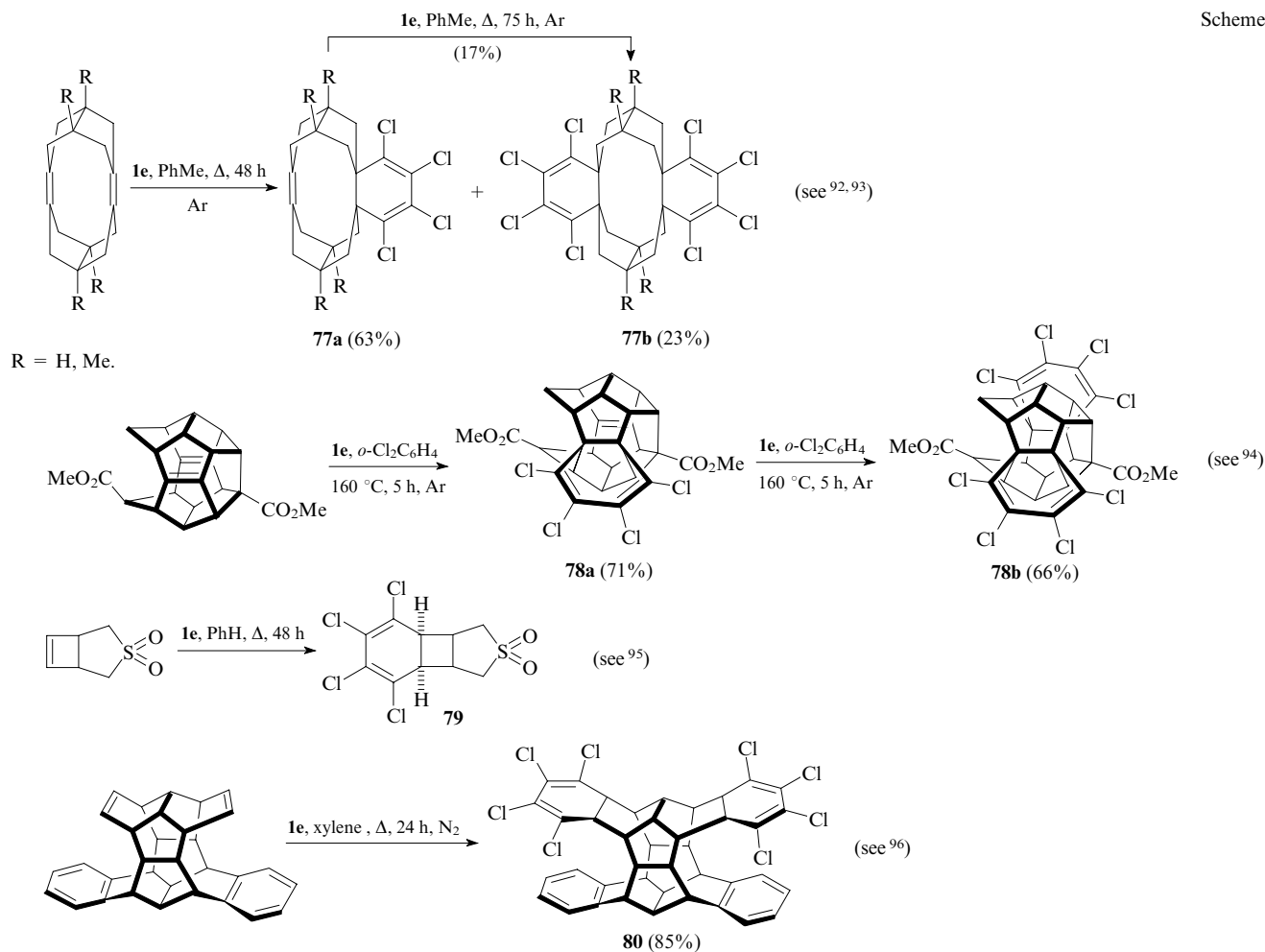
It is noteworthy that migration of hydrogen atoms in some thiophene dioxide adducts is well studied. For example, aldrin derivative **85** and its heterocyclic analogue **86** react with sulfone **1e** to give an intermediate compound in which the cyclohexadiene

ring protons are arranged in space near the neighbouring double bond. The regiospecific migration of hydrogen atoms in this adduct gives a saturated bond, while the tetrachlorocyclohexadiene fragment undergoes aromatisation, which is the driving force of the process. Thus, compounds **87** and **88** containing a benzene ring are the only products of these reactions.^{98–100}

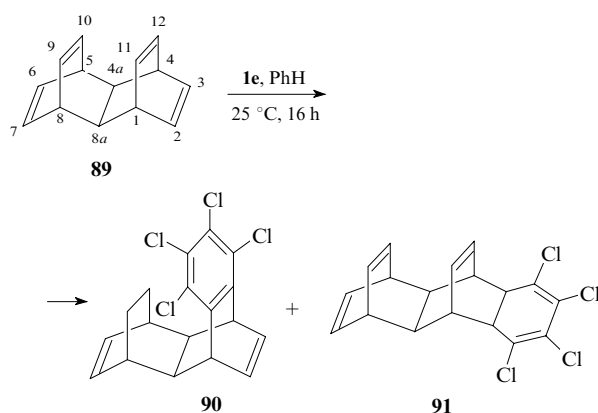


The oligomeric derivatives of bicyclo[2.2.2]octadiene undergo a similar rearrangement.^{101, 102} The reaction of tetracyclic compound **89** with dioxide **1e** yields a mixture of adducts **90** and **91** in

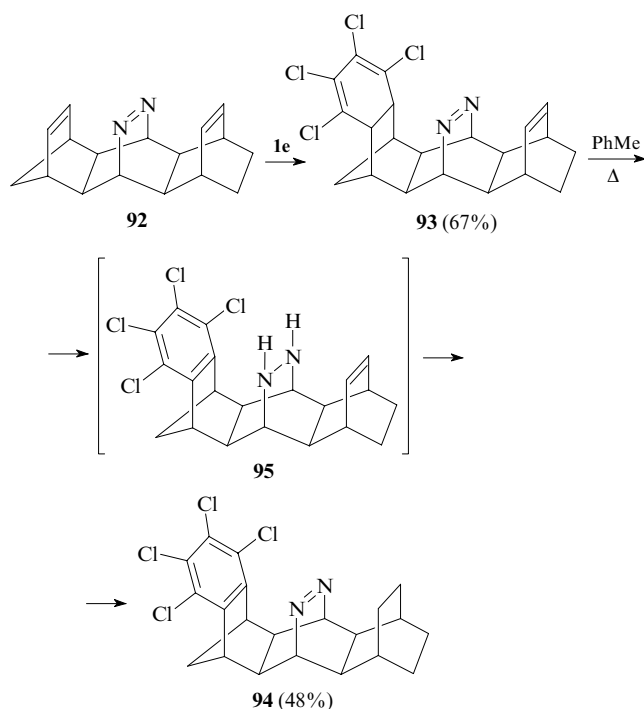
Scheme 5



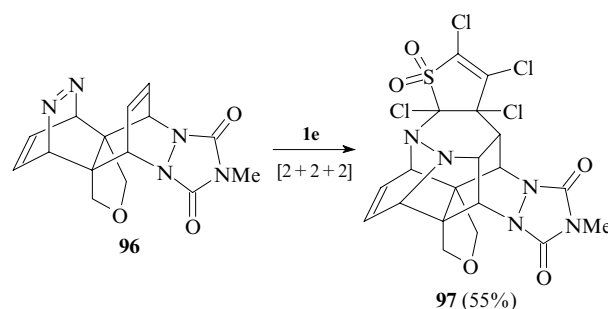
6:1 ratio (overall yield 95%). The diene addition to the C(11)=C(12) bond followed by hydrogen atom migration affords compound **90**, whereas compound **91** is the product of 'normal' [4 + 2] cycloaddition of sulfone **1e** to the C(2)=C(3) bond.



Nevertheless, when tetrachlorothiophene dioxide **1e** reacts with oligocyclic compound **92** containing two vinylene and one azo bridge, the annulation product **93** can be isolated and characterised.¹⁰³ The process is regioselective and gives the corresponding adduct involving only the norbornene fragment. The hydrogen atom migration described above can also occur for this type of structures but at higher temperatures. Heating of compound **93** in toluene gives hydrogen migration product **94**, presumably, *via* the intermediate formation of hydrazine **95**.¹⁰³

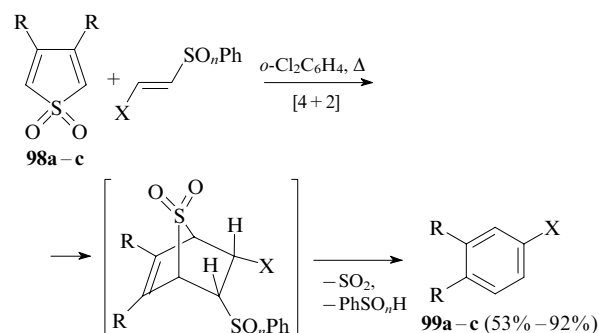


However, cycloaddition of sulfone **1e** to compound **96** with a structure similar to those described above follows an absolutely different route. The azo bridge does not undergo 'normal' [4 + 2] addition but undergoes unusual [2 + 2 + 2] cyclocondensation to give adduct **97**.¹⁰⁴



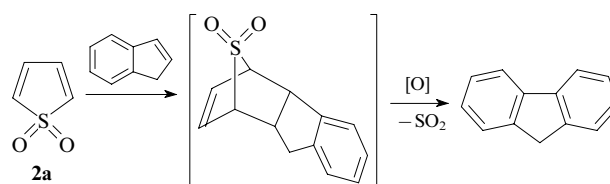
The preparation of substituted benzenes from thiophene dioxide adducts is a synthetically significant transformation for the chemistry of this class of compounds. The rearrangements described above represent a possible way to address this problem; however, cycloaddition of thiophene dioxides to substituted alkenes and alkynes giving the corresponding benzene derivatives is most practically valuable.

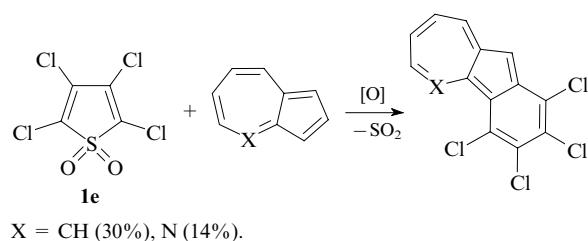
The elimination of SO₂ from thiophene 1,1-dioxide adducts with alkenes and the subsequent elimination of the leaving group or oxidation often result in aromatic derivatives without isolation of the intermediate adducts. This type of reactions has been thoroughly studied for thiophene dioxides **98a–c** containing bulky substituents: *tert*-butyl, adamantyl and neopentyl groups. The use of phenyl vinyl sulfoxide and phenyl vinyl sulfone as dienophiles gave sterically hindered benzenes, **99a–c**, difficult to prepare by other methods, in good yields.^{20–22} In these transformations, benzenesulfenic and benzenesulfinic acids are the leaving groups.



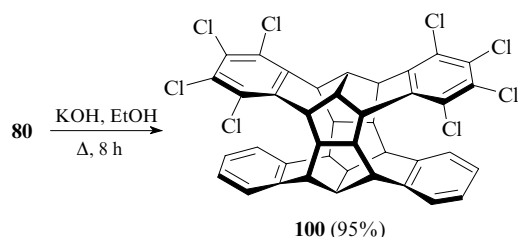
R = Bu^t (**a**), *neo*-C₅H₁₁ (**b**), 1-Ad (**c**); X = H, SO₂Ph; n = 1, 2.

As noted above, oxidation of the intermediate cycloadducts represents yet another method for the synthesis of substituted aromatic compounds starting from thiophene dioxides. This procedure often does not require additional reagents: in air, the products can be obtained without isolation of the initial cyclohexadiene derivative. For example, the reaction of unsubstituted thiophene 1,1-dioxide (**2a**) with indene affords fluorene resulting from oxidation of the intermediate adduct with atmospheric oxygen.⁴⁴ The dehydrogenation products were also isolated in the reactions of tetrachlorothiophene dioxide **1e** with both azulene¹⁰⁵ and its aza analogue.¹⁰⁶

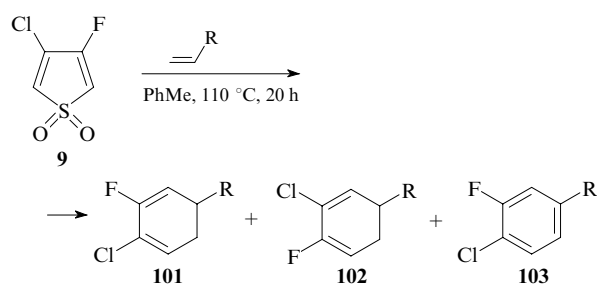




However, the cage adduct **80** mentioned above is not oxidised in air; it is converted into dibenzo derivative **100** on heating in an ethanolic solution of potassium hydroxide.⁹⁶

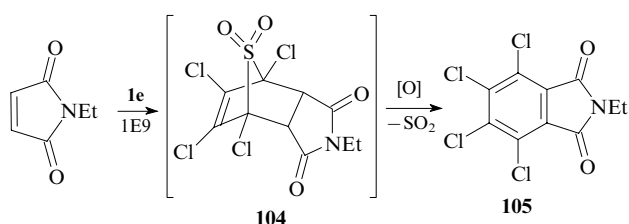


In some cases, reactions of thiophene 1,1-dioxides with alkenes give mixtures of aromatic compounds and cyclohexadiene derivatives. The reactions of asymmetric thiophene dioxide **9** with various monosubstituted alkenes can be considered as examples of such transformations. The presence of chemically similar substituents in positions 3 and 4 of the thiophene molecule precludes the preparation of adducts with a reasonable regio- and chemoselectivity. These reactions furnish mixtures of isomeric annulation products (**101**, **102**) and dehydrogenation products (**103**).



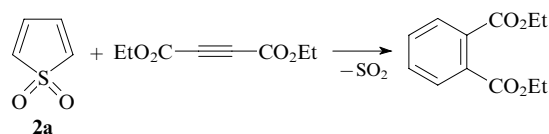
R = CH₂OH, CH₂Br, CO₂Me.

It can be seen from the foregoing data that halogen and alkyl derivatives of thiophene dioxide are fairly reactive dienes and can be converted into both mono- and bisannulated products. Drawbacks of these methods usually include high temperature and long reaction time and in some cases, low regioselectivity of the addition. An alternative approach^{107–109} is free from these drawbacks. This approach is cycloaddition of perhalogenothiophene dioxides **1e,f** to *N*-methylmaleimide catalysed by the enzyme diels-alderase (the 1E9 antibody as a chimeric Fab). The 1E9 antibody refers to the class of immunoglobulins having high affinity for some derivatives with cage structure. The ability to catalyse this reaction is due to the fact that bridged intermediate **104** has a structure similar to that of bicyclo[2.2.1]heptene and high affinity for the enzyme active site. Conversely, product **105** has a low binding constant with the enzyme, because the sulfone bridge is lost upon elimination of SO₂ and the structure becomes planar.

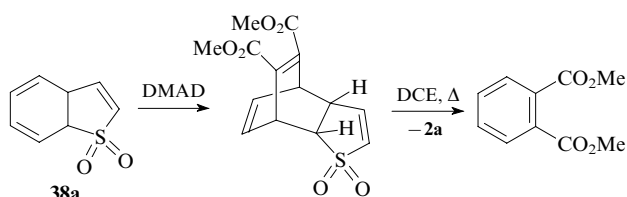


d. Reactions of thiophene dioxides with alkynes

Reactions of [4 + 2] cycloaddition of thiophene dioxides to alkynes also yield substituted benzenes. Thus unsubstituted thiophene 1,1-dioxide (**2a**) reacts with diethyl acetylenedicarboxylate to give diethyl phthalate.⁶⁰

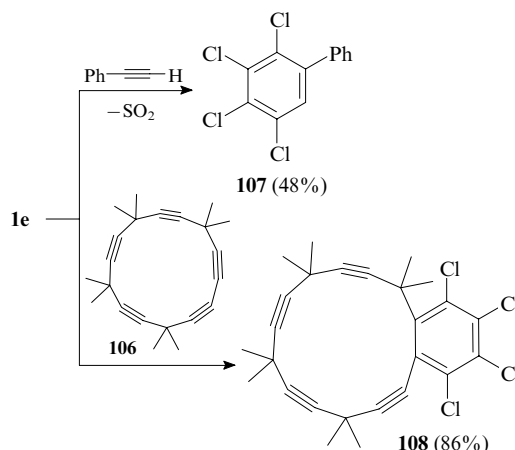


However, recent studies have shown⁴⁴ that this reaction involves the dimer of thiophene dioxide **38a**. This dimer forms an adduct with dimethyl acetylenedicarboxylate (DMAD), which decomposes on heating into dimethyl phthalate and thiophene dioxide **2a**.

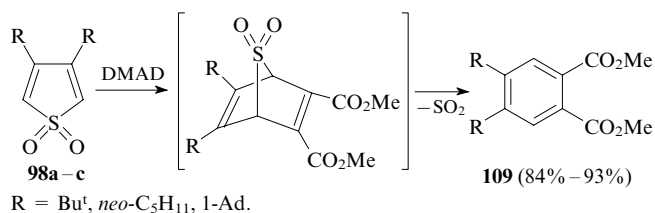


DCE = Cl(CH₂)₂Cl.

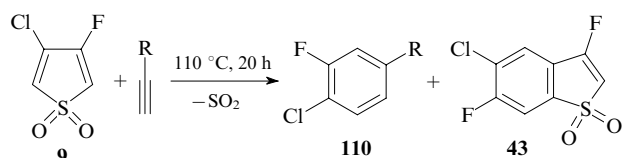
The reactions of tetrachlorothiophene 1,1-dioxide (**1e**) with phenylacetylene²⁸ and cyclic alkyne **106**¹¹⁰ yield 1,2,3,4-tetrachloro-5-phenylbenzene (**107**) and compound **108**, respectively.



The use of 3,4-di(*tert*-butyl, neopentyl or adamantyl)-thiophene dioxides **98a–c** in reactions with various acetylenes provides a route to sterically hindered substituted benzenes that are difficult to prepare by other methods.^{21,22} For example, the reaction with DMAD can serve as a convenient method for the synthesis of sterically hindered derivatives of phthalic acid **109**.

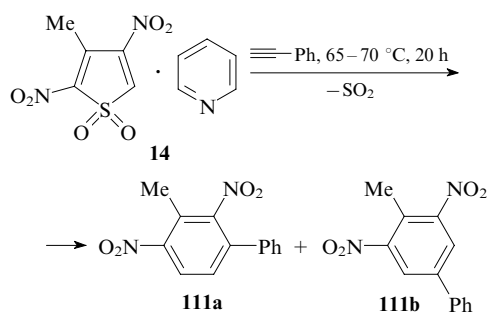


The reaction of thiophene dioxide **9** with various alkynes results in *ortho*-substituted chlorofluoroaromatic compounds **110**.⁶³ Dimerisation of thiophene dioxide **9** accompanied by elimination of HCl and SO₂ from the intermediate adduct to give benzothiophene dioxide **43** is a competing process in this case. It is noteworthy that the reaction is regioselective, giving only products **110** with *para*-positions of the chlorine atom and the R group.



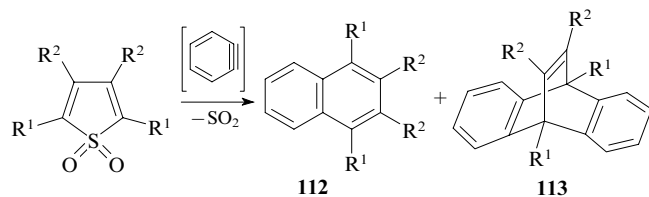
R	Yield (%)	
	110	43
Ph	57	—
CH ₂ OH	38	11
CH ₂ Br	45	14

The addition of phenylacetylene to complex **14** results in mixtures of adducts with equal contents of each regioisomer **111a,b** (total yield 20%). The lack of regioselectivity in this transformation was attributed to different directing effects of the substituents in the molecule of diene **14**.⁶⁷



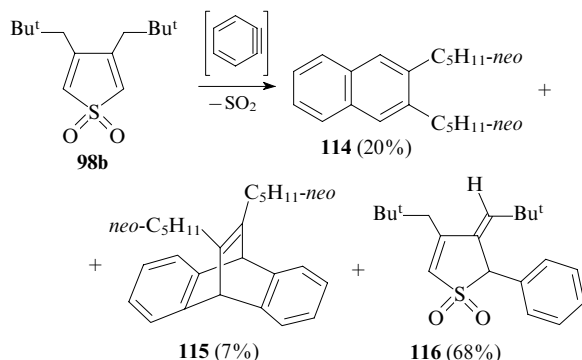
e. Reactions of thiophene dioxides with benzyne

Benzyne prepared by decomposition of diazonium salts readily reacts with thiophene dioxides. These cyclisations give substituted naphthalenes **112** (in up to 64% yields).¹¹¹ In some cases, the naphthalenes formed further react with benzyne to give benzo-barrelene derivatives **113**.



R¹, R² = H, Me, Bu^t, 1-Ad, Ph, Cl.

The reaction of 3,4-dineopentylthiophene 1,1-dioxide (**98b**) with excess dehydrobenzene gave the expected adducts, that is, respective derivatives **114** and **115**; however, the 'ene' reaction leading to product **116** (yield 68%) was the major route of the process. Apparently, the formation of sulfone **116** in which the

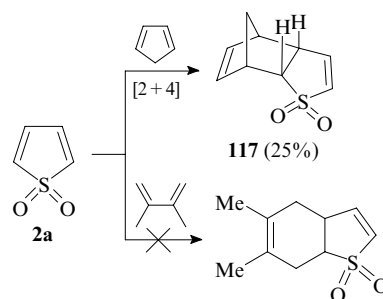


tert-butyl and neopentyl groups are most remote is more favourable than the formation of sterically hindered cycloadducts.²⁰

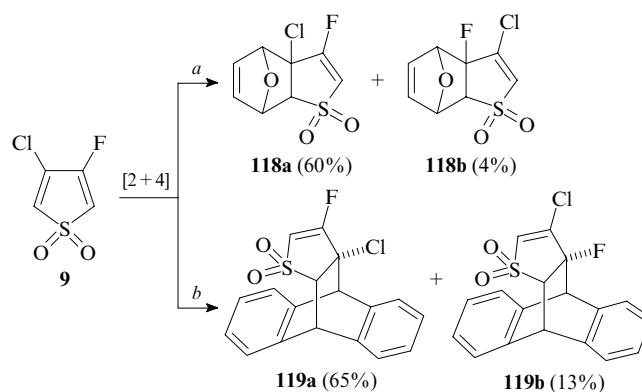
e. Thiophene dioxides as dienophiles in [2 + 4] cycloaddition

The reactions in which thiophene 1,1-dioxides function as dienophiles have long remained poorly studied. When reacting as the 2π-component, these sulfones are incapable of spontaneous elimination of SO₂ from the adducts; therefore, they should be more electron-withdrawing (dienophilic). Before 1997, only a few publications reported the formation of [2 + 4] adducts in reactions of thiophene dioxides. These studies are adequately reflected in reviews^{1,3} and we do not discuss them here.

It has been shown^{44,45} that, with a pronounced tendency for dimerisation even at low temperatures, unsubstituted thiophene dioxide (**2a**) is able to react as a dienophile only with cyclopentadiene. This process lasts for 18 h at 5 °C and gives [2 + 4] cycloadduct **117**, whereas the reaction with 2,3-dimethylbutadiene results only in dimerisation of sulfone **2a**. The *endo*-configuration of the resulting adduct **117** was unambiguously proved by NMR (NOESY) studies.

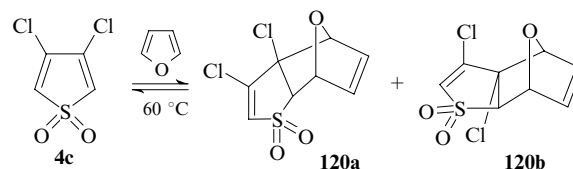


Thiophene dioxide **9** also acts as the dienophile in some reactions. For example, it reacts with furan and anthracene to give [2 + 4] cycloadducts **118** and **119**.⁶³ Due to non-symmetric structure of the initial sulfone, the cycloaddition results in a mixture of regioisomers. It should be noted that adducts with a chlorine atom at the bridging fragment are formed as predominant isomers (isomers **118a** and **119a**).

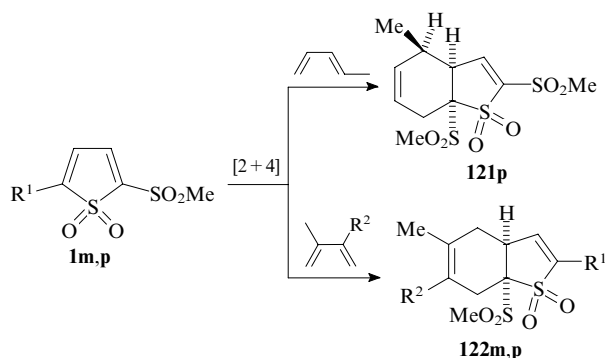


(a) furan, PhMe, 110 °C, 20 h; (b) anthracene, 110 °C, 20 h.

3,4-Dichlorothiophene 1,1-dioxide (**4c**) reacts as a dienophile with furan in a similar way to give a mixture of stereoisomers **120a,b** in almost equal amounts (**120a** : **120b** = 55 : 45). At elevated temperatures (> 60 °C), retro-Diels–Alder reaction takes place leading to the starting compounds.¹¹²



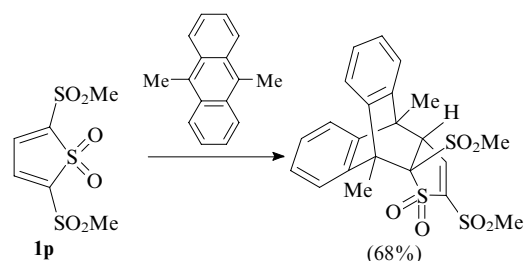
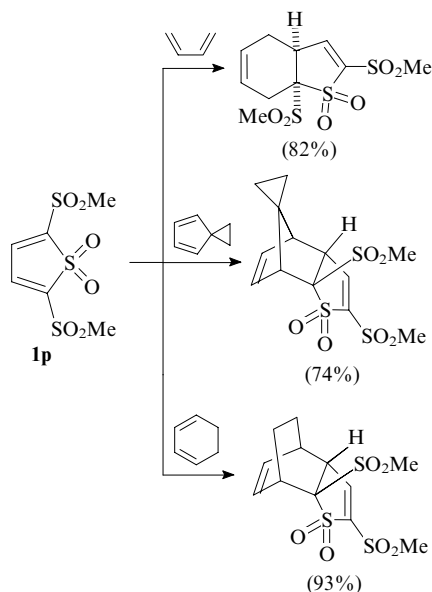
Study of previously known thiophene dioxides containing electron-withdrawing groups arouses considerable interest among organic chemists. These compounds should represent a new class of highly reactive dienophiles, because their molecules are characterised by low electron densities. Indeed, it has been found¹¹³ that sulfones **1m,p** react with 1,3-dienes, resulting in high yields of [2 + 4] adducts **121p** and **122m,p**.



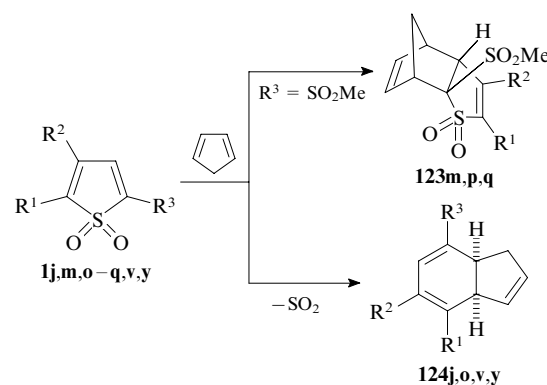
Product	R^2	Yield (%)
121p	—	98
122m	H	90
	Me	89
122p	H	98
	Me	96

In the reactions of non-symmetrical thiophene dioxide **1m** with isoprene and 2,3-dimethylbuta-1,3-diene, compounds **122m** are formed chemoselectively, in particular, the addition takes place from the side of the most electron-acceptor double bond. In addition, the reaction with isoprene gives regioselectively adduct **122m** ($R^2 = \text{H}$) in which the Me and SO_2Me groups occur in the *para*-positions. An unexpected result was obtained in the reaction of 2,5-di(methylsulfonyl)thiophene 1,1-dioxide (**1p**) with piperylene (penta-1,3-diene). Instead of the expected 1,2(or *ortho*)-adduct, the reaction gave isomeric 1,3(or *meta*)-*endo*-adduct **121p**. This outcome was interpreted using quantum-chemical calculations of the transition state energies (see Section V).¹¹³

The reactions of thiophene dioxides containing electron-withdrawing groups (for example, **1p**) with various open-chain and cyclic dienes are of general character resulting chemo-, regio- and stereoselectively in the corresponding [2 + 4] adducts.

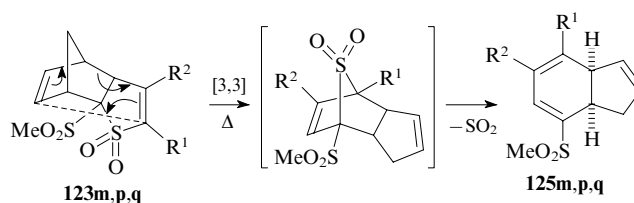


However, it was found¹¹⁴ that similar reaction with cyclopentadiene follows two pathways, *i.e.*, thiophene dioxide can act as either dienophile or diene. Thiophene dioxides containing two strong electron-withdrawing groups act as dienophiles to give bridged adducts **123**, while substrates with one electron-withdrawing group react as dienes to give regioselectively dihydro-1*H*-indene derivatives **124**. The corresponding bridged adducts are formed as a single *endo*-stereoisomer, the structure of which was confirmed by X-ray diffraction and ^1H NMR spectroscopy. The high regioselectivity of this reaction was interpreted using quantum-chemical calculations (see Section V).



Adduct	R^1	R^2	R^3	Yield (%)
123m	Cl	H	SO_2Me	66
123p	SO_2Me	H	SO_2Me	85
123q	H	SO_2Me	SO_2Me	67
124j	Me	H	SO_2Me	67
124o	Cl	CO_2H	Cl	71
124v	Me	H	CN	73
124y	Me	H	CO_2Me	65

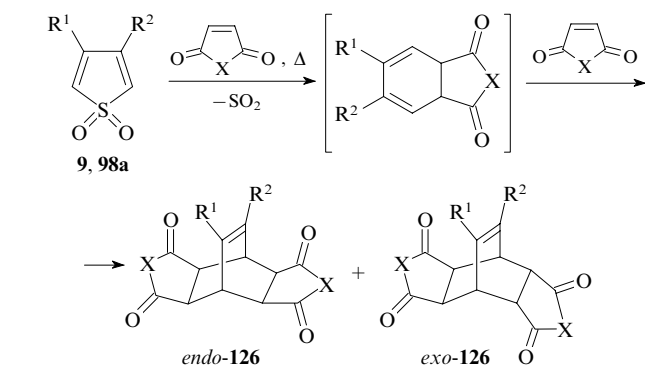
It was also found that bridged adducts **123** undergo the Cope rearrangement on heating. This gives respective dihydro-1*H*-indenes **125** in high yields.¹¹⁴



$R^2 = \text{H}$: $R^1 = \text{Cl (m, 76\%)}, \text{SO}_2\text{Me (p, 98\%)}$;
 $R^1 = \text{H}, R^2 = \text{SO}_2\text{Me (q, 84\%)}$.

g. Preparation of bis-adducts

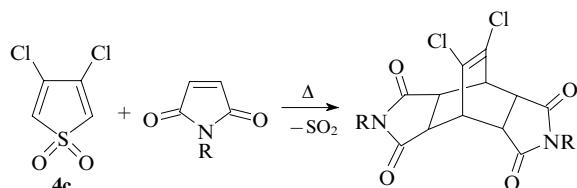
Substituted cyclohexadienes are always formed as the primary products in the reactions of thiophene dioxides with dienophiles. These compounds can further react as dienes with another dienophile molecule to give bis-adducts.



Sulfone	R ¹	R ²	X	Yield (%)	
				endo-126	exo-126
9	Cl	F	O	45	—
98a	Bu ^t	Bu ^t	O	73	25
	Bu ^t	Bu ^t	NPh	26	40

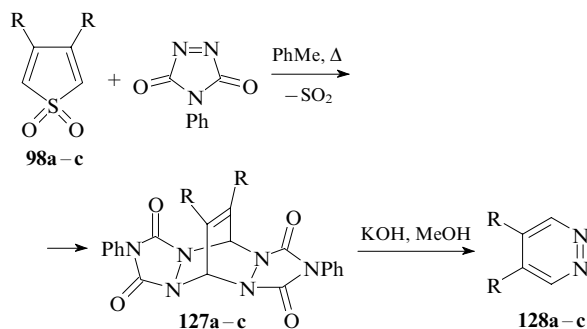
Thus reactions of maleic anhydride and *N*-phenylmaleimide with 3,4-di-*tert*-butylthiophene 1,1-dioxide (**98a**) result in bis-adducts **126** in high yields.¹¹⁵ The reaction products were identified in this case as *endo*- and *exo*-isomers. However, the reaction of 4-chloro-3-fluorothiophene 1,1-dioxide (**9**) with maleic anhydride gives only the *endo*-isomer.⁶³

Bis-adducts were prepared by reactions of 3,4-dichlorothiophene 1,1-dioxide (**4c**) with *N*-butyl- and *N*-(*p*-nitrophenyl)-maleimides.



R = Buⁿ (87%), 4-O₂NC₆H₄ (81%).

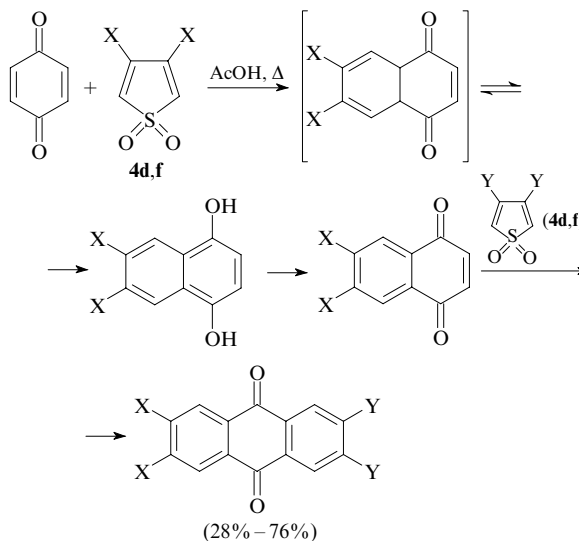
Thiophene dioxides **98a–c** containing bulky groups (*tert*-butyl, neopentyl or adamantyl) in positions 3 and 4 react with two equivalents of 4-phenyl-4*H*-1,2,4-triazole-3,5-dione (PTAD) in boiling toluene. On treatment with a solution of KOH in methanol, bis-adducts **127a–c** are converted into substituted pyridazines **128a–c** in high yields.^{20, 21, 116}



Sulfone	R	Yield (%)	
		127	128
a	Bu ^t	58	80
b	<i>neo</i> -C ₅ H ₁₁	77	74
c	1-Ad	72	82

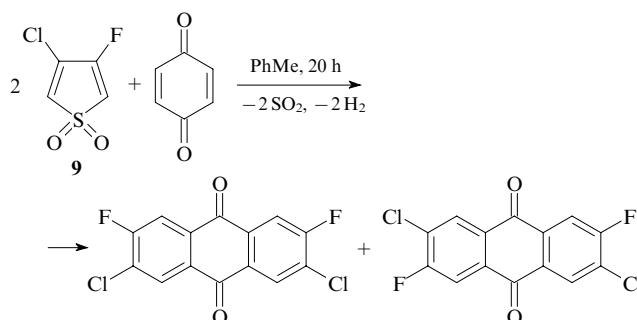
The reactions of substituted thiophene dioxides with benzoquinones were used to prepare symmetrical and non-symmetrical naphtho- and anthraquinones.¹¹⁷ The dehydrogenation (aromatization) apparently includes enolisation of the primary adduct

and subsequent oxidation with excess benzoquinone. The best results in the reaction with 3,4-diphenyl- (**4d**) and 3,4-dibromothiophene 1,1-dioxides (**4f**) were attained with a tenfold excess of 1,4-benzoquinone.



X, Y = Ph, Br.

Two regioisomeric bis-adducts were obtained in 1 : 1 ratio in the reaction of 4-chloro-3-fluoro-thiophene 1,1-dioxide (**9**) with benzoquinone (overall yield 86%).⁶³ As in analogous reactions of other thiophene dioxides, the primary adduct is oxidised with excess benzoquinone to give an aromatic structure.



Recently, sulfone **1p** has been used in the cascade cycloaddition of dienes resulting in bis-adducts **129a–f** based on one thiophene 'core'.¹¹⁸ The great difference between the temperatures

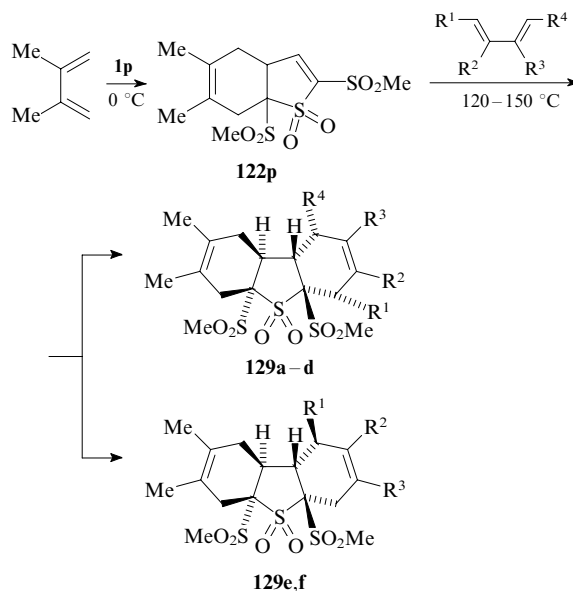


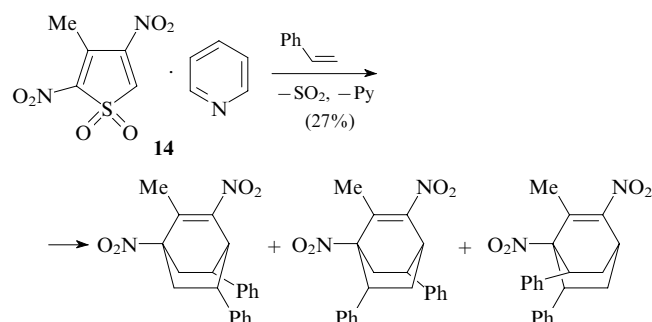
Table 4. Bis-adducts prepared by the reaction of sulfone **122p** with dienes.

Diene				Products (ratio)	Yield (%)
R ¹	R ²	R ³	R ⁴		
H	Me	Me	H	129a	55
H	Me	H	H	129b + 129e (3 : 2)	34
Me	H	H	H	129c + 129f (5 : 2)	35
See ^a	H	H	see ^a	129d	51

^a R¹–R⁴ = CH₂.

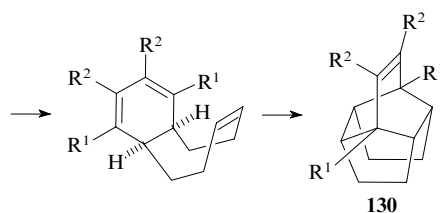
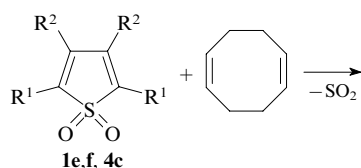
required in the first and second cycloaddition stages permits the synthesis of double adducts with different dienes. Thus the reaction of compound **1p** with 2,3-dimethylbuta-1,3-diene readily proceeds in dichloromethane at 0 °C, and adduct **122p** thus formed can be isolated and introduced in the subsequent cycloaddition with some acyclic 1,3-dienes or cyclopentadiene. The annulation to the second double bond of thiophene dioxide **1p** is carried out in acetic anhydride at temperatures of 120–150 °C. When 2,3-dimethylbuta-1,3-diene or cyclopentadiene is used, the corresponding products **129a,d** are formed as single stereoisomers, while in other cases, isomer mixtures are isolated. The structure of bis-adduct **129a** was determined unambiguously by X-ray diffraction (Table 4).

The reaction of complex **14** with styrene gives addition products of two alkene molecules. As in the case of phenylacetylene, the transformation is non-selective, giving equal amounts of three regioisomers (overall yield 27%).⁶⁷ This unusual type of bis-adduct formation and the lack of regioselectivity were attributed to high activity of complex **14**.



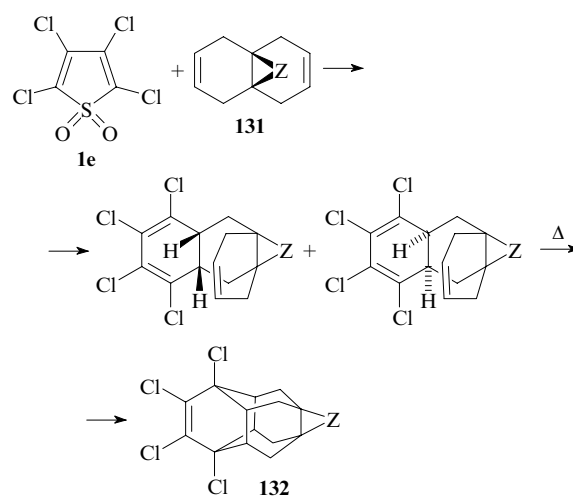
h. Tandem reactions. Rearrangements

Of considerable interest are tandem reactions of thiophene dioxides with acyclic or cyclic 1,5- and 1,6-dienes, which allow one to prepare complex carbo- and heteropolycyclic structures. Annulation of one double bond of cyclic 1,5- or 1,6-diene to halogeno-substituted thiophene dioxides creates a diene system convenient for intramolecular Diels–Alder reaction with the other double bond of the diene. This cyclisation affords isotwistane and homoisotwistane type structures. For example, a number of polycyclic structures **130** have been prepared using cycloocta-1,5-diene.^{1, 3, 28}



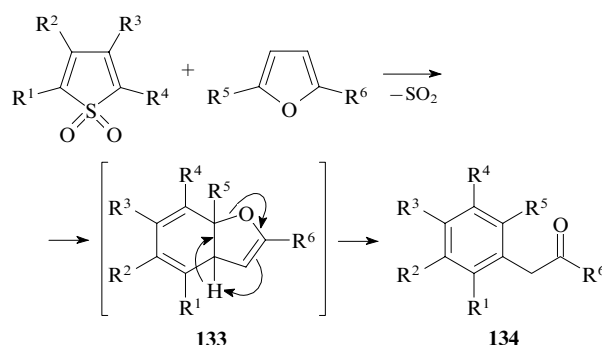
R¹ = R² = Cl (89.5%); R¹ = R² = Br (56%);
R¹ = H, R² = Cl (66.5%).

This approach was utilised for the synthesis of halogenated iceanes.^{119, 120} Tetrachlorothiophene 1,1-dioxide (**1e**) reacts with substituted propellane **131** to give two stereoisomeric trienes, one cyclising according to intramolecular Diels–Alder reaction to iceane **132**. In the absence of fragment Z, the intermediate product does not undergo further cyclisation. By varying Z and the reaction temperature, a series of tetrachloroicene derivatives **132** have been prepared.¹²⁰



Z	Reaction conditions	Yield of 132 (%)
CCl ₂	neat, 120 °C	33
NHC(O)	DCE	66
CO ₂ C(O)	PhMe	70
CH ₂ CH ₂	PhMe	40
OCH(Me)O	K ₂ CO ₃ , PhMe	41

Halogeno- and alkylthiophene dioxides react with substituted furans as dienes; adducts **133** undergo spontaneous rearrangement to give aromatic carbonyl compounds **134**.¹²¹



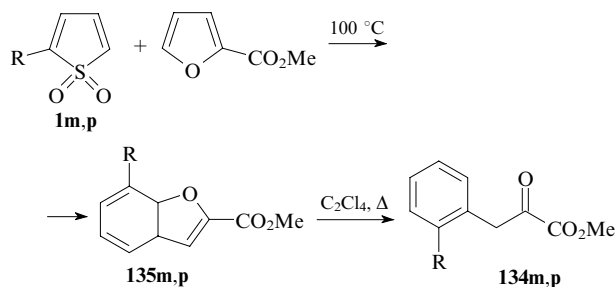
2,5-Dimethoxy-2,5-dihydrofuran reacts similarly to 2-methoxyfuran, *i.e.*, eliminates methanol during the process. If methyl 2-furancarboxylate or 2-acetylfuran react as the 'furan components', the reaction gives predominantly the enol form of the corresponding benzyldicarbonyl compound.

Table 5. Preparation of benzylcarbonyl compounds **134** by the reaction of thiophene dioxides with substituted furans.

Thiophene dioxide					Furan		Reaction conditions	Yield (%)	Ref.
No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶			
1e	Cl	Cl	Cl	Cl	H	Me	hexane, 65 °C, 0.5 h	92	121
					H	Bu ⁿ	hexane, 65 °C, 0.5 h	93	121
					H	CH ₂ OAc	DCE, 83 °C, 1 h	84	121
					H	CH ₂ NHAc	DCE, 83 °C, 1 h	62	121
					H	OMe	CH ₂ Cl ₂ , 30 °C	77	121
					H	Ac	125 °C, 1 h	37	121
					H	CO ₂ Me	100 °C, 22 h	62	121
					Me	Me	93 °C, 0.5 h	90	121
1f	Br	Br	Br	Br	Me	Me	93 °C, 0.5 h	90	121
1h	Cl	H	H	Cl	H	Me	CH ₂ Cl ₂ , 0 °C, 1 h	91	121
1j	Me	H	H	SO ₂ Me	H	Me	CH ₂ Cl ₂ , 0 °C, 1 h	95	122
1l	Br	H	H	CO ₂ Me	H	Me	CH ₂ Cl ₂ , 0 °C, 1 h	88	122
1m	Cl	H	H	SO ₂ Me	H	Me	CH ₂ Cl ₂ , 0 °C, 1 h	81	122
					H	CO ₂ Me	C ₂ Cl ₄ , 120 °C	90	122
1n	Br	H	H	SO ₂ Me	H	Me	CH ₂ Cl ₂ , 0 °C, 1 h	70	122
1p	SO ₂ Me	H	H	SO ₂ Me	H	Me	CH ₂ Cl ₂ , 0 °C, 1 h	96	122
					H	CO ₂ Me	C ₂ Cl ₄ , 120 °C	87	122
					Me	Me	CH ₂ Cl ₂ , 0 °C, 1 h	93	122
9	H	F	Cl	H	H	Me	PhMe, 110 °C, 20 h	90	63
98a	H	Bu ^t	Bu ^t	H	Me	Me	<i>o</i> -Cl ₂ C ₆ H ₄	51	123
4c	H	Cl	Cl	H	Me	Me	93 °C, 0.5 h	77	121

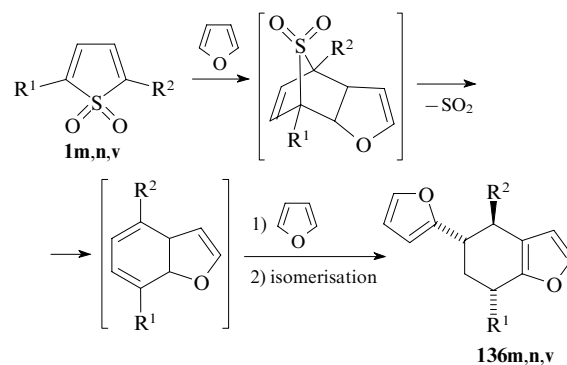
The use of thiophene 1,1-dioxides containing functional groups furnished a series of previously unknown benzylcarbonyl compounds, important precursors for the synthesis of alkaloids and other physiologically active products. The process is regioselective, in particular, furan adds only at the side of the double bond most activated by the functional group (Table 5).¹²² It is worth noting that functionally substituted thiophene dioxides react with furans under milder conditions than halogeno or alkyl derivatives.

Methyl pyromucate reacts with sulfones **1m,p** at 100 °C giving dihydrobenzofurans **135m,p**, which can be converted into benzylcarbonyl compounds **134m,p** by refluxing in tetrachloroethylene. The isolation of substituted dihydrobenzofurans **135m,p** apparently became possible due to the presence of the electron-withdrawing ester group in the furan molecule.



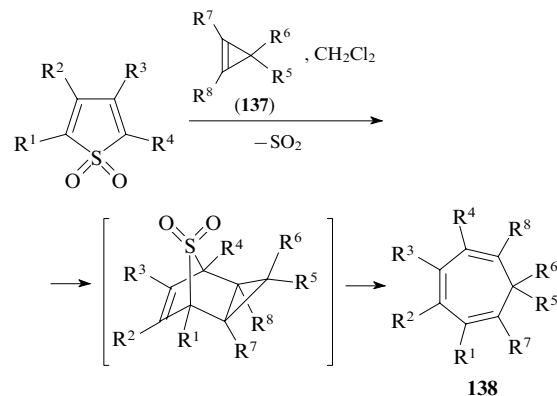
R = Cl (**m**), SO₂Me (**p**).

The reaction of electron-withdrawing thiophene 1,1-dioxides **1m,n,v** with unsubstituted furan proceeds in a different way.¹²² The intermediate adduct, *viz.*, the corresponding dihydrobenzofuran, reacts with excess furan. First, the Michael reaction takes place at the double bond activated towards nucleophilic addition and then double bond migration occurs, resulting in products **136m,n,v**. The formation of an aromatic structure is apparently the driving force of the transformation. The reaction is of general character: tricyclic products are also formed when other thiophene dioxides are used.



Compound 136	R ¹	R ²	Yield (%)
m	Cl	SO ₂ Me	41
n	Br	SO ₂ Me	33
v	Me	CN	72

Various substituted thiophene dioxides react with cyclopropenes **137** to afford cycloheptatrienes **138** in moderate

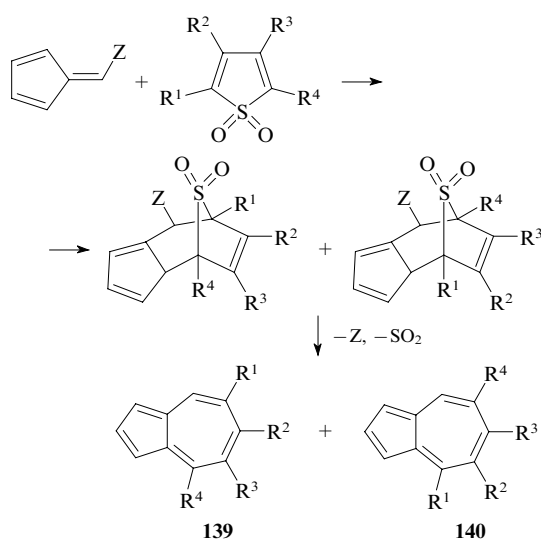


R¹–R⁴ = H, Me, Bu^t; R⁵, R⁶ = H, Me, Br, Cl; R⁷, R⁸ = H, Me.

yields.^{124–127} Probably, cleavage of the three-membered ring and extrusion of sulfur dioxide take place synchronously. 3,3-Dialkylcyclopropenes and heteroanalogues of cyclopropenes do not react. In the case of substituted thiophene dioxides and 2-alkylcyclopropenes, a mixture of regioisomers is formed. Using this approach, all possible methylated tropylium ions have been prepared.¹²⁶

i. Reactions of [6 + 4]-cycloaddition. Synthesis of azulenes

An extensive series of thiophene dioxides, including unsubstituted thiophene dioxide, have been introduced into [6 + 4] cycloaddition with 6-dimethylaminofulvene and some its derivatives.^{24, 128–132} The six-electron component in this reaction is represented by 6-substituted fulvene, while thiophene 1,1-dioxide is the four-electron component. The extrusion of SO₂ from the intermediate bridged adducts and elimination of the dimethylamino group afford azulene derivatives substituted in the seven-membered ring. The yields of the target azulenes usually do not exceed 16%; however, in some cases, azulenes were prepared in 25%–33% yields. The highest yield (60%) was attained in the reaction of 3,4-dichlorothiophene 1,1-dioxide (**4c**).¹²⁸ Electron-acceptor thiophene dioxides do not react with 6-dimethylaminofulvene. Variation of the fulvene component in this reaction has shown that fulvenes with less nucleophilic leaving groups (Z = MeO, NMePh) are the substrates of choice for the synthesis of azulenes with functional groups. In these cases, the target functionally substituted azulenes were synthesised in moderate yields.¹³³ In the case of non-symmetrical thiophene dioxides, regioisomeric azulenes **139** and **140** are formed; these were isolated as a mixture and characterised by ¹H NMR spectroscopy. The predominance of one of the azulene isomers in the reaction products was interpreted using quantum-chemical calculations (see Section V).

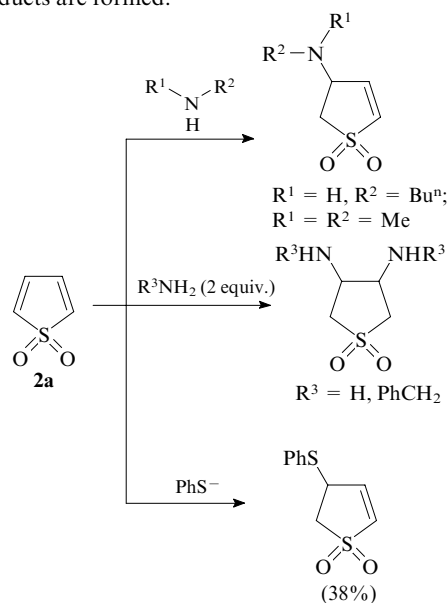


Z	R ¹	R ²	R ³	R ⁴	Yield (%)		Ref.
					139	140	
NMe ₂	H	H	H	H	31	—	45
	Cl	Cl	Cl	Cl	10	—	36
	H	Br	H	Br	32	—	37
OMe	Cl	H	H	Cl	19	—	133
	Cl	Cl	Cl	Cl	11	—	133
NMePh	Br	H	Br	H	32	—	133
	Br	H	H	Br	9	—	133
	Me	H	H	CO ₂ Me	35	5	133
	Cl	H	H	SO ₂ Me	40	2	133
	Br	H	H	SO ₂ Me	15	3	133

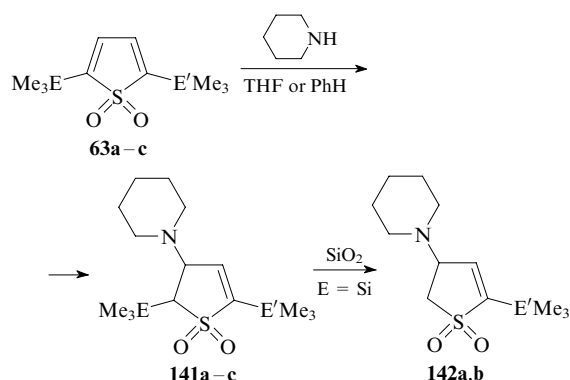
2. Reactions of thiophene 1,1-dioxides with nucleophiles

Thiophene 1,1-dioxides are typical 1,2-unsaturated sulfones functioning as acceptors in the Michael reactions with numerous nucleophiles. If the substituted thiophene dioxide contains a good leaving group, addition–elimination reactions are possible.

Various amines and the benzenethiolate ion were used as nucleophiles in reactions with unsubstituted thiophene 1,1-dioxide (**2a**).^{61, 134–136} With an excess of the nucleophilic reagent, bis-adducts are formed.



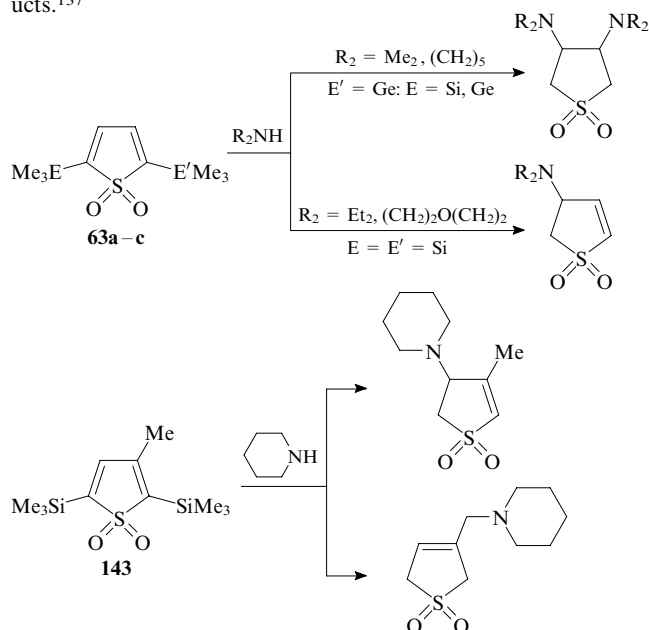
The addition of one piperidine molecule to symmetrical trimethylsilyl- and -germylthiophene dioxide **63a,c** in THF and benzene results in 2,3-dihydrothiophene 1,1-dioxides **141a,c**. Storage or chromatography on silica gel of the silyl derivative **141a** is accompanied by elimination of the trimethylsilyl group from the sp³ carbon atom of the heterocycle. In the case of non-symmetrical 2-trimethylgermyl-5-trimethylsilylthiophene 1,1-dioxide (**141b**), the reaction occurs regioselectively, the amine molecule being added only to the vinylsilyl fragment. The subsequent desilylation of this product takes place during chromatographic purification on SiO₂, and the structure of 3-piperidino-5-trimethylgermyl-2,3-dihydrothiophene 1,1-dioxide (**142b**) was confirmed by X-ray diffraction.¹³⁷ Germlyl derivative **141c** is stable against SiO₂.



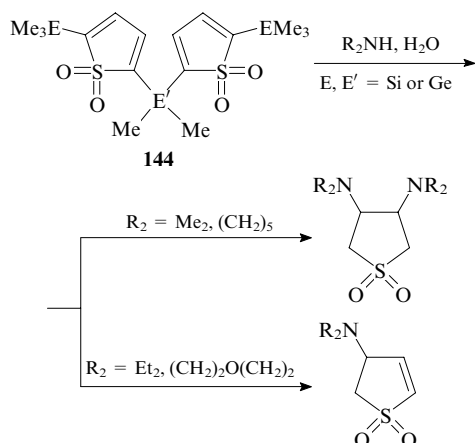
E = Si; E' = Si (**a**), Ge (**b**); E = E' = Ge (**c**).

The reactions of silyl- and germlyl-substituted thiophene dioxides with other amines also occur regioselectively. The reaction with excess of piperidine and dimethylamine yields bis-adducts, whereas silyl-substituted thiophene dioxide **63a** reacts with only one morpholine or diethylamine molecule. The reactions of 2,5-bis(trimethylsilyl)-3-methylthiophene 1,1-dioxide

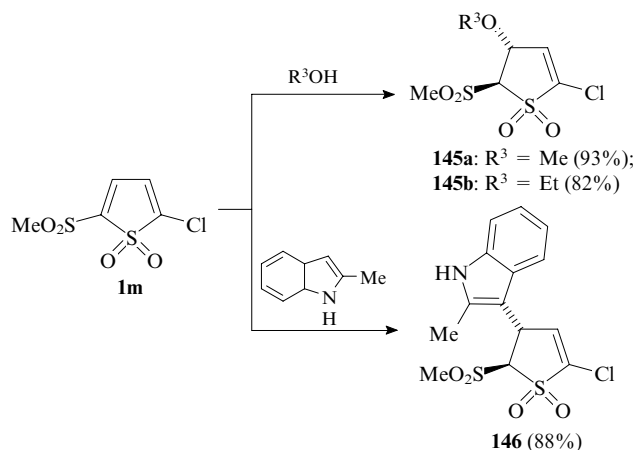
(**143**) with piperidine afford a mixture of two desilylated products.¹³⁷



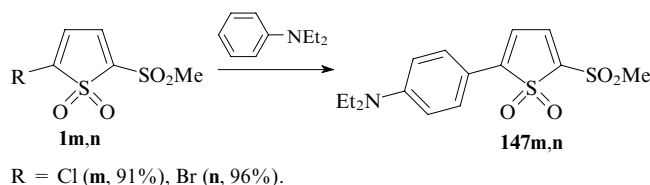
Tetroxides **144** react with amines in a similar way. Depending on the nucleophile used, the reaction may yield both mono- and bis-adducts. In both cases, the products are formed with elimination of the Me_3E and $E'Me_2$ groups.¹³⁸



Thiophene dioxides containing functional groups can serve as efficient acceptors in the Michael reactions. The use of lower alcohols and 2-methylindole as nucleophiles in reactions with sulfone **1m** results in the corresponding *trans*-adducts **145a,b** and



146 in high yields. *N,N*-Diethylaniline reacts with compounds **1m,n** in a different way to give the products of replacement of the halogen atom **147m,n**. This difference between the reaction routes can be attributed not only to different nature of the nucleophiles, but also to the substantial difference in their basicities.¹³⁹

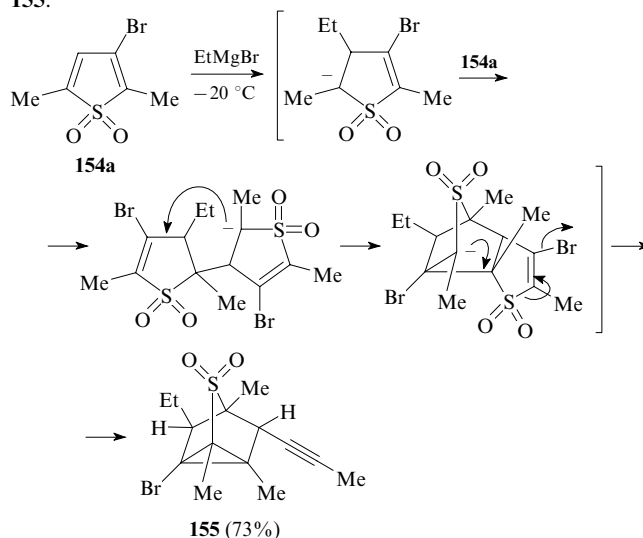


A sequence comprising the Diels–Alder reaction and the nucleophilic addition is an attractive synthetic route. For example, the reaction of thiophene dioxide **1p** with 2,3-dimethylbuta-1,3-diene gives adduct **122p** ($R = Me$) containing a double bond activated by the $MeSO_2$ group (Scheme 6).¹³⁹ A strong nucleophile such as *p*-methoxybenzenethiol easily reacts with compound **122p** to give the corresponding Michael *trans*-adduct **148**; however, in the case of other nucleophilic reagents (alcohols, nitromethane or diethyl malonate), additional activation with potassium fluoride as a base is required. In this case, elimination of the methylsulfonyl group takes place simultaneously with the nucleophile addition. If the reaction mixture contains no other nucleophile, the eliminated $MeSO_2^-$ anion attacks position 3 of the dihydrobenzothiophene molecule to give compound **149**. In all addition products **148–153**, the methylsulfonyl group and the newly introduced fragment occupy *trans*-positions with respect to each other. It is noteworthy that in the presence of the KF catalyst, diethyl malonate forms the double addition product, bis-adduct **152**; however, the use of caesium fluoride results in monoadduct **153**.¹³⁹

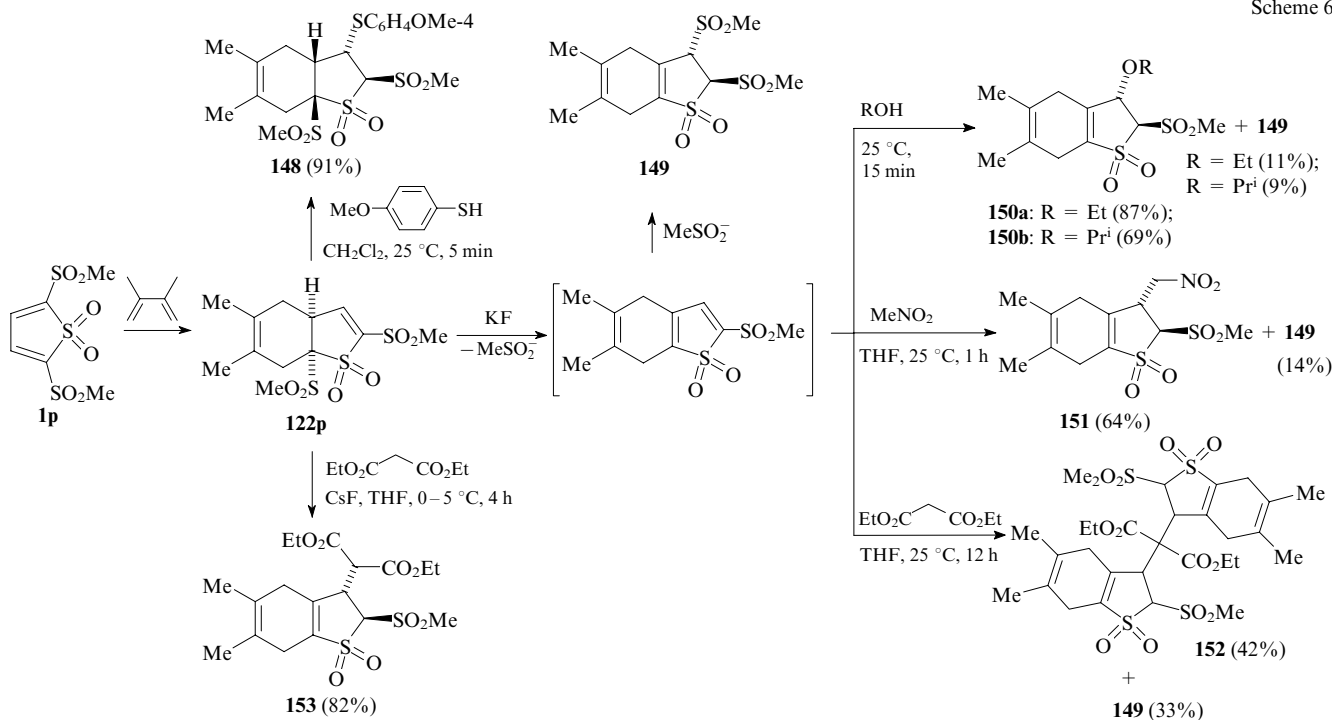
3. Reactions resulting in ring opening

The reaction of 3-bromo-2,5-dimethylthiophene 1,1-dioxide (**154a**) with organolithium reagents RLi ($R = Me, Et, Bu^n, Ph$) revealed two possible pathways preceding the ring opening: halogen–lithium exchange or the Michael addition of the lithium derivative.^{140–142} No metallation of 3-chloro-2,5-dimethylthiophene 1,1-dioxide (**154b**) with *n*-butyllithium (replacement of Cl by Li) takes place, *i.e.*, the reaction follows only the second pathway (Scheme 7).

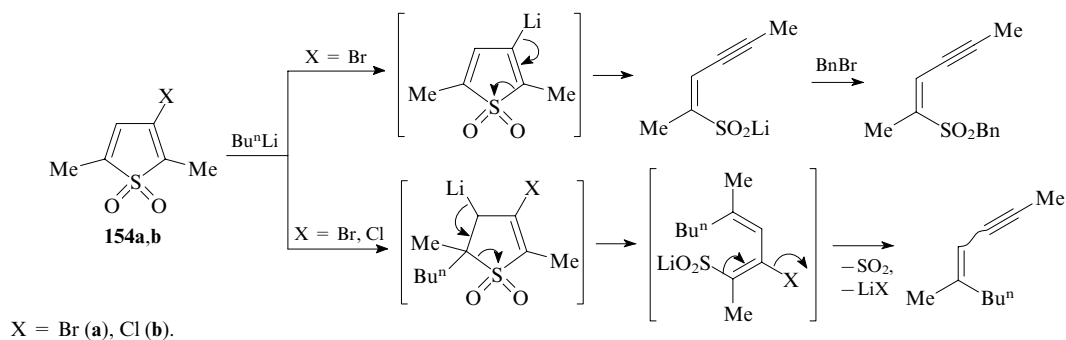
Interesting results were obtained in a study of the reaction of the Grignard reagents and thiophene 1,1-dioxide **154a**. Instead of the expected ring opening products according to the above scheme, treatment of **154a** with ethylmagnesium bromide or propylmagnesium chloride at $-20^\circ C$ gives tricyclic compound **155**.¹⁴³



Scheme 6

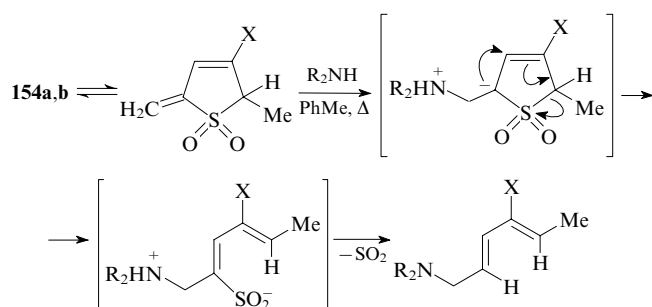


Scheme 7



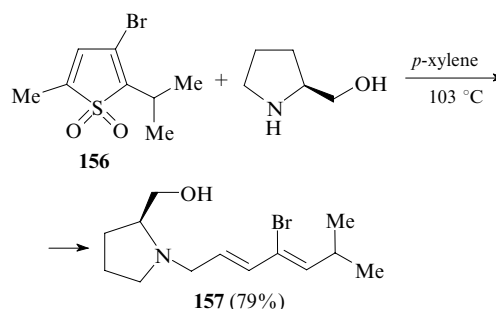
The structure of the tricyclic compound was determined and a mechanism for its formation was proposed. The use of methyl (or phenyl)magnesium bromide in this reaction resulted in a mixture of products that could not be identified.

In recent years, ring opening in 3-halogeno-2,5-dimethylthiophene 1,1-dioxides **154a,b** and trimethylsilyl-substituted thiophene dioxides induced by secondary amines has been the subject of active studies.³⁴ It was found that the reactions of compounds **154** with piperidine, pyrrolidine and morpholine in boiling toluene give stereoselectively one of the four possible dialkylaminomethyl-substituted butadienes.

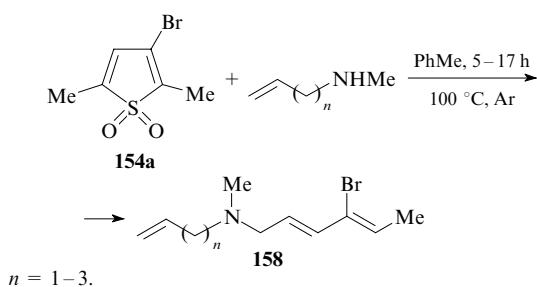


$\text{X} = \text{Cl, Br}$; R_2NH is piperidine, morpholine, pyrrolidine.

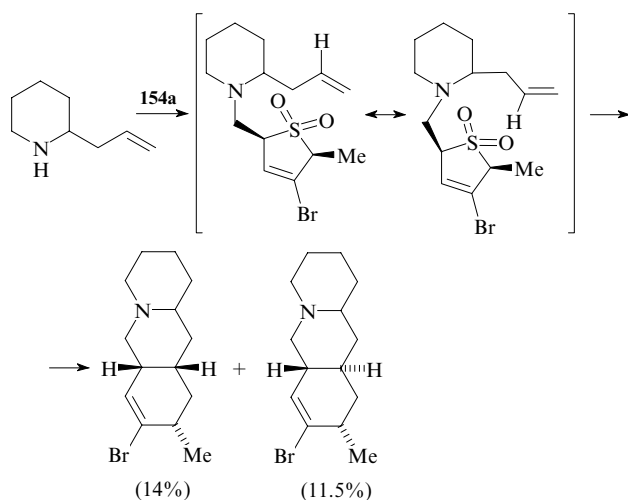
The reactions of thiophene dioxides with 2-(2-hydroxy-alkyl)pyrrolidines and -piperidines have also been studied.^{144, 145} For example, dioxide **156** reacts stereoselectively with 2-(2-hydroxymethyl)pyrrolidine to give diene **157**.



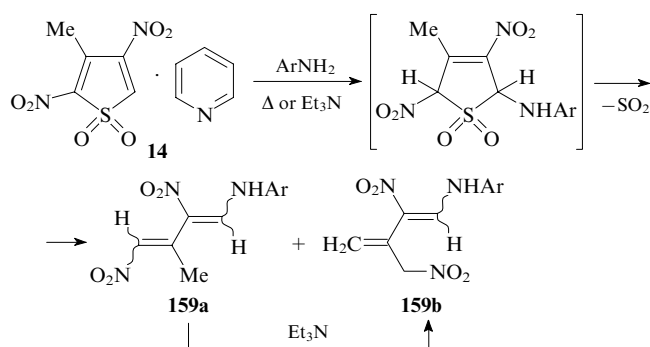
The use of allyl- and homoallylamines in a similar reaction gives azatrienes **158**.¹⁴⁰



Azatrienes **158** can undergo intramolecular Diels–Alder reaction, thus opening a new synthetic approach to the substituted indolizines, quinolizines and their benzo analogues.^{146,147} For instance, the reaction of 3-bromo-2,5-dimethylthiophene 1,1-dioxide (**154a**) and 2-allylpiperidine affords *cis*- and *trans*-isomers of substituted quinolizines in 55:45 ratio.



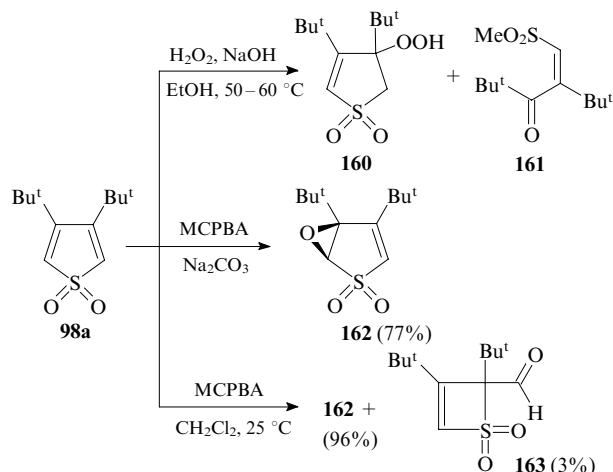
The molecular complexes **14** mentioned above react with primary aromatic amines to give ring opening products, namely, isomeric aminonitrodiene **159a,b** (ratio 1:4).¹⁴⁸ Compound **159b** is formed upon base-induced isomerisation of aminodinitrobutadiene **159a**. Dinitrobutadienes **159a,b** exist in solutions as mixtures of four geometric isomers, as shown by ¹H and ¹³C NMR spectroscopy.



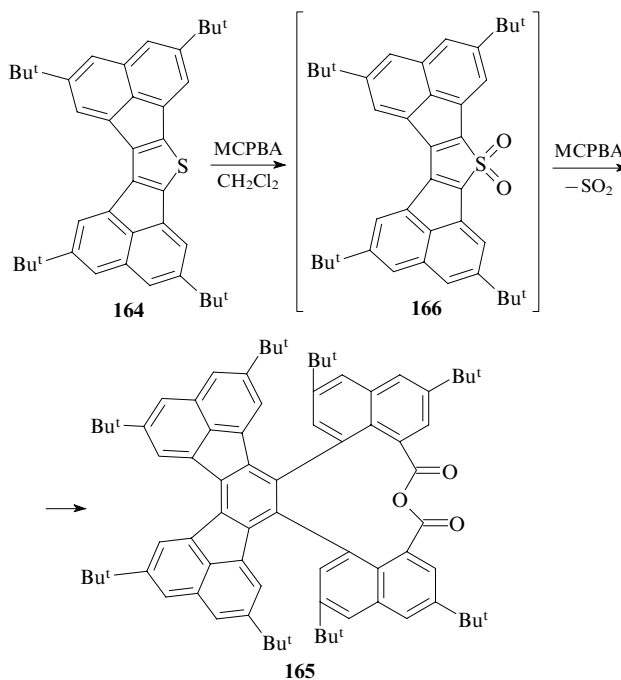
4. Oxidation of thiophene 1,1-dioxides

The oxidation of sterically hindered thiophene dioxides has been studied.^{149,150} The reaction of 3,4-di-*tert*-butylthiophene 1,1-dioxide (**98a**) with H₂O₂ under basic conditions at room temperature furnishes Michael adduct **160**, whereas at 50–60 °C ring opening takes place and compound **161** is formed as a by-product (15%).¹⁴⁹ On treatment with MCPBA in the presence of sodium carbonate, thiophene dioxide **98a** is oxidised to epoxide

162.¹⁵⁰ The oxidation without Na₂CO₃ gives thiethiodioxide **163** as a minor product.



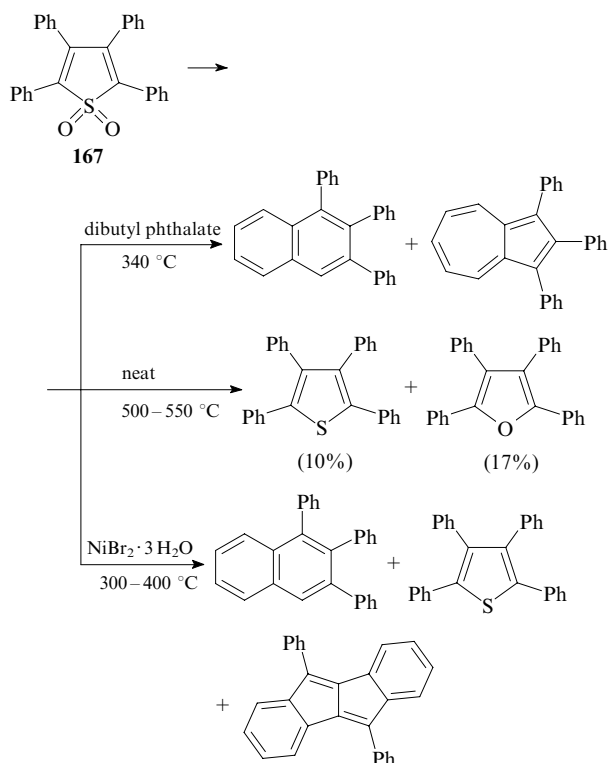
Recently, an interesting transformation of diacenaphthothiophene **164** derivative under the action of peroxy acids has been found.¹⁵¹ Treatment of compound **164** with *m*-chloroperoxybenzoic acid at room temperature in dichloromethane yielded unusual macrocyclic anhydride **165**. Presumably, the mechanism of this reaction includes a sequence of transformations in which sulfone **166** is postulated as an intermediate



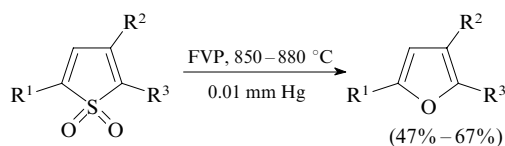
5. Pyrolysis of thiophene 1,1-dioxides

High-temperature reactions involving thiophene dioxides have no synthetic value, as they usually give complex mixtures of products in low yields. This type of transformation has been described comprehensively in a recent review;¹⁵² therefore, in this study, we consider it expedient to give only several examples providing a general idea of thermolysis of these compounds.

Thermal decomposition of thiophene dioxides may give different compounds. The products of high-temperature pyrolysis of tetraphenylthiophene 1,1-dioxide (**167**) depending on the reaction conditions are presented below.¹⁵³



Under conditions of flash vacuum pyrolysis (FVP), 3,4-di-*tert*-butylfuran has been prepared and characterised.¹⁵⁴ A similar selenophene was formed in the reaction of thiophene dioxide **98a** with selenium (benzene, 210 °C).¹⁵⁴ Heating of dimethyl-, di-*tert*-butyl- and diphenylthiophene dioxides in a high vacuum to 880 °C gave the corresponding furans in moderate yields.¹⁵⁵



R² = H; R¹ = R³ = Me, Bu^t, Ph; R¹ = R² = Bu^t, R³ = H.

IV. The applications of thiophene 1,1-dioxides

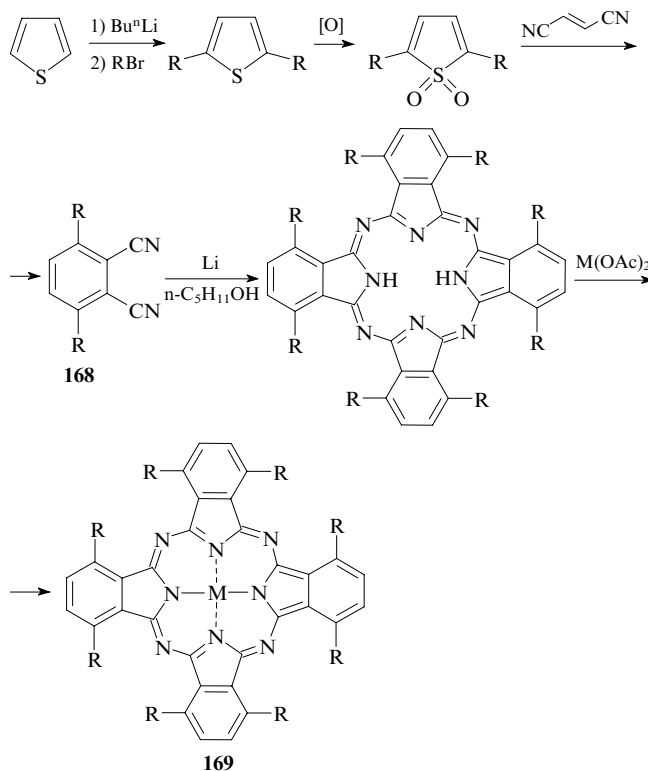
In recent years, thiophene 1,1-dioxides and their derivatives have been attracting increasing attention of scientists working in various fields of chemistry: biochemistry, medicinal chemistry, chemistry of polymers and supramolecular structures and also researchers engaged in the design of new organic materials. This attention is due not only to high reactivity of thiophene dioxides, but also to their unique physicochemical properties. In addition, recently it has been found that this class of compounds possess diverse biological activities. As a result, the number of publications devoted to practically valuable properties of thiophene 1,1-dioxides has markedly increased during the last 10 years. However, data on the use of thiophene dioxides have not yet been described systematically.

1. Thiophene 1,1-dioxides in supramolecular chemistry

Until recently, a small number of papers in which thiophene 1,1-dioxides have been used as building blocks in supramolecular chemistry has been published. However, the last decade is marked by a vigorous growth of the number of publications devoted to this topic; therefore, considering the modern trends in these studies would allow one to identify the key lines of further development.

The ability of thiophene dioxides to easily form aromatic structures with SO₂ elimination has been employed in the synthesis of substituted phthalocyanines. Unique physicochemical properties of the latter make them promising intermediates in the design of new materials, dyes, chemical sensors and catalysts. However, many projects associated with the application of this class of compounds are faced with the problem of low solubility of unsubstituted phthalocyanines in organic solvents. To solve this problem, various phthalodinitriles containing long alkyl chains were synthesised as the starting compounds for the synthesis of phthalocyanines.

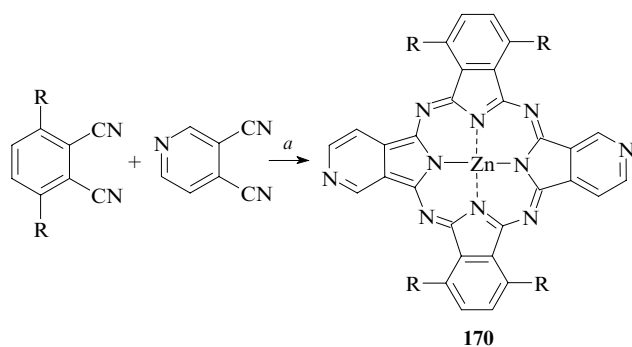
The alkyl groups promoting the solubility of phthalocyanines were introduced using a complex sequence of transformations. The metallation of thiophene followed by treatment with alkyl bromides containing from 10 to 18 carbon atoms in the chain results in 2,5-dialkyl derivatives. The oxidation of these products with MCPBA^{27, 156} or another oxidant¹⁵⁷ affords substituted thiophene 1,1-dioxides, which undergo the Diels–Alder reaction with fumarodinitrile. The extrusion of SO₂ from the intermediate adducts and oxidative aromatisation yields phthalodinitriles **168**. Lithium-induced cyclisation in pentyl alcohol furnishes the target phthalocyanines. In addition, metal complexes of these compounds **169**, possessing liquid crystal properties, have been synthesised.^{156, 157}



R = n-C₁₀H₂₁, n-C₁₂H₂₅, n-C₁₈H₃₇;

[O] = NaBO₃, MCPBA, DMD; M = Cu, Zn.

An interesting modification of phthalocyanines is the introduction of heterocyclic fragments into their structures. For example, complexes of pyridoporphyrazine derivatives have been prepared by the reaction of phthalodinitrile containing decyl substituents with pyridine-3,4-dicarbonitrile (1 : 1 ratio) in the presence of zinc chloride and 1,8-diazabicyclo[5.4.0]undec-7-ene. By varying the ratio of the dinitrile components, various pyridoporphyrazine isomers, including compound **170**, have been prepared, isolated and characterised.

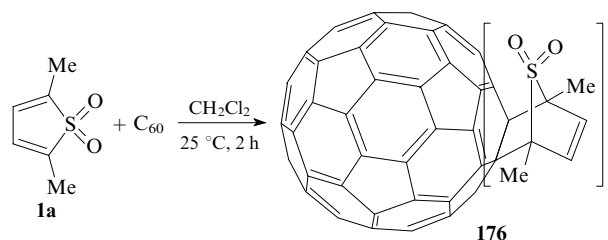


R = $n\text{-C}_{10}\text{H}_{21}$; (a) ZnCl_2 , DBU, $n\text{-C}_5\text{H}_{11}\text{OH}$.

The selective modification of β -cyclodextrins is an important problem of supramolecular chemistry not yet entirely solved. An elegant approach based on the use of a protective group, which was synthesised from dibenzothiophene 1,1-dioxide, has been proposed.¹⁵⁸ It was found that reagent **171** containing this group can form disulfonates **172** and **173** in the presence of molecular sieves 4 Å. The subsequent treatment of the resulting compounds with NH_3 or NaOH in methanol gave β -cyclodextrins **174** and **175**, modified at fragments **A** and **D**, in high yields (Scheme 8).

Modification of fullerene C_{60} was accomplished using 2,5-dimethylthiophene 1-oxide and 2,5-dimethylthiophene 1,1-dioxide (**1a**). The latter reacts with fullerene C_{60} to form tetra-adduct **176**, whereas analogous thiophene 1-oxide forms only a bis-adduct. It is of interest that this Diels–Alder reaction is not accompanied by spontaneous extrusion of SO_2 resulting in cyclohexadiene derivatives (see above); tetra-adduct **176** containing an

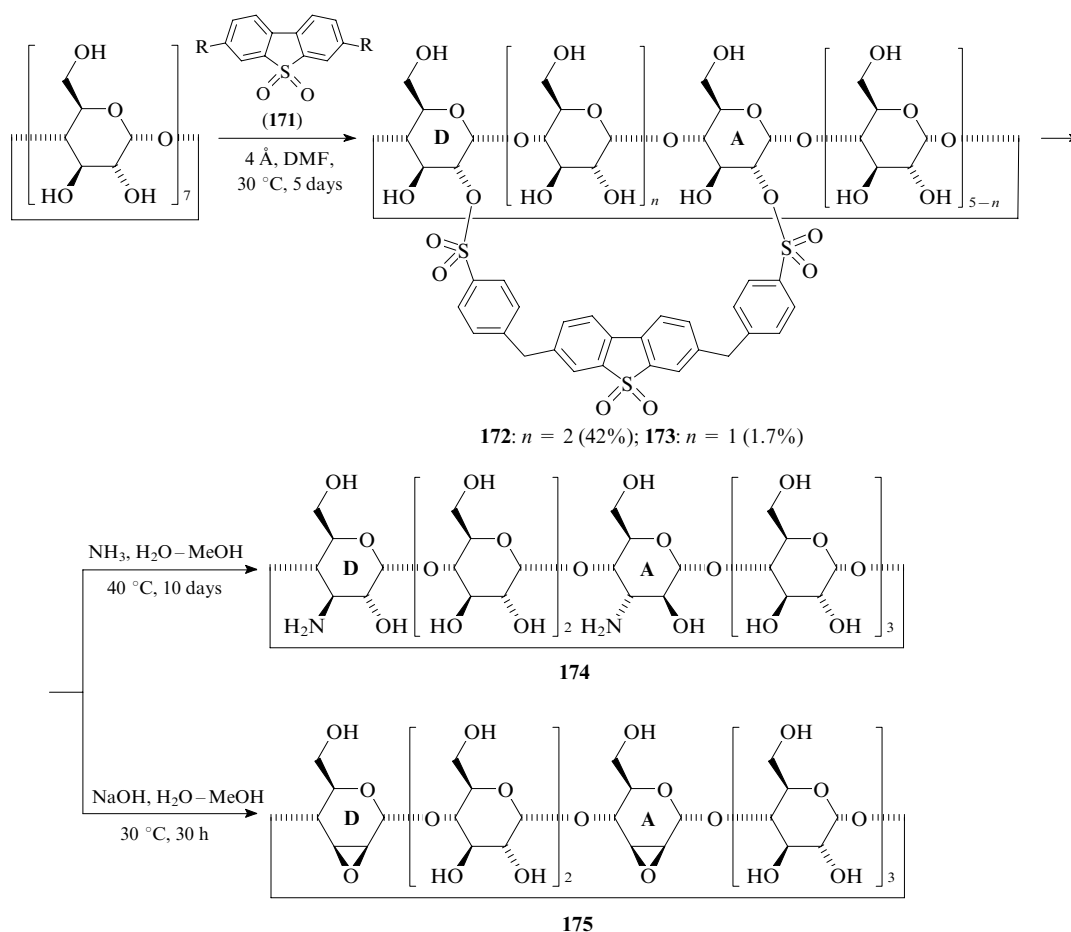
SO_2 bridge can be isolated and characterised. The structure of the obtained compound was confirmed by a number of physicochemical analytical methods.^{159, 160} The symmetry of the adduct has not been considered in the study cited.



2. New materials based on thiophene 1,1-dioxides

Currently, oligomeric and polymeric materials based on thiophene are under comprehensive investigations in view of their potential use in new types of electronic and optical instruments. Since 1989, when oligomers comprising several thiophene units were shown to be applicable as field-controlled transistors, the annual number of publications on this topic has been skyrocketing.^{161–164} The efficiency of such devices is related to the energy gap between the highest occupied (HOMO) and the lowest unoccupied (LUMO) molecular orbitals in the materials used. According to theoretical calculations for poly- and oligothiophenes,^{165, 166} the replacement of some of the sulfur atoms by sulfonyl groups sharply decreases this value (see Section V). For this reason, various research groups have attempted to synthesise oligomeric structures containing a thiophene 1,1-dioxide core.

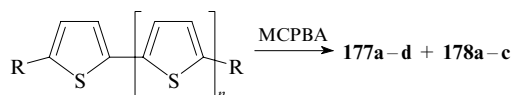
Scheme 8



R = $4\text{-CH}_2\text{C}_6\text{H}_4\text{SO}_2\text{Im}$ (Im is imidazol-1-yl).

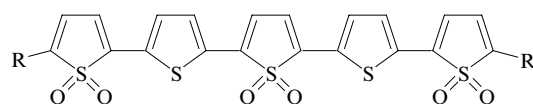
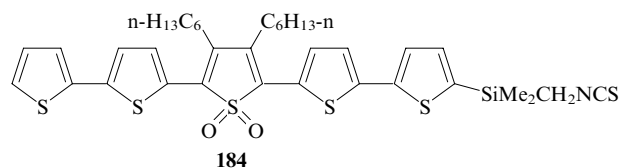
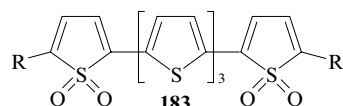
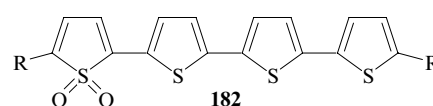
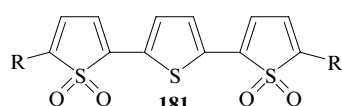
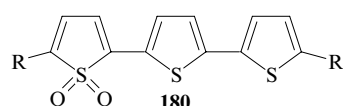
a. Oxidation of oligothiophenes

The simplest derivatives of oligothiophene 1,1-dioxides are prepared by oxidation of oligothiophenes. Mono- (**177a–d**) and bisulfones (**178a–c**) have been synthesised from chains containing 2–4 thiophene units using variable amounts of MCPBA.¹⁶⁶ The main shortcomings of this method are as follows: (i) starting thiophenes with electron-donating substituents, viz., alkyl or silyl groups, should be used; (ii) it is impossible to prepare oligomers containing more than two thiophene 1,1-dioxide fragments; (iii) the yields of the target products are relatively low.



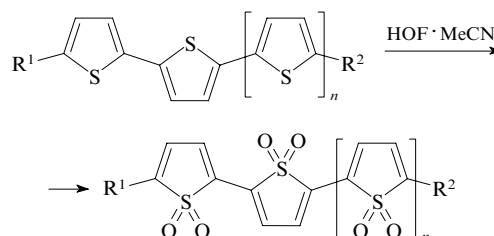
R = SiMe₂Bu^t; n = 1–3.

Compound	Structural formula	n	Yield (%)
Monosulfones			
177a		1	31
177b		2	17
177c		3	25
177d		3	8
Bisulfones			
178a		1	47
178b		2	54
178c		3	10



R = H, SiMe₂Bu^t.

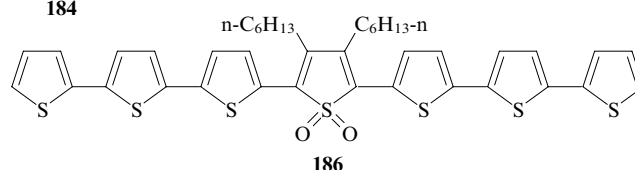
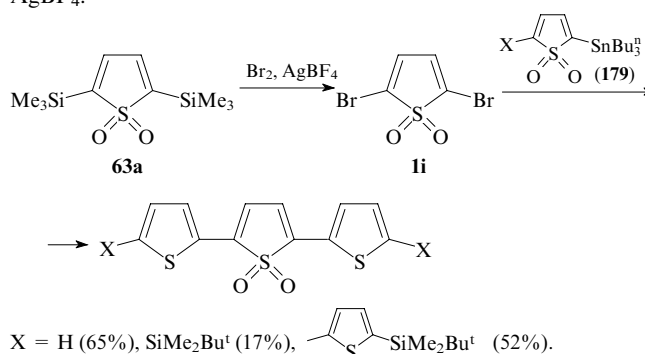
Recently, the complex of hypofluorous acid with acetonitrile has been used to prepare oligothiophene 1,1-dioxides.¹⁶⁷ Using this oxidant, oligomers containing 2–4 thiophene 1,1-dioxide units were prepared in high yields. In addition, unlike MCPBA, this complex provides the synthesis of oligomers containing bromine atoms.



n	R ¹	R ²	Yield (%)
0	Me	Me	85
0	Bu ^t	Bu ^t	83
0	Br	n-C ₆ H ₁₃	87
0	Br	Br	66
1	Bu ^t	Bu ^t	82
1	Br	Br	60
2	Bu ^t	Bu ^t	52

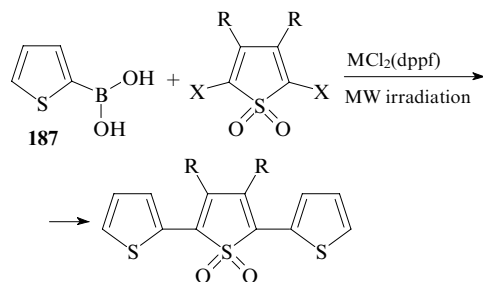
b. Cross-coupling reactions

It has been shown¹⁶⁸ that oligomers with alternation of thiophene and thiophene dioxide units possess the optimal properties. The key approach to the synthesis of these compounds is based on cross-coupling of trialkylstannylthiophenes **179** and substituted mono- or dibromothiophene dioxide. The latter are prepared by the replacement of silyl groups by halogen atoms under the action of bromine or iodine in dichloromethane in the presence of AgBF₄.



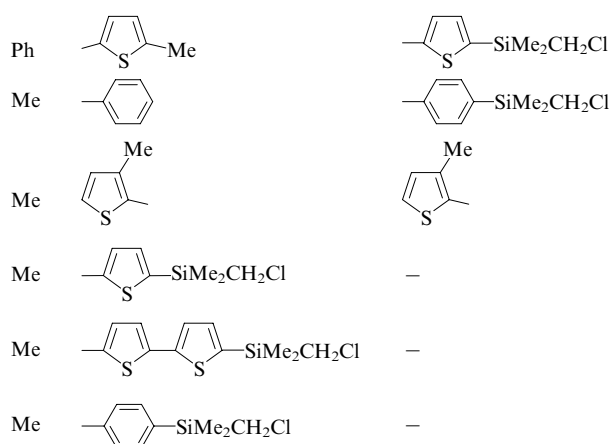
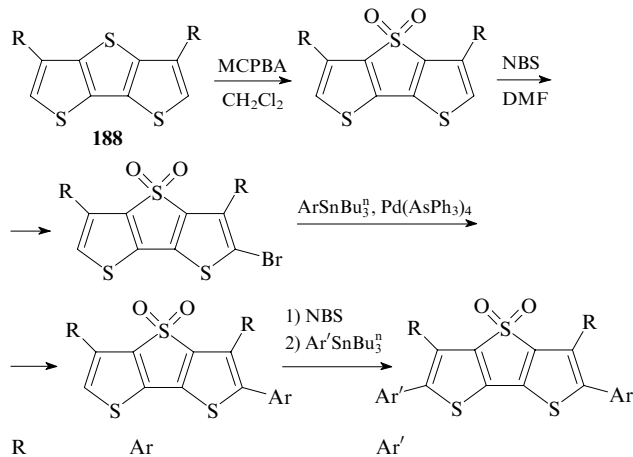
This method allows easy and selective introduction of a thiophene 1,1-dioxide fragment into ter-, quater- and quinque-thiophene chains.^{169–171} For example, this route was used to prepare oligothiophenes with terminal and/or central sulfonic groups: trimers **180**, **181**, tetramer **182**,¹⁶⁸ pentamers **183–185**^{168, 170, 171} and heptamer **186**.^{170, 171}

Cross-coupling of boronic acids of the thiophene series **187** with dihalothiophene 1,1-dioxides developed in recent years allows the synthesis of sulfone-containing oligomeric materials.¹⁷² The reaction is initiated by MW irradiation in the presence of 5 mol % of the $\text{MCl}_2(\text{dppf})$ catalyst [$\text{M} = \text{Pd}$ or Ni , dppf is 1,1'-bis(diphenylphosphino)ferrocene]. This method is of limited utility, as the yields of the target products do not exceed 30% (for $\text{M} = \text{Ni}$) or 15% (for $\text{M} = \text{Pd}$).

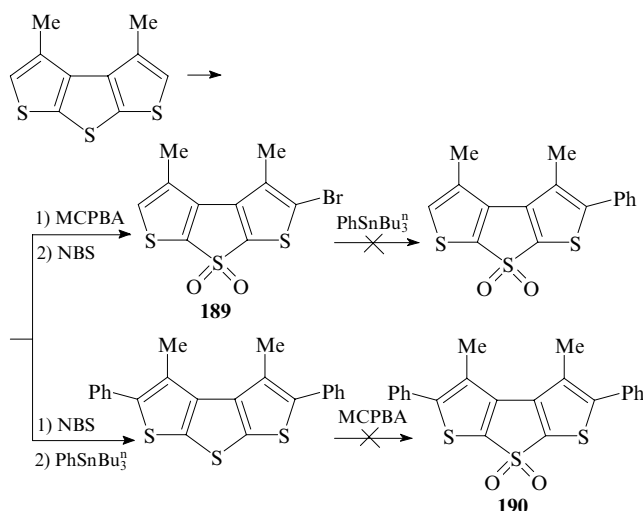


$\text{X} = \text{Br}$: $\text{R} = \text{H}$, Me , *neo*- C_5H_{11} ; $\text{X} = \text{I}$, $\text{R} = \text{H}$; $\text{M} = \text{Pd}$, Ni .

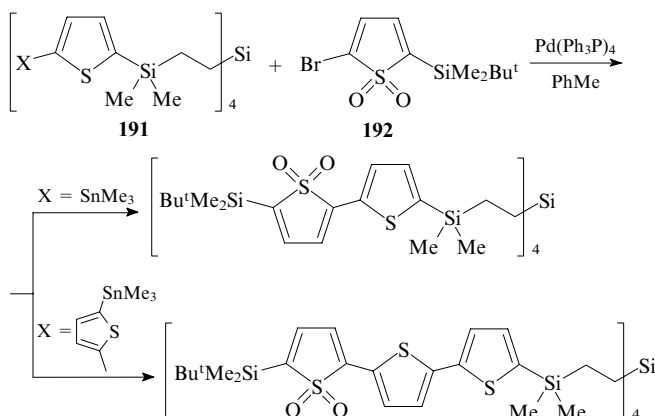
The oxidation of substituted dithieno[3,2-*b*:2',3'-*d'*]thiophenes **188** with MCPBA followed by successive bromination with *N*-bromosuccinimide (NBS) and cross-coupling gives selectively both symmetrical and non-symmetrical oligomers containing a dithieno[3,2-*b*:2',3'-*d'*]thiophene 4,4-dioxide core.^{173, 174} It was shown that the obtained materials possess photoluminescence properties in solutions and in the solid state.



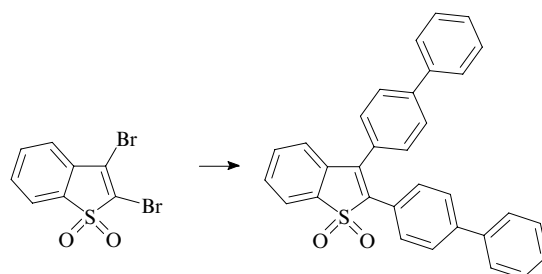
It should be noted that the use of isomeric dithieno[2,3-*b*:3',2'-*d'*]thiophenes in this sequence of transformations did not lead to the desired outcome.¹⁷⁵ The researchers were unable to carry out cross-coupling with bromide **189**, and the alternative approach, *i.e.*, the initial bromination and cross-coupling and subsequent oxidation did not give the target product **190** either.

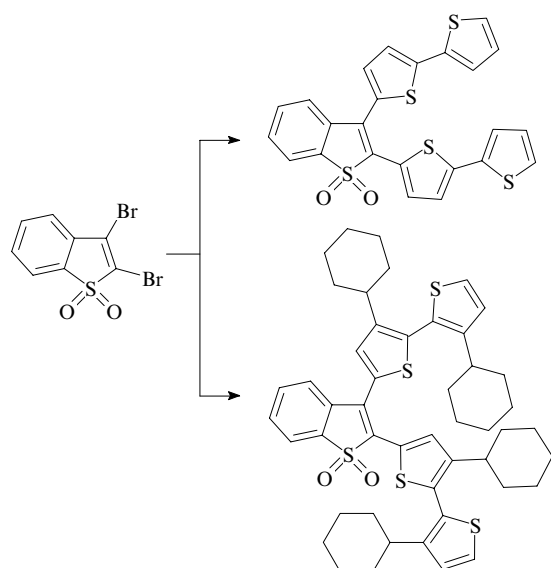


Cross-coupling with bromo derivatives of thiophene 1,1-dioxides is successfully used in the synthesis of dendrimers. Thus coupling of oligothiophene **191** and sulfone **192** in the presence of $\text{Pd}(\text{Ph}_3\text{P})_4$ as a catalyst gives dendrimers containing a thiophene 1,1-dioxide ring in the terminal fragment.¹⁷⁶

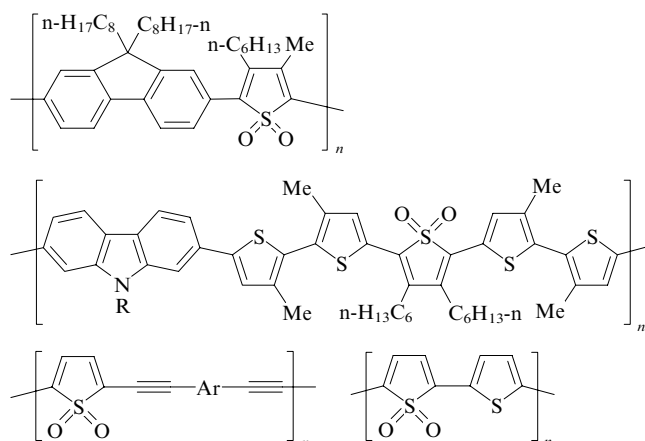


A new family of branched oligomers has been synthesised by the reaction of trialkylstannanes with bromo derivatives of benzothiophene dioxide. Owing to the non-symmetrical structure, these compounds crystallise much more difficultly than their linear analogues, which makes them suitable for the formation of thin films with optical diode properties.^{163, 177, 178}



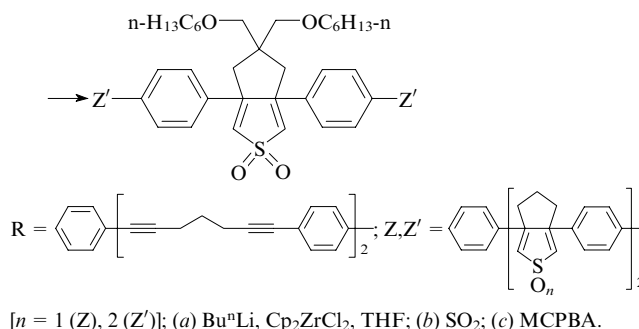
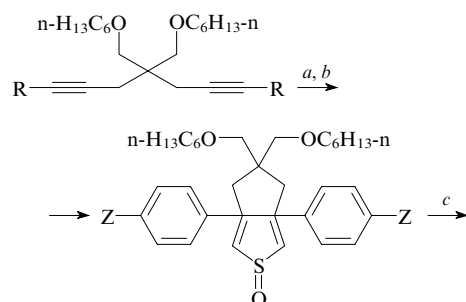


To conclude this Section, we will give examples of diverse polymeric materials containing a thiophene 1,1-dioxide fragment that have been efficiently synthesised by means of cross-coupling.^{179–183}



c. Miscellaneous methods of synthesis

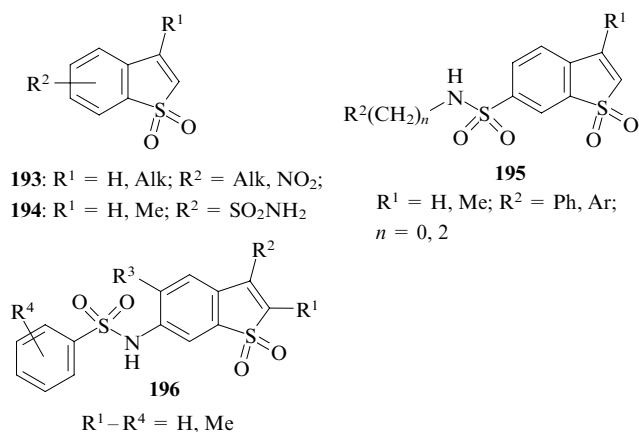
The synthesis of oligomers containing alternating phenyl and dioxide fragments was accomplished by the addition of zirconocene to 1,6-diacetylenes. Using this method, oligomers with various alternating fragments, namely, phenylene–dienylene, phenylene–thiophene, phenylene–thiophene 1-oxide and phenylene–thiophene 1,1-dioxide, can selectively be obtained in nearly quantitative yields.¹⁸⁴



3. Biological activity

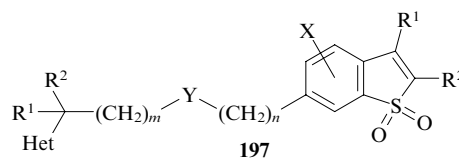
The biological activities of compounds of the thiophene 1,1-dioxide series have been studied rather extensively for benzo derivatives and for sulfones obtained from thieno[2,3-*b*]- and thieno[3,2-*b*]thiophenes. Since the properties of these compounds, including their biological action, have been considered in detail in recent reviews^{185,186} devoted to thienothiophenes, in this review we restrict ourselves to considering the benzo analogues of thiophene dioxides.

A method for the preparation of benzo[*b*]thiophene 1,1-dioxide derivatives **193** has been patented.¹⁸⁷ These compounds were shown to be applicable for the therapy and prevention of various inflammatory processes, including sepsis, myeloma, leukaemia, diabetes, hepatitis, etc.



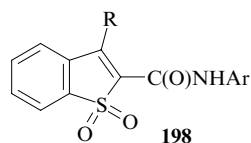
In recent years, benzo[*b*]thiophene 1,1-dioxide sulfamides **194–196**, which are potential antitumour drugs, have been extensively studied. Compounds **194–196** were prepared as salts and studied as tumour cell inhibitors *in vitro* and *in vivo*. Due to their high lipophilicity, derivatives **195** and **196** exhibit cytotoxic activities on human tumour cell cultures, in particular, leukaemia and solid tumour cells (HT29, HTB54, MI13443, K562 and CCRF-CEM).^{32,188,189}

Methods for the synthesis of compounds **197** as drugs for the therapy of hypercholesterolemia, hyperlipidemia, arteriosclerosis and various blood vessel diseases have been patented.¹⁹⁰ In addition, various sulfones are efficient drugs for decreasing the cholesterol level in blood (IC₅₀ is from 1 nM to 10 μM).



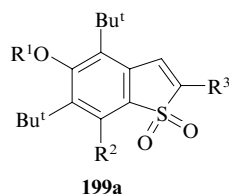
R¹, R² = H, Alk; Het is N-heterocycle;
Y = O, NR₂, CH₂; X is halogen; m, n = 0–7

Methods for the synthesis of benzo[*b*]thiophene-2-carboxanilide 1,1-dioxides **198** exhibiting high antiinflammatory activity have been developed.¹⁹¹

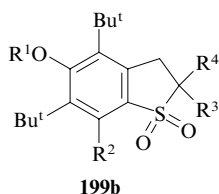


R = Cl, OH, OMe

The salts of benzothiophene dioxide **199a** and dihydrobenzothiophene dioxide **199b** derivatives containing *tert*-butyl groups suppress the oxidative denaturation of low-density lipoproteins and can be used to treat atherosclerosis and cardiac diseases, such as infarction and cardiac arrhythmia.¹⁹²



199a



199b

R¹ = H, Alk, Ac; R², R⁴ = H, Alk; R³ = Alk.

Thus, functionally substituted benzothiophene 1,1-dioxides exhibit a broad spectrum of biological activities.

V. Theoretical calculations

The structures of thiophene 1,1-dioxides have been studied in substantial detail using both spectroscopic methods (including X-ray diffraction analysis) and quantum chemical calculations. According to X-ray diffraction data, thiophene dioxide molecules are nearly planar, the oxygen atoms of the SO₂ group being located on both sides of the plane accommodating the heterocycle molecule. The bond lengths in the molecule are indicative of the loss of aromaticity to give a conjugated butadiene structure. Characteristic features of the molecular structure of various substituted thiophene dioxides and also some oligomers containing thiophene dioxide units in the chain have been considered in detail in recent reviews,^{3,193} which cover rather comprehensively the bibliography on this subject over the last ~20 years. Nevertheless, the theoretical studies of the structure and reactivity of thiophene dioxides have not yet been generalised within the framework of a single paper and this Section is meant to fill this gap.

1. Structure and reactivity

The existence of conjugation of the SO₂ group with the system of double bonds in thiophene dioxides has been the subject of intense studies nearly since the first representatives of compounds of this class have been prepared. The earliest studies used *ab initio* (HMO, LCGO and CNDO/2) calculations of molecular orbitals of unsubstituted thiophene dioxide (**2a**) and some benzo and dibenzo derivatives. The results of these studies were often contradictory and different conclusions were often drawn from the calculations. Indeed, Koch and Moffitt^{194,195} found that the SO₂ group is involved in conjugation; however, the calculations carried out in later studies showed the absence of conjugation in these sulfones.^{196,197}

For interpretation of the UV spectra of some trimethylsilyl- and trimethylgermylthiophene 1,1-dioxides, quantum-chemical calculations were carried out for their molecules in the ground and excited states.⁹⁰ The researchers demonstrated that the unusual bathochromic shift of the absorption band by 42–59 nm for these sulfones with respect to this band for the corresponding thiophenes can be interpreted as follows: the first excited state of the sulfone molecules is characterised by equal-

isation of the C–C bond orders in the heterocycle, resulting in a decrease in the energy of the state and, hence, of the electron transition energy. For example, the bond orders in 2,5-bis(trimethylsilyl)thiophene 1,1-dioxide (**63a**) are as follows:

State	C(2)–C(3)	C(3)–C(4)	C(4)–C(5)
Ground	1.896	1.012	1.896
Excited	1.205	1.433	1.205

A theoretical proof for the non-aromatic nature of thiophene dioxides has been obtained using the LCGO and AM1 methods. Comparison of the degree of aromaticity of unsubstituted thiophene dioxide and various isomeric thiadiazole *S,S*-dioxides has shown that sulfone **2a** is the least aromatic in the series of compounds studied.¹⁹⁸

The high reactivity of thiophene dioxides and their involvement in the Diels–Alder reactions as dienes were also theoretically substantiated. Using model reactions with ethylene, cyclopropene and benzoquinone, Jursic¹⁹⁹ studied characteristic features of the cycloaddition of thiophene, thiophene 1-oxide and thiophene 1,1-dioxide by AM1 calculations. The transition states and the activation energies of the reactions (*E_A*) were calculated. Thiophene 1,1-dioxide and cyclopentadiene were found to be the most reactive dienes with respect to ethylene, the activation energies of these reactions being equal to each other and to 28.50 kcal mol^{−1} (for thiophene *E_A* = 44.14 kcal mol^{−1}; for the *exo*- and *endo*-adducts of thiophene 1-oxide, *E_A* = 31.58 and 30.16 kcal mol^{−1}, respectively). It was also found that in the reaction of sulfone **2a** with cyclopropene, the formation of the *endo*-isomer is preferred. The ability of thiophene dioxides to act as dienes and to form dimers was theoretically substantiated by CNDO/2 and LCGO quantum-chemical calculations.²⁰⁰

For theoretical investigation of the oxidation susceptibilities of various substituted thiophenes and the reactivities of the respective thiophene 1,1-dioxides **1a–x**, DFT quantum-chemical calculations with the PBE96 functional were carried out. The obtained data allow one to identify the trends of variation of the global electrophilicity indices[†] depending on the nature of substituents in the thiophene ring (Fig. 1).⁴²

The introduction of any electron-withdrawing substituents markedly decreases the nucleophilic properties of the initial thiophenes. One can easily notice that the HOMO energy

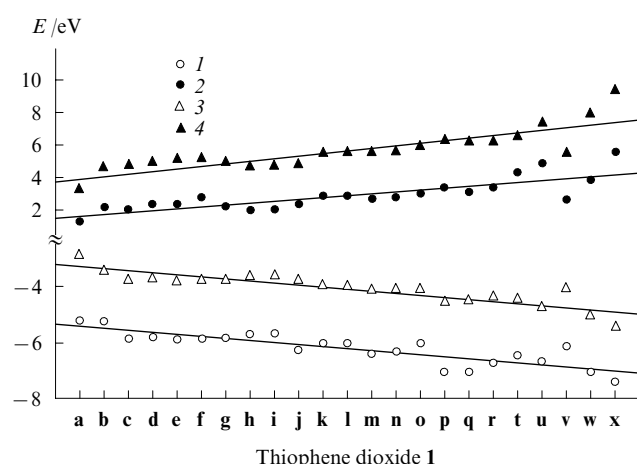


Figure 1. HOMO of the initial thiophenes (**1**) and LUMO of the corresponding thiophene dioxides **1** (**3**) and global electrophilicity indices for these compounds (**2** and **4**, respectively).

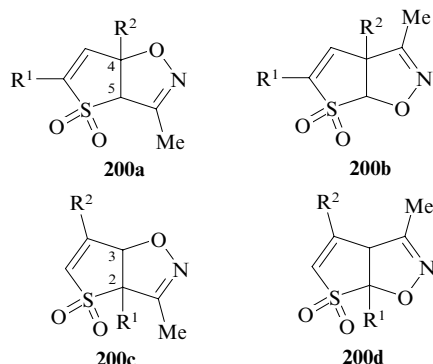
[†] Global electrophilicity index (ω /eV) is a semiempirical parameter reflecting the energy change upon electron transfer to the LUMO of the studied molecule.

decreases most appreciably and, conversely, the electrophilicity index increases. For example, on passing from electron-donating substituents in the thiophene ring to strong electron-withdrawing ones, the global electrophilicity index increases virtually by 5 eV, which is well correlated with experimental results: acceptor thiophenes cannot be obtained using standard oxidants. In addition, quantum-chemical calculations show pronounced increase in the electrophilic properties of the acceptor thiophene dioxides, which is also in good agreement with experimental results: acceptor thiophene dioxides readily react with dienes and nucleophiles, in some cases, to form bis-adducts.

2. Theoretical substantiation of regioselectivity in the Diels–Alder and dipolar addition reactions

It is obvious that if cycloaddition involves a diene or a dienophile containing different substituents or if the reaction can occur by different reaction centres, this can give regioisomeric products. The predominant formation of one or another isomer cannot be interpreted, in some cases, based on the classical views on the structure and reactivity of organic compounds. In recent years, modern quantum-chemical methods have been used to substantiate the reaction regioselectivity. Calculations of the transition state geometry, orbital coefficients of the initial compounds and activation energies were used to interpret regiochemistry of transformations involving thiophene 1,1-dioxides.⁹⁰

The dipolar addition of acetonitrile oxide to various 2,4-disubstituted trimethylsilyl- and trimethylgermylthiophene dioxides **70** may give addition products at the C(4)–C(5) bond (isoxazolines **200a,b**) and at the C(2)–C(3) bond (**200c,d**). Compounds **200a,c** and **200b,d** contain in pairs the same heterocyclic core.



R¹, R² = Me₃E (E = Si, Ge).

This process was studied in detail by the numerical MPDP method. The kinetic factor of isoxazoline formation was found to prevail over the thermodynamic factor: the calculated heats of formation are minimum for adduct **200b**, whereas **200a** was detected experimentally. The calculations of the process kinetics using the molecular orbital perturbation theory showed that the addition to the C(4)–C(5) bond is most probable; hence, the formation of isomers **200c,d** is ruled out.

Theoretical investigations of the cycloaddition of acceptor thiophene 1,1-dioxides **1m,p** provided explanation for regioselectivity of their reactions with dienes. The formation of unusual *meta-endo*-addition product **121p** in the reaction of sulfone **1p** with perylene was well interpreted by DFT calculations with the PBE functional (Table 6). The activation energy for the *meta-endo*-transition state to the formation of compound **121p** is minimum being equal to 5.0 kcal mol^{−1}. The reaction energy (*E_R*) is also most favourable in this case (−43.0 kcal mol^{−1}). Other transition states and the corresponding products have higher energies than *meta-endo*-**121p**. Thus, this is kinetically and thermodynamically controlled product. The *endo*-position of the methyl group in the six-membered ring in the adduct **121p** with respect to the MeSO₂ group was confirmed by X-ray diffraction.¹¹³

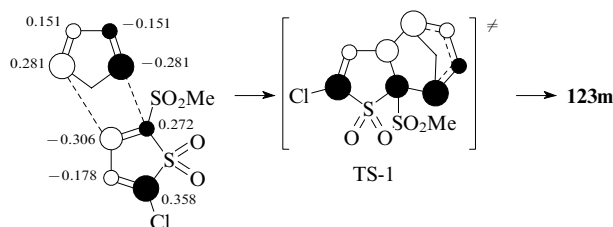
Table 6. Activation energies (*E_A*) and reaction energies (*E_R*) (in kcal mol^{−1}) of sulfone **1p** with *trans*-perylene.

Configuration of the transition state	<i>E_A</i>	<i>E_R</i>
<i>meta-endo</i>	5.0	−43.0
<i>meta-exo</i>	13.8	−40.5
<i>ortho-endo</i>	7.9	−38.7
<i>ortho-exo</i>	17.7	−38.2

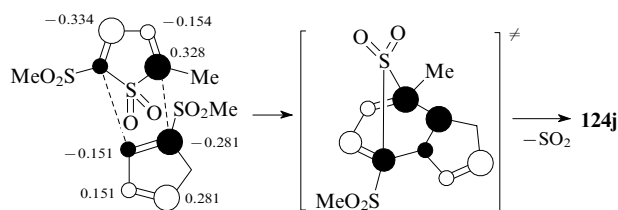
The results of DFT calculations with the PBE functional for the reactions of compounds **1m,p** with other dienes are in good agreement with experimental data and confirm the *endo*-stereoselectivity of cycloaddition.

The reactions of non-symmetrical thiophene 1,1-dioxides with cyclopentadiene may give two different adducts. However, it was found¹¹⁴ that the product exists as a single isomer, the addition involving the most acceptor double bond. Thiophene dioxides can react with cyclopentadiene both as dienes (normal cycloaddition) and as dienophiles (cycloaddition with inverse electronic demand), the reaction route being dependent on the nature of substituents in the initial sulfone. To explain the observed selectivity, quantum-chemical calculations of the orbital coefficients (riMP2 *ab initio* method) were carried out.¹¹⁴ Both types of cycloaddition discussed are known to be controlled by the cyclopentadiene HOMO and the thiophene dioxide LUMO. The calculated orbital coefficients and the HOMO and LUMO energies of the reactants are presented in Table 7.

It can be easily seen that the formation of isomer **123m** in the reaction of sulfone **1m** with cyclopentadiene is in good agreement with the calculated data as a result of overlap of the orbitals with the greatest orbital coefficients in the transition state TS-1.



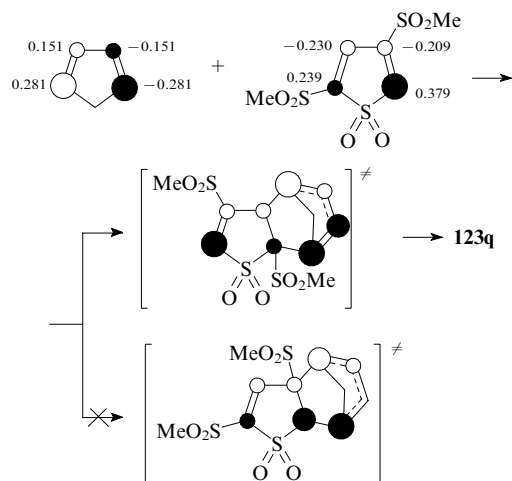
The regioselectivity of the Diels–Alder reaction is fully controlled by orbital interactions both in the normal reaction and in the reaction with inverse electronic demand where thiophene dioxide acts as the diene. The latter example is clearly illustrated by the reaction of sulfone **1j** with cyclopentadiene. The overlap of orbitals with the greatest orbital coefficients results in the formation of the only isomer **124j**.¹¹⁴



However, in the case of reaction of thiophene 1,1-dioxide **1q**, the regioselectivity predicted theoretically differs from that observed experimentally. We believe that this is due to the predominance of the steric requirements over the electronic interactions. Both double bonds of thiophene dioxide **1q** are activated by the MeSO₂ groups but the C(2)=C(3) bond is sterically more accessible for the reaction with the diene, which finally affords the observed adduct **123q**.

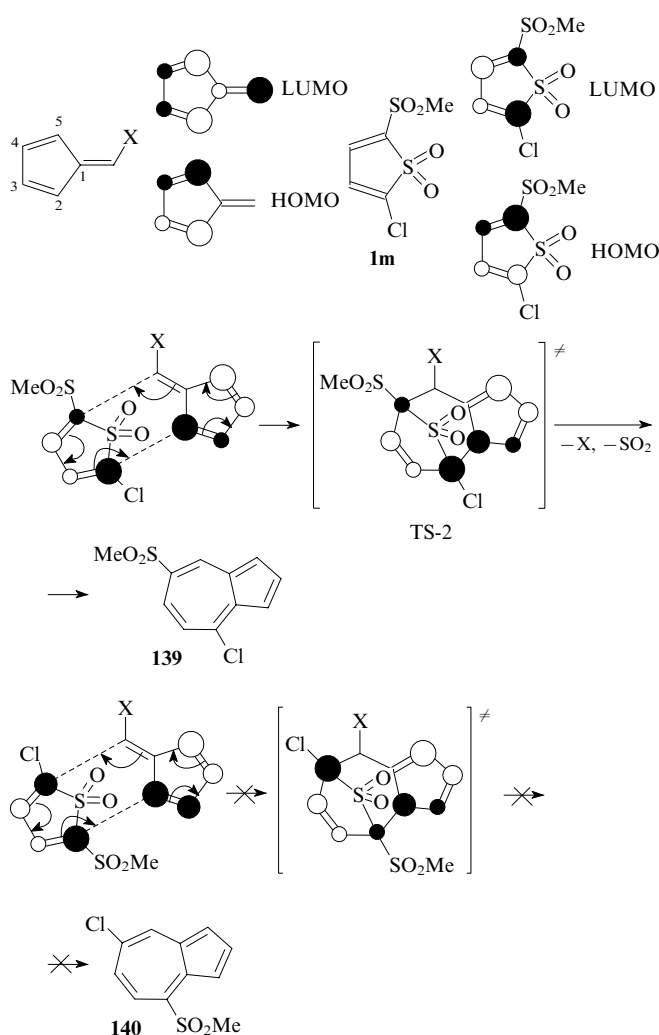
Table 7. Orbital coefficients of the diene system and HOMO and LUMO energies (in kcal mol⁻¹) of cyclopentadiene and thiophene 1,1-dioxides.

Orbital coefficients	HOMO	LUMO
	-8.46	3.60
 (1p)	-10.62	-0.18
 (1m)	-11.47	-0.18
 (1q)	-11.47	-0.29
 (1j)	-10.69	0.22
 (1o)	-10.31	0.31
	-10.52	0.69
 (1v)	-10.10	0.80

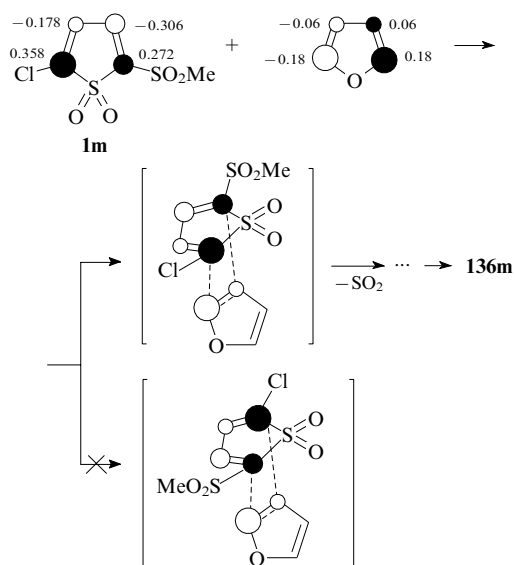


A similar approach has been used to interpret the regioselectivity in [6 + 4] cycloaddition reactions of thiophene dioxides with 6-substituted fulvenes. As an example, consider the diagrams of the orbital coefficients of sulfone **1m** and fulvene (Scheme 9). Thus the higher orbital coefficient for the LUMO of the chloro-substituted carbon atom of thiophene dioxide **1m** directs the attack towards the higher orbital coefficient of the fulvene HOMO. This results in a definite orientation of the reactants in the transition state TS-2, which accounts for the predominant formation of isomer **139** with the predetermined arrangement of substituents in the target azulene. The same pattern observed for other non-symmetrical thiophene dioxides; hence, the regioselectivity of the reaction is controlled by orbital interactions.¹³³

Scheme 9



The regular features of the reaction of furan with thiophene dioxide **1m** were considered using the frontier molecular orbital method.¹²² The reaction occurs in such a way that the molecular orbitals with the greatest coefficients of both diene and the dienophile overlap with each other resulting in the predominant formation of products with a definite arrangement of substituents. The regioselectivity of reactions of other substituted thiophene dioxides also obeys this rule.¹²²



The calculation of orbital coefficients and energies of the intermediates has also been used to interpret the formation of the by-product upon nucleophilic cleavage of thiophene dioxide **154a** induced by amines.¹⁴⁵ The orbital coefficients and the transition state energies of the two possible deprotonation products of the starting sulfone were determined by PM3/3-21G(*) calculations (Scheme 10). Anion **B** (counterion, $R_2N^+H_2$) was found to be + 5.68 kcal mol⁻¹ less stable than anion **A**. In addition, the charge is more uniformly distributed along the carbon chain in anion **B**, while in anion **A** it is largely concentrated on the methyl group at the C(5) atom having the greatest orbital coefficient. Thus, cleavage of the thiophene ring should give mainly diene **201** rather than its isomer **202**.¹⁴⁵

3. Theoretical studies of the oligomers and polymers

Since the first organic semiconductors and other materials based on thiophene oligomers have been developed, theoretical investigation of the structure and unique properties of these compounds has become a priority line of research in this field. Particular attention is devoted to quantum-chemical calculations having a predictive validity in order to use them to prepare compounds with pre-specified properties. A line of research is concerned with the development of modified oligothiophenes in which the HOMO–LUMO energy gap is as small as possible. These compounds should be efficient n-type semiconductors, which was confirmed experimentally.

Barbarella and co-workers^{165, 166} have shown that the introduction of thiophene dioxide fragments into an oligomer molecule substantially decreases the HOMO–LUMO energy gap. Hartree–Fock *ab initio* calculations in the 3-21G* basis set demonstrated a decrease in the HOMO and LUMO energies on passing from bithienyl derivatives to mono- and di-1,1-dioxides. It is noteworthy that the energy change is greater for the LUMO

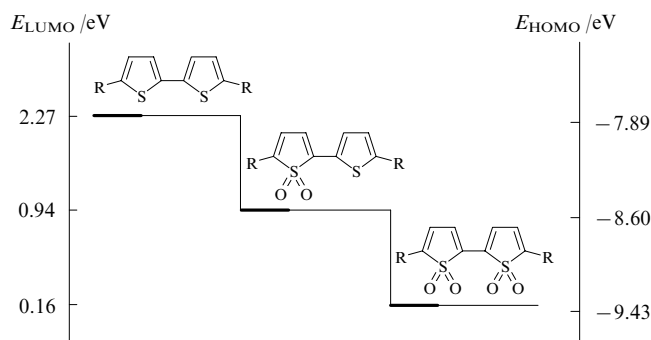


Figure 2. Frontier MO energies for bithienyl derivatives, and their mono- and di-1,1-dioxides ($R = SiMe_2Bu^t$).^{165, 166}

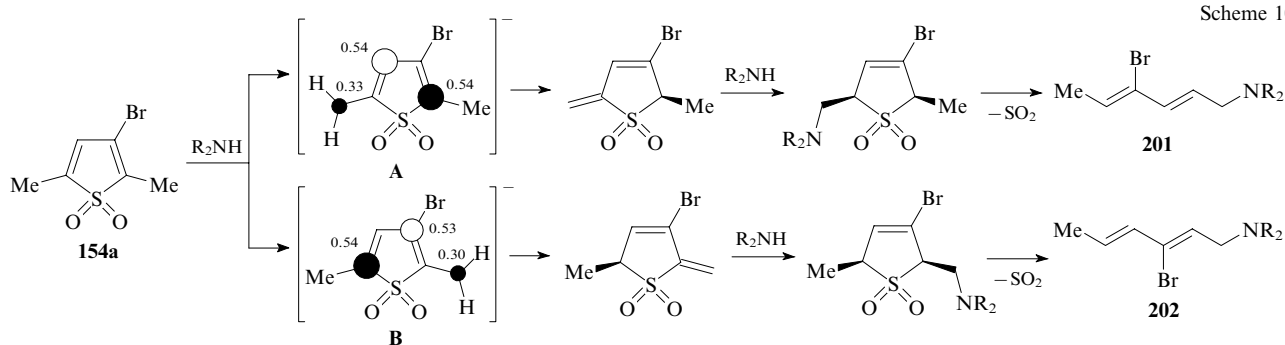
than for the HOMO of the oligomers (Fig. 2). Polarographic studies demonstrated good agreement with the calculated energies. It was found that oligomers with dioxide units are more prone to be reduced than to be oxidised, while the initial oligothiophenes are more prone to be oxidised than to be reduced. Thus, the introduction of a particular number of thiophene dioxide units into an oligothiophene molecule allows fine ‘tuning’ of the redox potentials and hence, provides control of the electronic properties of these materials.

In recent years, theoretical investigations of oligothiophenes have also been focused on the mechanisms of charge transfer in these compounds and in their completely or partially oxidised forms and on the interpretations of their optical and electronic properties.^{170, 173, 183, 201–205} Discussion of these subjects is beyond the scope of this review, as this is a special field of chemistry.

VI. Conclusion

For more than 90 years, thiophene 1,1-dioxides have been attracting the attention of researchers as compounds able to easily undergo cycloaddition, act as Michael acceptors and be transformed with ring opening. Currently, these derivatives are used more and more often for targeted synthesis of complex carbo- and heterocyclic structures. Analysis of the data published over the last 20 years indicates that thiophene 1,1-dioxides containing halogen atoms or alkyl or phenyl groups and their fused analogues have been studied fairly comprehensively. In recent years, a substantial contribution was made to the chemistry of unsubstituted and monosubstituted thiophene dioxides synthesised in the late 20th century. The synthesis and study of the synthetic potential of functionally substituted thiophene 1,1-dioxides carried out quite recently filled the gap in the chemistry of this class of compound.

The scope of application of thiophene 1,1-dioxides is not limited to their use as ‘building blocks’ for the design of desired molecules. Many systems containing this fragment are themselves



Scheme 10

valuable for investigations in various branches of science ranging from the development of new semiconductor or optical devices to the use in supramolecular chemistry.

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Certain aspects of the reactivity of carotenoids. Redox processes and complexation

N E Polyakov, T V Leshina

Contents

I. Introduction	1049
II. Redox reactions of carotenoids with quinones and metal ions	1051
III. Reactions of carotenoids with free radicals. Antioxidant properties of carotenoids	1052
IV. Pro-oxidant properties of carotenoids	1054
V. The role of electron-transfer processes in the <i>cis-trans</i> isomerisation of carotenoids	1054
VI. Inclusion complexes of carotenoids with cyclodextrins	1057
VII. Supramolecular complexes of carotenoids with glycyrrhizin	1057
VIII. Conclusion	1062

Abstract. The published data on the redox reactions of carotenoids, their supramolecular inclusion complexes and the composition, properties and practical application of these complexes are generalised. Special attention is given to the effect of complexation on radical processes involving carotenoids and on the antioxidant activity of carotenoids. The bibliography includes 151 references.

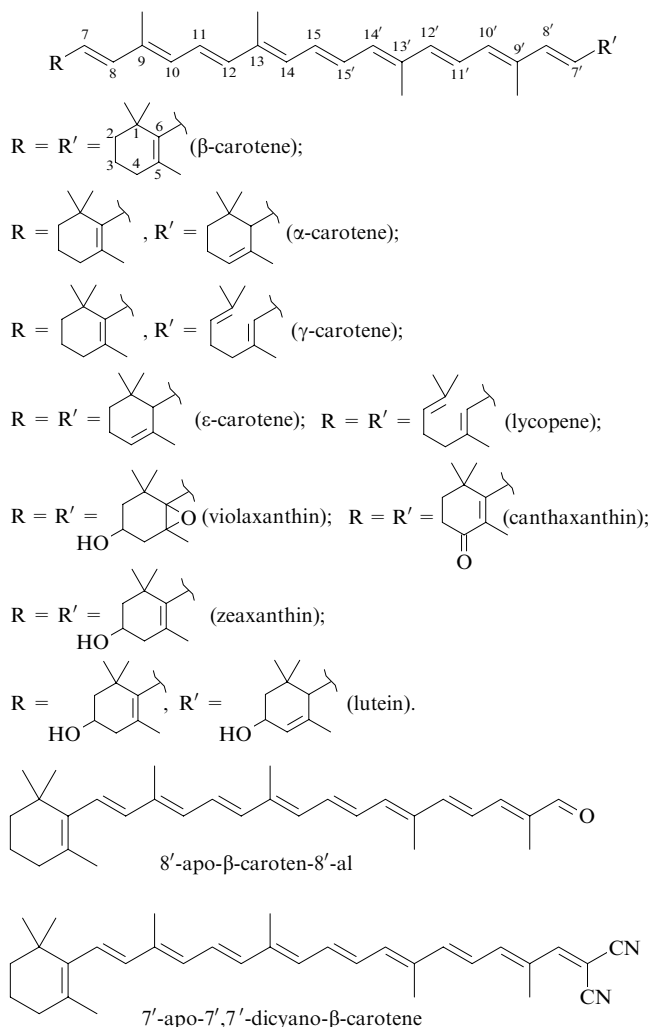
I. Introduction

Carotenoids, the natural pigments, are widely distributed in plants and animals.^{1–3} They are detected in cells and tissues of all living things. Higher plants, fungi, bacteria and microbes can synthesise carotenoids, while animals and humans get them with food. In nature, carotenoids can exist in different states, namely, in the free state, as esters with fatty acids, glycosides and as carotene–protein complexes. To date, more than 600 different carotenoids are known.

Carotenoids belong to a large class of terpenes. A carotenoid molecule contains a long polyene chain of isoprene units with a cyclohexene (ionone) ring or isoprene residues at one or both ends. The majority of natural carotenoid pigments are represented by tetraterpenes (C₄₀). In plants, two groups of C₄₀ carotenoids are usually present, namely, carotenes ('pure' hydrocarbons including β-carotene and its isomers, lycopene, see below) and xanthophylls (oxygen-containing carotenoids among which lutein, zeaxanthin, canthaxanthin, violaxanthin are the most abundant). Carotenoids with the number of carbon atom less than 40 (nor- and apocarotenoids, see below) and more than 40 (homocarotenoids) are also known.

Carotenoids play an important role in various physiological processes of critical importance for the life in its present form. In most natural processes, carotenoids are assumed to play the role of energy and electron carriers.⁴ For plants, the involvement of

carotenoids in the photosynthesis is of fundamental importance. In higher plants, the photosynthetic processes occur in chloroplasts, *i.e.*, specific energy-converting organelles of plant cells. Chloroplasts contain two photosystems, namely, PS1 and PS2, which differ in the composition of proteins and pigments and in



N E Polyakov, T V Leshina Institute of Chemical Kinetics and Combustion, Siberian Branch of the Russian Academy of Sciences, ul. Institutskaya 3, 630090 Novosibirsk, Russian Federation. Fax (7-383) 330 73 50, tel. (7-383) 333 29 47, e-mail: polyakov@ns.kinetics.nsc.ru (N E Polyakov), tel. (7-383) 333 14 05, e-mail: leshina@ns.kinetics.nsc.ru (T V Leshina)

Received 10 April 2006

Uspekhi Khimii 75 (12) 1175–1192 (2006); translated by T Ya Safonova

photophysical properties. Photosystem 2 is responsible for the photosynthetic oxidation of water, while PS1 catalyses the oxidation of plastocyanine and the reduction of ferredoxin. Both systems include a light-collecting antenna (a pigment–protein complex that contains chlorophyll, carotenoid and protein molecules), a photochemical reaction centre, which consists of chlorophyll dimers (P700 in PS1 and P680 in PS2), electron donors and acceptors and electron-transfer molecules bound to this centre.

In the first step of photosynthesis, the absorption of light quanta by chlorophyll and carotenoid molecules converts them into the excited state, which is followed by energy transfer to other molecules of the photosystem. The second step involves the charge separation in the photochemical reaction centre of the PS2 and electron transfer along the electron-transport system from PS2 to PS1. Finally, ferredoxin, which is the electron carrier from PS1 to nicotinamide adenine dinucleotide phosphate (NADP), is reduced in PS1. The process ends with the reduction of NADP and synthesis of adenosine triphosphate (ATP).

According to modern concepts, the photochemical reaction that occurs in the PS2 reaction centres includes electron transfer from the excited molecule of chlorophyll P680 (its absorption spectrum is characterised by a peak at 680 nm) to a pheophytin molecule (PH, a primary electron acceptor) to form a state with separated charges ($P680^+ \cdots PH^-$) followed by electron transfer from PH^- to a molecule of a secondary electron acceptor, namely, natural quinone (Q, a complex of plastoquinone with a Fe^{2+} ion) to afford a more stable state $P680^+ \cdots PH \cdots Q^-$. The electron is transferred further by quinone carriers. Oxidised $P680^+$ exhibits exceptionally high electron affinity, *i.e.*, it is a very strong biological oxidant. If, for some reasons, $P680^+$ is not consumed in water oxidation, it can oxidise molecules in its nearest environment thus damaging PS2.

It should be noted that the risk of damaging the photosynthetic system as a result of side photochemical processes that occur in chloroplasts under the action of light (photoinhibition) is very high. Photoinhibition can be caused by different factors, including the formation of singlet oxygen. In chloroplasts, singlet oxygen is formed in the reaction of oxygen with excited chlorophyll molecules. Carotenoids present in chloroplasts uptake the excess energy from the excited chlorophyll molecules, which reduces the hazard of the formation of singlet oxygen. Thus, carotenoids are assumed to play the key role in the protection of organic molecules against oxidation.

In animal and human organisms, carotenoids perform different protective functions, *viz.*,^{5–11}

- bind singlet oxygen and inhibit the formation of free radicals thus preventing their adverse effect on the organism;
- provide protection against UV radiation;
- play the role of antioxidants.

Of no less significance are the membrane-stabilising and immunostimulating functions of carotenoids as well as their provitamin A activity. Vitamin A and carotenoids favour normal metabolism, enhance the resistance of an organism against infections, provide normal operation of the organ of vision, exert a beneficial effect on the performance of skin and mucous membranes and are involved in redox processes.

Nowadays, a peak of interest in the studies of carotenoids is observed, being primarily associated with the discovery of their antioxidant properties. Now, it can be stated with confidence that it is the chemical and physicochemical studies of the reactivity of carotenoids in redox processes that are most promising. Scientists in different fields, namely, physics, chemistry, biology and medicine, are involved in the elucidation of the nature of the major factors that determine the antioxidant activity of carotenoids.^{12–17} Despite the consensus on the elementary mechanisms of the antioxidant effect of carotenoids, no quantitative data on the relationship between the physicochemical properties of these compounds and their antioxidant activity are available in the literature.

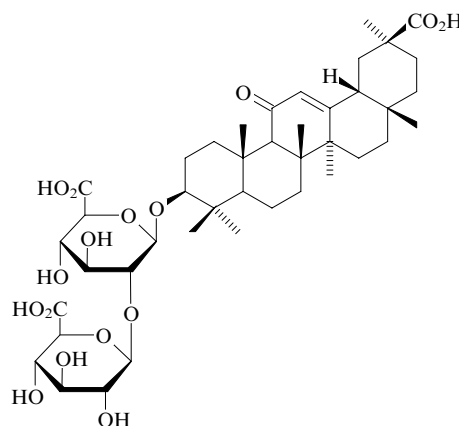
The information on short-lived paramagnetic and diamagnetic intermediates formed in reactions of carotenoids with free radicals is also very scarce,^{14–17} and the structure of such intermediates is as a rule merely suggestive. However, it is this information that is the most valuable when selecting carotenoids for their practical application as antioxidants.[†] In recent years, due to the use of EPR techniques, considerable advance has been made in the studies of the redox processes involving carotenoids.^{14, 18, 19}

Yet another important problem closely associated with the redox properties of carotenoids is the formation of carotenoid complexes and the effect of an organised medium on their reactivity in redox processes.

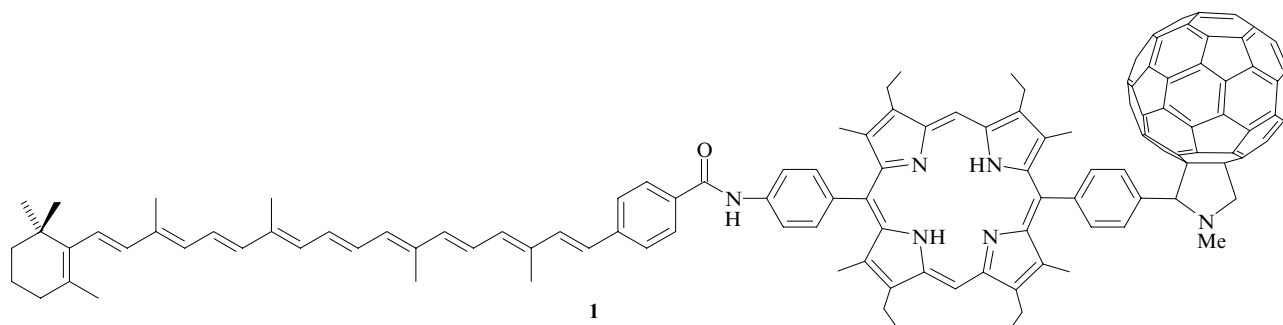
It is known that carotenoids are characterised by high lability in the free state and, at the same time, become more stable when being components of various complexes (*e.g.*, with proteins). Hydrophobicity, photosensitivity and chemical activity of free carotenoids substantially complicate their use as medicinal drugs; this is why active studies on the development of the methods for the synthesis of their complexes are in progress. Recently, a number of fundamental and applied studies on the synthesis and investigation of supramolecular inclusion complexes of carotenoids with different natural compounds, first of all, with cyclodextrins have appeared.^{20–29} Cyclodextrins not only protect carotenoids from external factors, but also improve their solubility in water and organic solvents. Upon formation of inclusion complexes of the ‘host–guest’ type of cyclodextrins with size-matching hydrophobic inclusion compounds (*e.g.*, carotenoids), the physical, chemical and biological properties of the latter can substantially change (for details, see Refs 30–32).

In the pharmaceutical, cosmetic and food industries, cyclodextrins are largely used for improvement of solubility of inclusion complexes (*e.g.*, vitamins, food pigments, *etc.*)^{33–35}. Complexation can also substantially increase the stability and bioaccessibility of inclusion complexes, eliminate objectionable taste and odour, prevent side effects of medicinal drugs and favour their assimilation.^{33, 35} Due to the ability of cyclodextrins to molecular recognition and separation of chiral isomers, they are used in the production of synthetic enzymes.^{36, 37} However, complexation can also have some negative consequences. Thus the increase in the stability and solubility of carotenoids upon formation of inclusion complexes with cyclodextrins is accompanied by the loss of their antioxidant activity.

β -Glycyrrhizic acid (GA),³⁸ which belongs to triterpene glycosides, is yet another natural compound for which supramolecular inclusion complexes with carotenoids are described.



[†] The ability of carotenoids to decelerate ageing processes and to prevent and stop the development of diseases caused by reactive oxygen species and free radicals (superoxide ion, singlet oxygen, *etc.*) are actively discussed in the literature. Carotenoids are used for treatment of serious illnesses such as cancer and cardiac and nervous system diseases and age-specific degenerative changes in muscular tissues.



Complexes of biologically active compounds with GA attract attention of scientists due to their unusually high stability^{39–41} and due to the fact that the activity of these compounds in such complexes increases by a factor of dozens[‡] with simultaneous reduction of their toxicity.^{39,42}

It should be noted that despite the interest in the synthesis of inclusion complexes aimed at purposeful changes in their properties, the problem of the nature of the effect of complexation on their reactivity is still open. The present survey of the studies that deal with single-electron transfer processes involving carotenoid complexes is one of few attempts to solve this problem.

The purpose of this review is to briefly generalise the studies of the redox properties of carotenoids, their complexation and reactions of these complexes. Carotenoid reactions that include the electron transfer step are described in more detail. The relationship between the efficiency of single-electron transfer and the antioxidant/pro-oxidant activity of carotenoids and their supramolecular complexes is discussed.

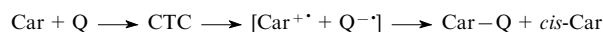
II. Redox reactions of carotenoids with quinones and metal ions

A long chain of conjugated double bonds in a carotenoid molecule provides the electron-donating activity of carotenoids and favours stabilisation of their radical forms.⁴³ Studying of physicochemical properties of carotenoid radical cations attracts the keenest attention of scientists, attempting to model the system of primary photosynthetic processes[§] involving carotenoids, aimed at the development of artificial solar cells.^{44–46} Successful solution of this problem is closely related to the efficient spatial separation of charges in an artificial photosystem involving carotenoids and porphyrins. In connection with this, the elucidation of how an organised medium affects the structure of carotenoid itself and the lifetimes and chemical properties of radical cations acquires special importance.

The studies of an isolated PS2 have shown⁴⁷ that its photoactivation includes selective oxidation of β -carotene accompanied by electron transfer from the carotene molecule (Car) to the primary donor P680⁺⁺ to form a radical cation Car⁺⁺. The formation of the radical cation Car⁺⁺ in the irradiation of PS2 was detected by optical absorption spectroscopy^{48–50} and low-temperature EPR,^{51,52} while the formation of quinone radical anions in PS1 and PS2 was detected by the EPR method.^{53–55} As it has been mentioned above, in PS2, the electron-transfer chain involves molecules of carotenoids, chlorophyll, pheophytin and natural quinones [plastoquinones, ubiquinones (Q)]. This is why triads of the [Car⁺⁺...P...Q^{•-}] type are also used in model electron-transfer systems.^{56–58} The use of a molecular triad carotenoid – porphyrin – fullerene (**1**) was a windfall.⁵⁸

The long lifetime of triads opens up wide possibilities for their use in molecular electronics as nanosized communication and data processing constructs in sensors. The principle of operation of molecular triads is rather simple. A porphyrin molecule excited upon absorption of a light quantum donates an electron to the fullerene molecule to form a primary radical-ion pair [Car...P⁺⁺...C₆₀^{•-}]. Being a strong oxidant (electron acceptor), the radical cation P⁺⁺ abstracts an electron from a carotenoid molecule to form a separated radical-ion pair [Car⁺⁺...P...C₆₀^{•-}]. This state is relatively long-lived and retains a considerable part of light energy by increasing the electrochemical potential.⁵⁸ Apparently, such a way of light energy transformation is similar to the mechanism used by plants for utilisation of solar energy in photosynthesis.

The formation of carotenoid radical cations in reactions with quinones in homogeneous media was observed both in the light and in the dark [using such a strong electron acceptor as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)].⁵⁹ In the first step, a charge-transfer complex (CTC) formed, which was followed by the formation of a radical-ion pair [Car⁺⁺+Q^{•-}]. Carotenoid-to-quinone adducts (Car–Q) and carotenoid *cis*-isomers[¶] were the final products.



The formation of CTC in reactions of β -carotene, canthaxanthin and 8'-apo- β -caroten-8'-al with quinones was detected by optical spectroscopy (Fig. 1) and EPR.⁵⁹ Thus the intense absorption at 1030 nm observed upon mixing of β -carotene with quinone in CH₂Cl₂ was assigned to a charge-transfer complex, while the free radical cation of β -carotene absorbs in this solvent at

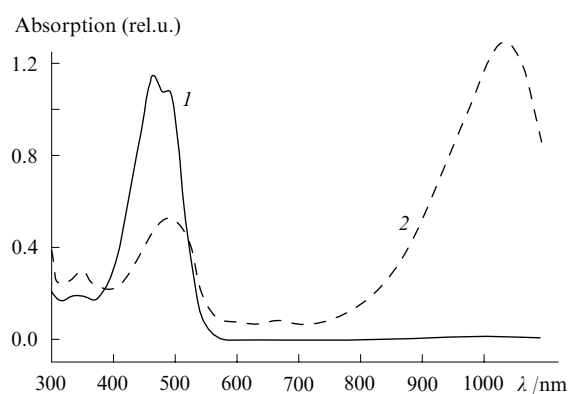
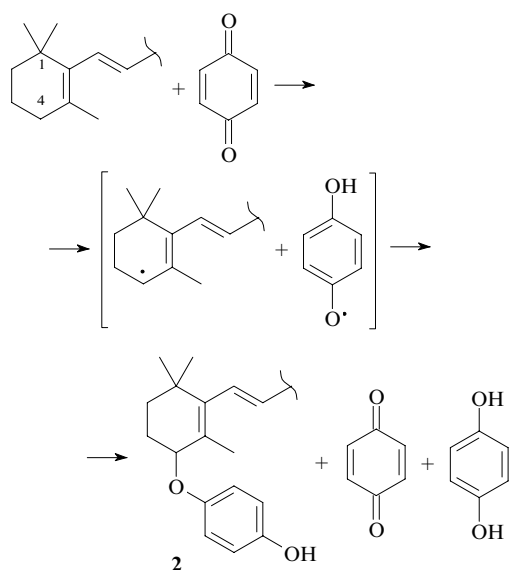


Figure 1. Absorption spectra of β -carotene and its CTC with quinone recorded before (curve 1) and after (curve 2) their mixing with DDQ in CH₂Cl₂ at -50°C .⁵⁹ The concentrations of β -carotene and DDQ are 12 $\mu\text{mol litre}^{-1}$.

[‡] The stability constant of GA complexes is 10⁵ litre mol⁻¹, which exceeds the mean stability constant of cyclodextrin complexes by two orders of magnitude.³⁰

[§] At present, photosynthesis is one of the most thoroughly experimentally studied biological processes.

[¶] Dissociation of radical-ion pairs escaped from recombination to free radical ions and their subsequent diffusion into the bulk are accompanied by *cis-trans* isomerisation of carotenoid radical cations to form *cis* isomers (see Section V).

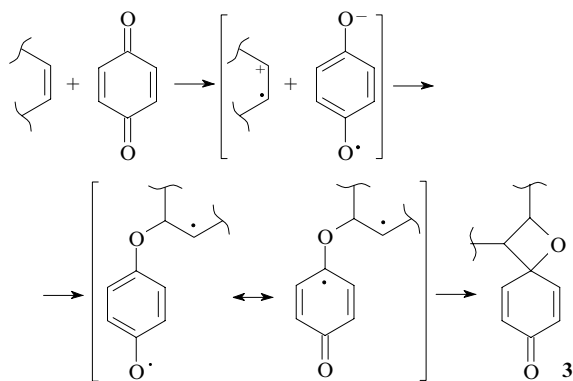


Scheme 1

1000 nm.⁶⁰ Further transformation of CTC might follow two pathways depending on the carotenoid structure. For β -carotene and 8'-apo- β -caroten-8'-al, the preferential reaction pathway is the abstraction of the allylic proton at C(4) atom of the cyclohexene ring to form a neutral carotenoid radical (Scheme 1).⁵⁹

Ether **2** is the final product of this reaction. Its formation was confirmed by IR and NMR spectroscopy.⁵⁹ In canthaxanthin, no abstraction of the allylic proton is possible and the reaction proceeds through the addition of quinone to the chain of conjugated double bonds of the carotenoid (Scheme 2).

Scheme 2



[The photoinduced cycloaddition of a carbonyl group (including that of quinone) to the double bond of the polyene molecule is known as the Paterno–Büchi reaction.^{61, 62}] It is assumed that the first pathway of this process also involves electron transfer from a Car molecule to Q to form a biradical, adduct **3** being the final reaction product.^{63, 64}

Metal ions can also be used for generation of radical cations of carotenoids in both homogeneous and organised media.^{65–67} The mechanism of the redox reaction of carotenoids with metal ions in a homogeneous medium was studied in detail by the example of the reaction of β -carotene with iron(III) chloride.^{43, 65} The first stage was shown to be electron transfer from the Car molecule to Fe^{3+} to form a Fe^{2+} ion and a radical cation $\text{Car}^{+\cdot}$. Recombination of the radical cations affords a dication and a neutral molecule.



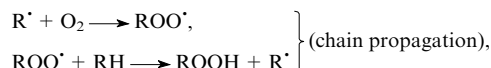
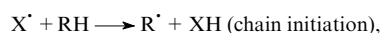
As in the above-discussed reaction with quinones, the carotenoid radical cations and dications formed undergo *cis*–*trans* isomerisation.^{43, 65, 68, 69} The oxidation of β -carotene with metal ions in the presence of oxygen affords a stable product, *viz.*, 5,8-peroxide.⁶⁵

The oxidation of carotenoids with metal ions in organised media was studied.^{66, 67, 70} In particular, by the example of β -carotene, canthaxanthin and 8'-apo- β -caroten-8'-al, it was shown that in metal-containing mesopores of MCM-41 these carotenoids form compact complexes with Cu^{2+} , Ti^{4+} and Fe^{3+} ions in which the distance between the metal ion and the nearest double bond of the carotenoid is $\sim 2 \text{ \AA}$.^{68, 70} The formation of these complexes results in acceleration of both the direct and reverse electron transfer between the carotenoid and the metal and in the increase in the quantum yield of the formation of carotenoid radical cation.

III. Reactions of carotenoids with free radicals. Antioxidant properties of carotenoids

The interest in the reactions of carotenoids with free radicals is aroused first of all by the discovery of their antioxidant properties. A comprehensive description of carotenoid reactions with peroxide radicals can be found in recent reviews;^{15–17} therefore, here we consider only the proposed mechanisms of these reactions. The role of electron transfer and its effect on the antioxidant activity of carotenoids will be considered in more detail.

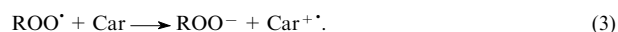
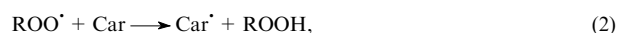
It is known^{71, 72} that in a living organism, peroxide radicals are formed during chain autoxidation of lipids.



Here, X is a free radical that initiates the radical chain reaction, RH is a lipid molecule. We do not consider possible sources of free radicals in the organism and only refer to the study by Chan⁷² in which the oxidation stress initiated by metal ions was assumed to be the main 'source' of free radicals. The process of free radical formation can be interrupted as a result of the chain termination by any antioxidant capable of reacting with peroxide radicals.^{3, 71–75} The reaction product is an antioxidant radical, which is less active than the starting peroxide radical. The low activity of the former makes impossible the chain propagation. Chain termination occurs as a result of the reaction of the antioxidant radical with either another radical or another antioxidant.

In the past decades, attempts were undertaken to compare the antioxidant activities of different carotenoids and to reveal the factors responsible for this activity.^{14–17} This required the elucidation of the detailed mechanism of the reaction of carotenoids with free radicals, first of all, peroxide radicals.

The following three pathways for the reaction of carotenoids with peroxide radicals were considered most often: addition of a free radical to a double bond of a carotenoid [reaction (1)], abstraction of a hydrogen atom from the allylic fragment of a carotenoid (2) and electron transfer from a carotenoid to a peroxide radical to form a carotenoid radical cation (3).^{7, 76–78}



(It should be mentioned that the radicals $\text{ROOCar}^{\cdot}$ and $\text{Car}^{\cdot}$ can in turn serve as the sources for the chain propagation of lipid oxidation with peroxides.) The analysis of the available literature data does not allow one to single out the major mechanism.^{15–17, 79}

It can be stated that the direction of the reaction of peroxide radicals with carotenoids depends on several factors, namely, the carotenoid structure, the activity of peroxide radicals and the nature of the solvent. Thus the analysis of absorption spectra and reaction products of β -carotene with peroxide radicals led to a conclusion that in non-polar media both a radical adduct $^{\bullet}\text{Car}-\text{OOH}$ (Refs 80–83) and a radical $^{\bullet}\text{Car}$ (Refs 84 and 85) are formed as the short-lived intermediates. However, the relative contributions of these reaction channels were not determined.

More detailed information on the mechanism and kinetics of the reaction of carotenoids with free radicals was obtained from the results of time-resolved pulse methods, first of all, flash laser photolysis and pulse radiolysis.^{7, 8, 86, 87} However, these methods did not provide the complete picture of the reaction of carotenoids with free radicals either. To date, the absorption spectra are adequately characterised only for carotenoid radical cations,^{88, 89} whereas the assignment of other signals in absorption spectra of intermediate species still remains hypothetical.

Based on studies of the reaction of β -carotene with the $\text{Cl}_3\text{COO}^{\bullet}$ radical in polar media, it was concluded¹⁶ that this reaction affords equal amounts of radical cations and radical adducts of β -carotene. Similar conclusions were also drawn based on the analysis of absorption spectra of intermediate species formed in the laser-induced photolysis of certain carotenoids in micellar solutions.⁷ In the latter case, the absorption spectra contained two bands in the region of 750–950 nm, which differed in the decay rate. The absorption in the range of 850–950 nm was assigned to carotenoid radical cations and the band in the region of 750–850 nm was assigned to the radical adduct.⁷ However, a different assignment was proposed.^{90, 91} In alcohols, the measurements of relative intensities of absorption bands in the regions of 750–850 and 850–950 nm have revealed a strong dependence of the signal intensity on the polarity of the medium in the former region.⁹¹ Thus, it was concluded that the observed intermediate is most likely a radical-ion pair of carotenoid and peroxide anion.

It is known that carotenoids reside preferentially in the lipophilic region of the membrane due to their hydrophobicity.^{76, 92} For a non-polar β -carotenoid incorporated into a membrane, the formation of a radical cation is improbable, because electron transfer in a non-polar medium is unfavourable for energy reasons. At the same time, carotenoids with polar substituents (*e.g.*, zeaxanthin and astaxanthin) are located at the membrane surface where the electron transfer is more favourable. Hence, the interaction of such carotenoids with radicals can easily lead to the formation of radical cations.^{77, 93}

The data obtained by EPR spin-trapping techniques on the rate constants for the reaction of carotenoids with free radicals suggest that electron transfer is the primary step.¹⁴ By the example of certain natural and specially synthesised carotenoids, it was shown that the scavenging rates of $^{\bullet}\text{OOH}$ radicals by carotenoids correlate with the oxidation potentials of the latter (Fig. 2).¹⁴ Stable spin adducts of $^{\bullet}\text{OOH}$ radicals with spin traps formed in the absence and in the presence of carotenoids and their yields were measured. In the presence of a carotenoid, the yield of the spin adduct decreased as a result of the side reaction of hydroperoxide radical with the carotenoid (Fig. 3). Based on the experimental dependence of the yield of the spin adduct on the carotenoid concentration, the relative rate constants ($k_{\text{Car}}/k_{\text{ST}}$) for scavenging of radicals by the carotenoid were calculated according to Eqn (4).

$$\frac{A_0}{A} = \frac{k_{\text{ST}}[\text{ST}] + k_{\text{Car}}[\text{Car}]}{k_{\text{ST}}[\text{ST}]} \quad (4)$$

Here, A_0 and A are the intensities of the spin adduct signal in the absence and in the presence of a carotenoid, k_{ST} and k_{Car} are the rate constants for radical scavenging by a spin trap (ST) and by a

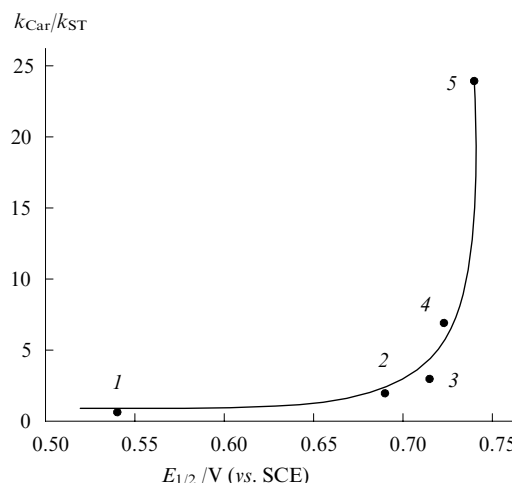


Figure 2. Dependence of the rate constant for scavenging of peroxide radicals by carotenoids on the oxidation potential of carotenoids (k_{Car} and k_{ST} are the rate constants for scavenging of the $^{\bullet}\text{OOH}$ radical by carotenoids and by spin traps, respectively).¹⁴ Carotenoids: β -carotene (1), canthaxanthin (2), 8'-apo- β -caroten-8'-al (3), 7'-apo-7',7'-dicyano- β -carotene (4), ethyl 8'-apo- β -caroten-8'-oate (5).

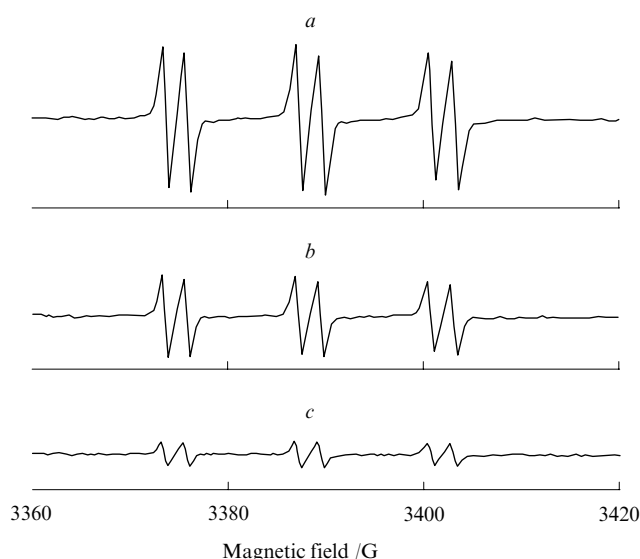


Figure 3. EPR spectra of the adduct PBN-OOH (PBN is *N-tert*-butyl- α -phenylnitron) recorded in the absence (a) and in the presence of 1.2 mmol litre⁻¹ (b) or 4.2 mmol litre⁻¹ (c) of canthaxanthin in DMSO.¹⁴ [PBN] = 5 mmol litre⁻¹, [FeCl₂] = 1 mmol litre⁻¹, [H₂O₂] = 0.5 mol litre⁻¹.

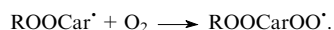
carotenoid (Car), respectively. *N-tert*-Butyl- α -phenylnitron (PBN), 2-methyl-2-nitrosopropane (MNP) and 5,5-dimethylpyrrolidine *N*-oxide (DMPO) were used as the spin traps.¹⁴ The available kinetic database (Spin Trap Data Base; <http://epr.niehs.nih.gov>) contains the following value for the reaction of PBN with the hydroperoxide radical in water: $k_{\text{ST}} \leq 10^6$ litre mol⁻¹ s⁻¹. The slowest and the highest reaction rates were observed for β -carotene and ethyl 8'-apo- β -caroten-8'-oate, respectively. Based on the comparison of the rate constants for the reactions of carotenoids with the hydroperoxide radical, it was concluded that reactions (1) and (2) make no substantial contribution to the reaction of carotenoids with these radicals.

IV. Pro-oxidant properties of carotenoids

Clinical trials of β -carotene gave contradictory results, which could be a reason for ambiguous attitude to carotenoids as antioxidants.^{94–96} Thus β -carotene demonstrated good results in curing certain types of tumours^{97–100} and at the same time proved to be ineffective or even exhibited pro-oxidant[†] activity in curing certain other diseases caused by free radicals.^{94–96}

It was shown that β -carotene exhibits the antioxidant activity only in low concentrations and at low oxygen pressures, whereas in high concentrations and at high oxygen pressures it exhibits the pro-oxidant activity.^{6, 9, 11, 17, 101}

Neutral radicals $\text{Car}^\bullet$ and $\text{ROOCar}^\bullet$ as well as radical cations $\text{Car}^{+\bullet}$, which are formed in reactions (1)–(3), were assumed to be responsible for the pro-oxidant activity of carotenoids.^{102–104} The mechanism of the pro-oxidant effect of carotenoids involves the reactions of neutral radicals of carotenoids $\text{Car}^\bullet$ and $\text{ROOCar}^\bullet$ with oxygen molecules to form the corresponding peroxide radicals

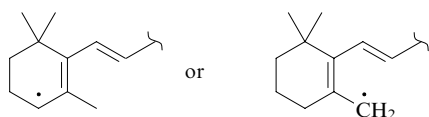


Neutral carotenoid radicals are also formed in the protonation/deprotonation of the corresponding radical ions. Thus the formation of neutral radicals of β -carotene, zeaxanthin, canthaxanthin, 8'-apo- β -caroten-8'-al and 7'-apo-7',7'-dicyano- β -carotene and their structural analogue, β -ionone, was registered¹⁸ by the EPR spin-trapping technique. The formation of neutral radicals $\text{Car}^\bullet$ was observed in chemical or electrochemical oxidation of these carotenoids to radical cations, which was followed by deprotonation of the latter [reaction (5)],¹⁸ and in their electrochemical reduction or a reaction with piperidine. The latter reaction proceeds through the protonation of the corresponding radical anions [reaction (6)].¹⁸

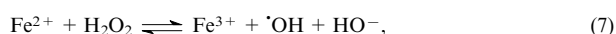


The formation of carotenoid radicals was judged from hyperfine coupling (HFC) constants of the corresponding spin adducts obtained in simulations of the EPR spectra.

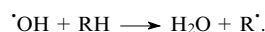
It was shown that the ability of carotenoid radical ions to undergo protonation/deprotonation is more typical of non-symmetrical apo-carotenoids with electron-withdrawing terminal groups. The calculation of the energy of deprotonation of carotenoid radical cations made it possible to assume that the abstraction of a hydrogen atom occurs from either the C(4) atom or the methyl group in position 5 of the cyclohexene ring. In both cases, the corresponding neutral radicals are formed.¹⁸



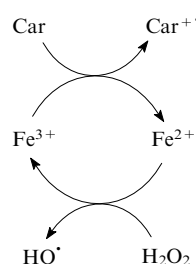
The reaction of carotenoids with metal ions, *e.g.*, with iron ions, may be considered as yet another possible mechanism of the pro-oxidant activity of carotenoids.^{103, 105} As was noted above, the oxidation stress initiated by metal ions is one of the major sources of free radicals in the organism⁷² and can result in the development of certain serious disorders including cancer.^{106, 107} It is assumed that in this case, the mechanism of free radical generation is similar to the well-known Fenton reaction.¹⁰⁸



[†] The pro-oxidant activity of a compound usually implies the increase in the yield of active oxygen-centred radicals in the presence of this compound.



By the example of β -carotene and canthaxanthin, it was shown experimentally that the involvement of a carotenoid in this reaction results in an increase in the yield of free radicals due to the chain reaction.¹⁰⁵



Reactions of carotenoids with peroxide and carbon-centred radicals were studied.¹⁰⁵ Based on the experimental results,^{14, 105} it can be assumed that, in the presence of metal ions, carotenoids can either decrease or increase the yield of free radicals depending on the oxidation potential of the carotenoid and the nature of the radical. The efficiency of the carotenoid-induced Fenton reaction increases as the oxidation potential of the carotenoid decreases and its reaction with the radical decelerates. According to Polyakov and co-workers' data,¹⁰⁵ β -carotene, which has the lowest oxidation potential among all the carotenoids studied, exhibits the highest pro-oxidant activity in the Fenton reaction (note that it is for β -carotene that the highest pro-oxidant activity was observed *in vivo*^{6, 94–96}).

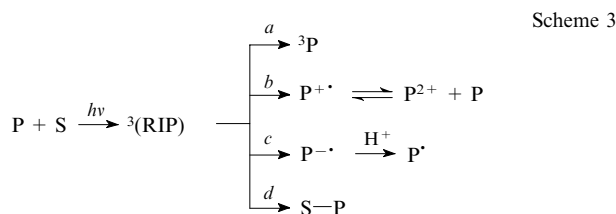
V. The role of electron-transfer processes in the *cis*–*trans* isomerisation of carotenoids

Light-induced *cis*–*trans* isomerisation of carotenoids is one of characteristic pathways of their phototransformations.^{109–113} It is usually meant that the isomerisation process involves molecules in the excited triplet state.^{112, 113} For the processes of sensitised *cis*–*trans* photoisomerisation, the formation of the excited triplet state is possible as a result of transfer of either energy or an electron.^{113–115} The latter process occurs in polar media in the presence of electron donors or electron acceptors to afford the corresponding radical ions. In connection with this, studies of the properties of radical ions of natural polyenes acquire special importance, because these compounds are incorporated in many biological systems.^{4, 45, 116} Thus *cis*-retin-11-al is the chromophore of the visual pigment rhodopsin. It is assumed that its *cis*–*trans* isomerisation initiates the visual perception process in eyes of humans and mammals.^{117, 118} This is the first and the only photochemical reaction that triggers the primary vision process, namely, phototransduction. Certain *cis*-carotenoids play an important role in photosynthetic processes in bacteria.¹¹⁹

Let us consider in more detail the mechanisms of *cis*–*trans* isomerisation of polyenes that involve the electron-transfer step. The major part of results discussed here were obtained using the following methods of spin chemistry:¹²⁰ chemically induced dynamic nuclear polarisation (CIDNP) and magnetic field effect (MFE) methods. These methods are the most efficient for studying the mechanisms of complex reactions of radicals and radical ions.[‡]

It has now been shown experimentally that *cis*–*trans* isomerisation of polyenes (P) that proceeds in the presence of electron donors or electron acceptors (S) can involve the following short-

[‡] It should be noted that it is the methods of spin chemistry that have provided evidence for the occurrence of single-electron transfer in *cis*–*trans* photoisomerisation of substituted ethylenes in the presence of electron donors or electron acceptors. This is acknowledged among the most important achievements of spin chemistry.^{121, 122}



P are polyenes (carotenoids, β -ionone), S are electron donors or electron acceptors (amines, quinones, aromatic hydrocarbons).

lived species (Scheme 3):¹¹⁴ excited triplet states (^3P) formed in the recombination of a triplet radical-ion pair (RIP) (pathway *a*); radical cations ($P^{+\cdot}$) and dication (P^{2+}) (pathway *b*); neutral radicals ($P^\cdot$) and biradicals ($P-S$ adducts), *i.e.*, secondary intermediates formed from radical ions (pathways *c* and *d*, respectively).

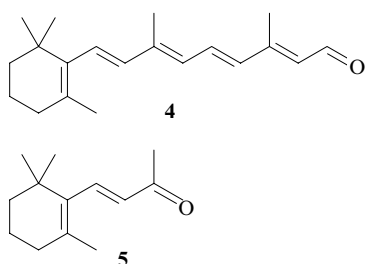
The formation of excited triplet states was observed in the isomerisation of substituted ethylenes and β -ionone in the presence of amines and aromatic hydrocarbons. Radical cations are formed in the presence of substituted ethylenes and carotenoids. Neutral radicals and biradicals are formed in the isomerisation of β -ionone in the presence of quinones.

1. *cis-trans* Isomerisation of alkenes in the excited triplet state

Triplet states of alkenes are formed either upon UV irradiation (direct isomerisation) or as a result of energy transfer (sensitised isomerisation).¹²³ There is the third mechanism of isomerisation of triplet alkenes established using the methods of spin chemistry.^{121, 122} According to this mechanism, triplet molecules are formed as a result of reverse electron transfer in a triplet RIP formed in the irradiation of substituted ethylenes in the presence of electron donors or electron acceptors in polar media.

In contrast to substituted ethylenes, polyenes are represented by a larger number of isomers, which often differ in the energy of the triplet states, redox potentials and their reactivities with respect to electron donors and electron acceptors.

Retinal (**4**) and β -ionone (**5**) were the first polyenes of the terpene series for which the radical ion mechanism of photoisomerisation in the presence of electron donors or electron acceptors was confirmed.^{115, 124, 125}



Let us consider how the isomerisation of β -ionone proceeds in the presence of electron donors, *viz.*, pyrene or triphenylamine.¹¹⁵ Four β -ionone isomers, namely, (*E*)- β -ionone (**A**), α -pyran (**B**), (*Z*)- β -ionone (**C**) and (*Z*)-*retro*- γ -ionone (**D**) are known.¹²⁶

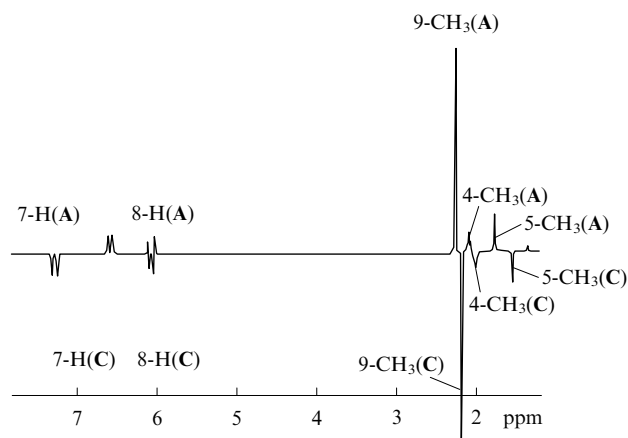
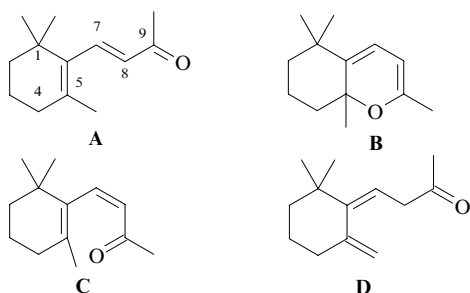
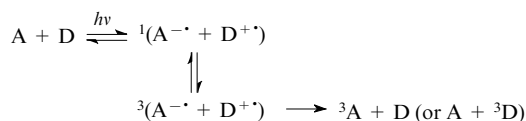


Figure 4. CIDNP spectrum observed in the photolysis of a photostationary mixture of β -ionone isomers in the presence of triphenylamine in acetonitrile.¹¹⁵ A procedure of presaturation of the NMR spectrum was used for elimination of equilibrium signals.

NMR studies have shown that the kinetics of accumulation and the ratio of isomers formed in the irradiation of β -ionone in the presence of pyrene and triphenylamine substantially differ from those in direct photolysis.¹¹⁵ During the photolysis of β -ionone in the NMR tube, the CIDNP effects of the main isomers were registered. Figure 4 shows the CIDNP spectrum recorded in the photolysis of a mixture of β -ionone isomers in the presence of triphenylamine. The mechanisms of transformations of β -ionone isomers could be proposed on the analysis of this spectrum.

In the CIDNP spectrum observed during the irradiation of a photostationary mixture of isomers **A–D** in the presence of triphenylamine, only signals for the triplet isomers **A** and **C** were detected. This made it possible to conclude that *cis* isomer **C** is the transformation product of the excited triplet *trans* isomer **A** and *vice versa*. Triplet states were formed in the recombination of the corresponding radical-ion pairs (Scheme 4).¹¹⁵ In turn, it was shown that in the presence of triphenylamine, isomers **B** and **D**, namely, α -pyran and *retro*- γ -ionone, are not formed *via* RIP.^{114, 115} However, in the presence of pyrene, the formation of a RIP with α -pyran as the radical cation and pyrene as the radical anion was observed.

Scheme 4



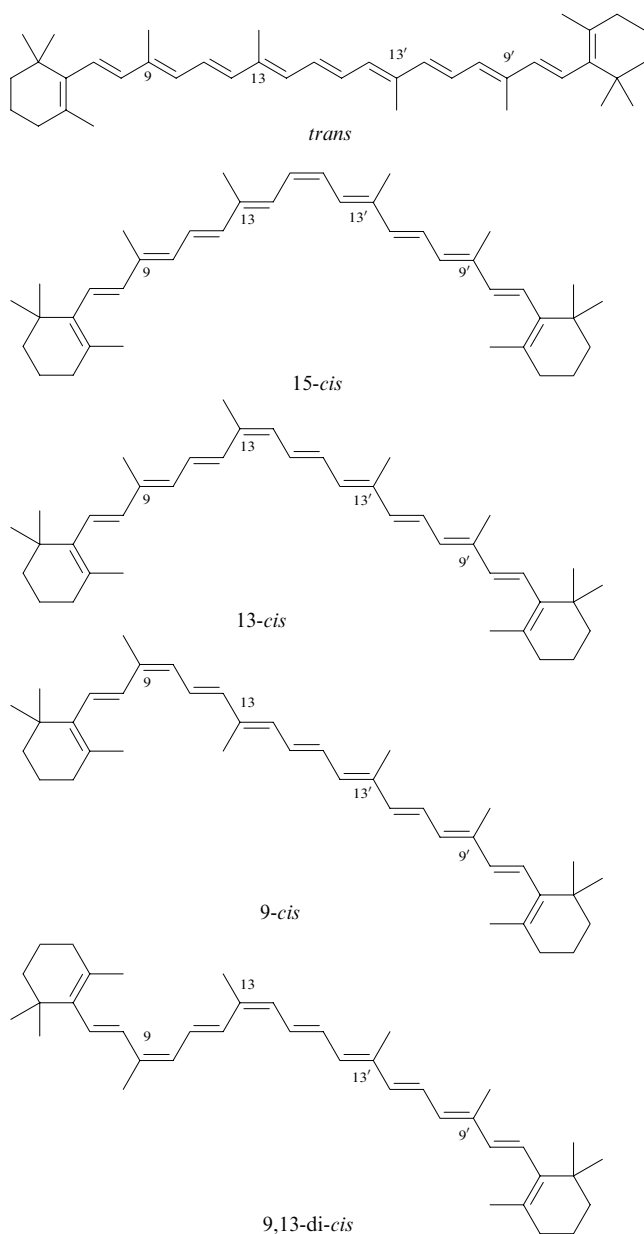
A is an electron acceptor, D is an electron donor.

The CIDNP sign and the intensities of polarised lines corresponded to the signs and distribution of HFC constants (*a*) in the β -ionone radical anion ($a_4 = 1.2$, $a_5 = 0.65$, $a_7 = -1.0$ and $a_9 = 0.65$ mT).¹²⁷ It should be noted that Scheme 4 is versatile, *i.e.*, it can be used for describing the reactions of β -ionone with both electron acceptors (*e.g.*, quinones)¹²⁵ and electron donors (*e.g.*, pyrene and triphenylamine).¹¹⁵ β -Ionone plays the role of the electron donor in the former case and the electron acceptor in the latter case.

This example shows that CIDNP is indeed an effective tool for studying the geometrical isomerisation of polyenes that involves radical stages.

2. *cis*–*trans* Isomerisation of C=C bonds in radical ions of polyenes

cis–*trans* Isomerisation of radical ions was described for the first time also for substituted ethylenes.^{122, 128, 129} The CIDNP method did not allow us to observe the isomerisation of radical ions of short polyenes, namely, of β -ionone (**5**) and retinal (**4**), in the microsecond time interval suitable for the CIDNP manifestation.^{124, 125} This means that even if the radical ions of these polyenes isomerise, this process takes much longer time than the microsecond interval of the lifetime of short-lived RIP. Indeed, as follows from quantum-chemical calculations, the activation barrier to the *cis*–*trans* isomerisation of β -ionone radical ions is 10–20 kcal mol^{–1}, which corresponds to the isomerisation rate of $\sim 10^4$ s^{–1}. However, we managed to observe the *cis*–*trans* isomerisation of radical cations of β -carotene, canthaxanthin and 8'-apo- β -carotenal generated either chemically or electrochemically.^{65, 68, 130, 131} These observations became possible due to the longer lifetimes of these radical cations as compared with those of β -ionone and retinal. Thus the lifetimes of radical cations of β -carotene and canthaxanthin in dichloromethane solutions were equal to several minutes.^{59, 132} HPLC analysis of the electrolysis products of β -carotene indicated the formation of five isomers, namely, *trans*, 15-*cis*, 13-*cis*, 9-*cis* and 9,13-di-*cis*, in a ratio of



50 : 4 : 21 : 21 : 4.^{59, 132} This isomer ratio was observed for both the electrochemical generation of radical cations and chemical oxidation of carotenoids in the presence of FeCl₃ or quinones.

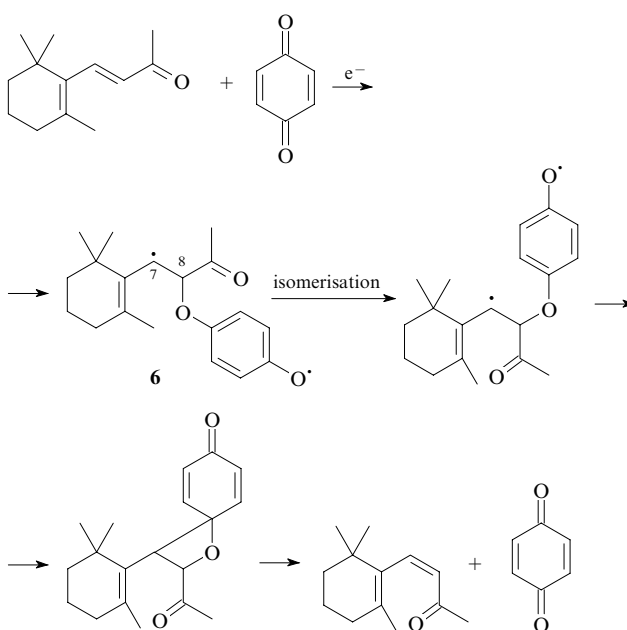
It should be emphasised that this ratio substantially differs from that obtained by Hashimoto and Kayama¹³³ for the triplet-sensitised isomerisation of β -carotene. Under photostationary conditions, these authors observed only four isomers, namely, *trans*, 15-*cis*, 13-*cis* and 9-*cis*, in a ratio of 84 : 1.5 : 4 : 10.5.

According to AM1 calculations,¹³⁴ the energy barriers to isomerisation of bonds in the β -carotene radical cation (~ 20 kcal mol^{–1}) and the dication (~ 0 kcal mol^{–1}) were substantially lower than those of the neutral molecule (~ 55 kcal mol^{–1}). The calculated¹³⁴ lengths of C=C bonds in the middle part of the conjugated chain substantially differ for the neutral molecule, the radical cation and the dication: they change from 1.35 Å in the neutral molecule to 1.40 Å in the radical cation and to 1.45 Å in the dication. The latter value corresponds to the length of a single C–C bond in a carotenoid molecule.

3. *cis*–*trans* Isomerisation of C=C bonds in biradicals and neutral radicals

Due to the presence of many double bonds, carotenoids are potential reagents for the addition of ketones or aldehydes to alkenes (the Paterno–Büchi reaction) to form biradicals. Thus the formation of biradicals in the photoreaction of β -ionone with quinones was inferred from the results of CIDNP.¹²⁵ The formation of the polarised *cis*-isomer of β -ionone in the reaction with chloranil under the conditions of insufficient energy for the triplet recombination of the RIP points to the 'biradical' isomerisation route (see Scheme 2).

Isomerisation of β -ionone can occur as a result of rotation around the C(7)–C(8) bond in biradical **6**.



A similar mechanism for the *cis*–*trans* photoisomerisation of alkenes has been described earlier.^{63, 64} As was noted above, once photoexcited, β -ionone can exhibit not only electron-donating, but also electron-withdrawing properties.^{115, 125} Isomerisation of β -ionone in the photolysis in the presence of electron donors can proceed *via* either triplet β -ionone or a neutral radical, namely, the protonation product of the β -ionone radical anion. (It is known that the β -ionone radical anion undergoes fast protonation in the presence of hydrogen donors.¹¹⁶) According to results of CIDNP, the only isomerisation product of the neutral radical *trans* form is the corresponding *cis* isomer.¹¹⁵

Thus, the results accumulated to date make it possible to state that *cis-trans* isomerisation, which is the most important process in carotenoid chemistry, proceeds in the presence of electron acceptors or electron donors through the single-electron transfer stage.

VI. Inclusion complexes of carotenoids with cyclodextrins

As was mentioned above, the high reactivity, hydrophobicity and photosensitivity of carotenoids complicate their application; hence, in practice (food industry, cosmetology and medicine), their complexes with natural compounds are used. Inclusion complexes of carotenoids with cyclodextrins are studied most comprehensively. Cyclodextrins readily react with organic molecules to form inclusion complexes, which is explained by the peculiarities of their structure (the inner cavity of a cyclodextrin molecule is hydrophobic, while its outer surface is hydrophilic). Hydrophobic carotenoid molecules easily interact with the hydrophobic cavity. The complexes themselves are hydrophilic due to the hydrophilic outer surface of the cyclodextrin molecule. Numerous studies were devoted to the synthesis and properties of these complexes. In applied studies, attention was focused on the improvement of solubility of carotenoids and enhancement of their stability in aqueous solutions,^{20–22, 25, 28, 134} while the fundamental studies considered the structure of complexes,^{23, 24, 29} bioaccessibility of carotenoids at the cell level, penetration of carotenoids through cell membranes,^{26, 27} antioxidant properties of complexes²⁹ and the use of cyclodextrins as a model of a natural enzyme responsible for β -carotene cleavage.^{37, 135}

In food industry, carotenoids are used most widely as food pigments. The use of carotenoid complexes with cyclodextrins in place of free carotenoids allows one not only to obtain more stable colour of foodstuffs, but also to increase the storage life of food pigments themselves. Particularly, substitution of a cyclodextrin complex of astaxanthin for pure astaxanthin in the ration of salmon fish substantially increased the stability of salmon meat during storage.¹³⁴

Recently, the problem of provision of humans with optimum amounts of vitamins becomes more pressing. Now, it is evident that this cannot be achieved with ordinary foodstuffs. A demand for the development of foodstuffs enriched with vitamins and biologically active additives has arisen. The most promising food additives include carotenoids, *e.g.*, β -carotene. A β -carotene complex with β -cyclodextrin (in Russia, it is produced under a name 'Tsiklokar') is widely used as a bioactive additive. Recently, it has been shown that the use of other cyclodextrins, *e.g.*, α -cyclodextrin and, especially, methylated β -cyclodextrins produces a greater effect;²⁸ however, in practice, the use of β -cyclodextrin rather than its derivatives are apparently associated with its availability and low cost.

In cosmetology, carotenoids are largely used as antioxidant additives in the production of protective creams. β -Carotene is used most often. However, its addition to make-up preparations results in their strong brick-red colour; this is why cosmetologists proposed to add not carotene as such, but its complexes, *e.g.*, a cyclodextrin complex of β -carotene. Its colour is much weaker⁸ as compared with β -carotene solutions in organic solvents, and creams prepared with this additive have a nice rose colour.²²

It should be noted that the applied studies did not discuss the problem of retention of useful properties of carotenoids upon their complexation, particularly, of their antioxidant activity. Insofar as the antioxidant activity of carotenoids is associated with their ability to scavenge free radicals, it can be assumed that its complexation would affect the latter process. Indeed, the ability of cyclodextrin to conserve, in its cavity, benzyl radical formed

upon photolysis of an inclusion complex of cyclodextrin with dibenzyl ketone has been demonstrated.¹³⁶

The interaction of a water-soluble cyclodextrin complex of 8'-apo- β -caroten-8'-al with free peroxide radicals was studied.²⁹ The EPR spin-trapping method has shown that the complexation of 8'-apo- β -caroten-8'-al with β -cyclodextrin blocks almost completely the ability of this carotenoid to scavenge peroxide radicals. Apparently, this effect of cyclodextrin on the reactivity of carotenoids can be explained by the fact that the formation of complexes makes the cyclohexene ring of the carotenoid[†] inaccessible for these radicals.¹³⁷ However, the increase in the carotenoid stability in complexes should not prevent their use *in vivo*, *e.g.*, for the delivery of carotenoids directly to the cell. Insofar as carotenoid complexes with cyclodextrins are not covalently bound rigid structures, but are in equilibrium with their starting components, it can be assumed that on the surface of a cell membrane, the complex will dissociate to release a carotenoid, which will penetrate into the membrane.

The role of cyclodextrins as the carriers of drugs, for example, carotenoids, was studied *in vitro* by many scientists (*e.g.*, see Refs 26, 27 and 138). In all the cases, the positive role of cyclodextrins in the delivery of carotenoids to cells was emphasised. Thus a comparison of such properties of β -carotene complexes with methylated β -cyclodextrin as bioaccessibility, toxicity and stability with those of homogeneous solutions of β -carotene in a THF–DMSO solvent mixture has shown that the β -carotene complexes with cyclodextrin are, first, non-toxic, and, second, characterised by better bioaccessibility. For instance, after several days of incubation of cells with these complexes the level of β -carotene was substantially higher than that observed upon the use of homogeneous solutions of β -carotene.²⁷

In conclusion, we consider yet another interesting application of cyclodextrins, *viz.*, the development of new enzymes, particularly, the enzyme responsible for splitting of β -carotene in organism. Thus an attempt was undertaken to model the action of the enzyme, namely, 15,15'-dioxygenase, which consists of the cleavage of the central C(15)–C(15') bond of β -carotene to form two molecules of vitamin A.^{37, 135} The goal was to obtain an unstable β -carotene intermediate, namely, the adduct of a H_2O_2 molecule to the central double bond of the carotenoid, which would readily decompose to afford two retinal molecules under the action of the synthetic enzyme.

The implementation of this idea involved the use of the Fenton reaction (7) where Fe^{2+} ions were replaced by a metalloporphyrin molecule. The enzyme model consisted of two β -cyclodextrin molecules covalently attached to the metalloporphyrin molecule. It was assumed that both cyclohexene rings of β -carotene will be captured by cyclodextrin molecules in such a way that the metal ion of the metalloporphyrin fragment will be located near the central double bond of the carotenoid. In this case, the reaction of H_2O_2 with the metal ion would proceed in the immediate vicinity of the central double bond of the carotenoid. Presumably, it is this double bond that would undergo the attack by the hydroxyl radical formed in the Fenton reaction. However, the use of the model iron porphyrin-containing enzyme resulted in the formation of not only retinal, but also a wide set of other products, which suggests that oxygenation of different double bonds occurred.¹³⁵ At the same time, a synthetic enzyme containing ruthenium porphyrin did catalyse the cleavage of the central double bond of β -carotene.³⁷

VII. Supramolecular complexes of carotenoids with glycyrrhizin

The revealed effect of complexation on the physical properties and reactivity of inclusion compounds initiated the search for new

[§]Japanese authors also used the term 'colourless' to characterise this complex.²¹

[†]Peroxide radicals attack the terminal double bond of the cyclohexene fragment of a carotenoid.²⁹

natural complexation agents that would exhibit certain advantages over cyclodextrins and, first of all, have no limitations with respect to the size of the 'guest' molecule. These compounds should form more stable complexes, reduce the toxic effect of drugs on the organism and, at the same time, enhance their therapeutic activity. Despite the complexity of this problem, one of such compounds has been found. This is glycyrrhizic acid (another popular name is glycyrrhizin), which is isolated from liquorice root (*e.g.*, of *Glycyrrhiza uralensis* Fish).³⁸ This compound has long been used in medicine as an anti-inflammatory agent or an expectorant. It is glycyrrhizin that provides the sugary taste to liquorice root.

In contrast to cyclodextrin, the glycyrrhizin molecule has an open-chain structure and contains both hydrophilic (glucuronic acid) and hydrophobic (glycyrrhetic acid) parts. Glycyrrhizin has several important advantages over cyclodextrins. First, it belongs to open-type ligands, hence, its complexes have no rigorous restrictions for the size of the guest molecule. Second, its inclusion complexes are extraordinarily stable,^{39–41} their stability constants exceed the mean stability constant of cyclodextrin complexes by two orders of magnitude.³⁰

Glycyrrhizin is a component of many medicinal preparations. This is known to increase the therapeutic activity of drugs, which was attributed to their complexation with glycyrrhizin,^{30, 39} and to affect the reactivity of inclusion compounds.^{42, 139}

The above-mentioned aspects were studied by modern physicochemical methods by the example of carotenoid complexes^{19, 140} and two antiarrhythmic preparations, namely, Nifedipine and Lappaconitine.^{42, 139} The formation of inclusion complexes with glycyrrhizin was judged from the changes in the absorption and fluorescence spectra upon the addition of glycyrrhizin and from the changes in the reactivity of carotenoids.

1. Measurements of the stability and stoichiometry of carotenoid complexes with glycyrrhizin

The determination of stoichiometry and the measurements of stability constants of inclusion complexes formed upon mixing of carotenoids with glycyrrhizic acid were carried out using standard procedures (*e.g.*, see Refs 31, 141 and 142), *viz.*, Job's method and spectral methods, which allow determination of the stoichiometry and the stability constants of complexes, respectively, based on the dependence of the optical density of a solution on the GA concentration.

The structure, stability and reactivity of inclusion complexes of certain carotenoids with β -glycyrrhizic acid were studied.¹⁴⁰ The absorption spectra of carotenoids were shown to change with the GA concentration. The changes were observed only in aqueous solutions and their magnitude did not exceed 10%. It should be noted that the NMR method which is often used in the analysis of carotenoid complexes with cyclodextrins,¹⁴³ proved to give little information on these complexes. This is explained first of all by low solubility of carotenoids and GA in aqueous solutions and also by insufficient sensitivity of the NMR technique due to small concentrations of the components (10^{-4} – 10^{-5} mol litre⁻¹).¹⁴³

At the same time, fluorescence spectra of carotenoids complexes proved to be very sensitive to the formation of carotenoid complexes with glycyrrhizin (Fig. 5*a*). Thus studies of the dependence of the intensity of fluorescence of canthaxanthin on the glycyrrhizin concentration have shown that the stability of complexes at the GA concentration lower than 1 mmol litre⁻¹ [$K = (0.3–1.0) \times 10^4$ litre mol⁻¹, curve 1 in Fig. 5*b*] differs substantially from that at the GA concentration larger than 1 mmol litre⁻¹ ($K < 10^2$ litre mol⁻¹, curve 2 in Fig. 5*b*). Earlier, Romanko and Murinov¹⁴⁴ have observed a sharp change in the dynamic viscosity of aqueous–ethanolic solutions (5%–10% ethanol) of glycyrrhizin at the GA concentration of ~ 1 mmol

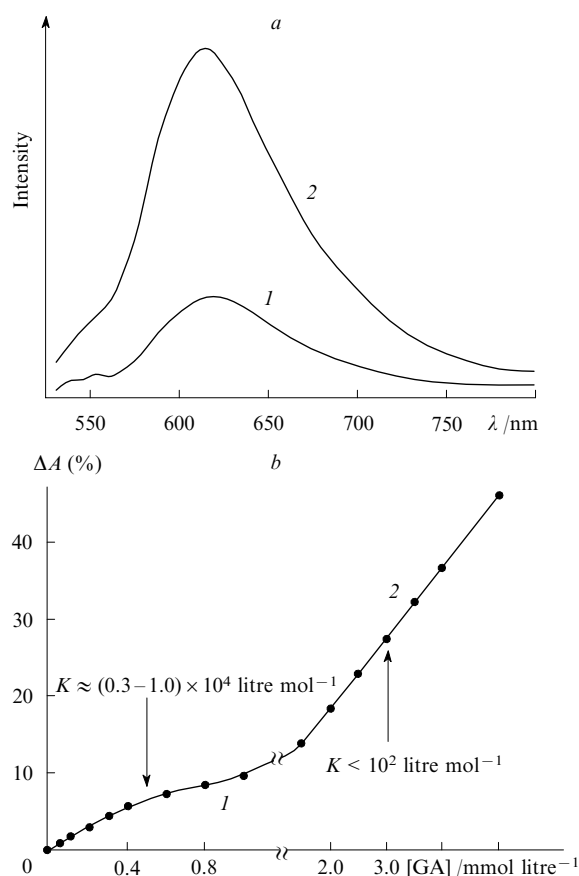


Figure 5. Fluorescence spectra of a canthaxanthin solution (0.02 mmol litre⁻¹) in the absence (curve 1) and in the presence (curve 2) of glycyrrhizic acid (5 mmol litre⁻¹) in DMSO containing 5% of water (*a*); changes in the fluorescence intensity (ΔA) of canthaxanthin as a function of the GA concentration in solution (*b*).¹⁴⁰ Excitation wavelength was 470 nm, detection wavelength was 620 nm.

litre⁻¹. It was assumed that at this concentration glycyrrhizin forms micelle-like associates in aqueous solutions.[†]

The stoichiometric ratios of components in associates were estimated based on the dependence of the changes in the optical density of the solution of carotenoid and glycyrrhizin (ΔD) on the carotenoid molar fraction $r = [\text{Car}]/([\text{Car}] + [\text{GA}])$ at a constant overall concentration of the components (Job's diagram, Fig. 6).¹⁴⁰ For example, the position of the maximum in the $\Delta D = f(r)$ curve at $r = 0.33$ corresponds to 1 : 2 ratio of carotenoid and glycyrrhizin molecules in the associate.

Earlier, it was supposed that GA molecules in aqueous solution form cylindrical dimers of the torus⁴⁰ or podand⁴¹ types. It can be assumed that the hydrophobic interaction of carotenoids with glycyrrhizin will favour the penetration of the carotenoid molecule into the cyclic dimer formed. To check this hypothesis, the thermodynamic parameters (ΔG , ΔH and ΔS) of complexation of carotenoids with glycyrrhizin were measured.¹⁴⁰ Using standard relationships

$$-\Delta G = RT \ln K,$$

[†] The hypothesis of micelle formation was confirmed later by Japanese authors¹⁴⁵ who studied the formation of micelles of water-soluble derivatives of glycyrrhizin, particularly, Na salt of GA sulfate. We failed to find the data on the micelle formation in other solvents in the literature.

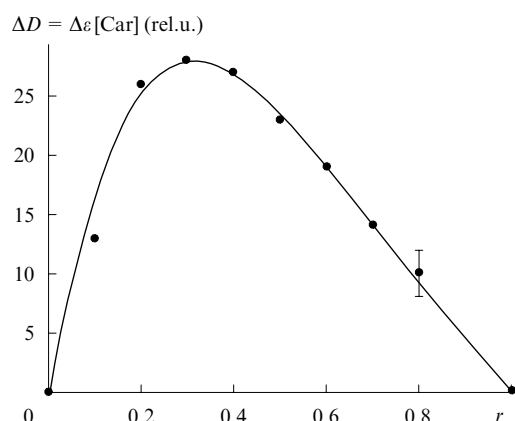


Figure 6. Job's diagram plotted based on the changes in the optical density of a solution in 20% ethanol at 433 nm as a function of the mole fraction of carotenoid (r);¹⁴⁰ ϵ is the extinction coefficient.

$$\Delta G = \Delta H - T\Delta S$$

and

$$\ln \frac{K_2}{K_1} = -\frac{\Delta H}{R} \left(\frac{1}{T_2} - \frac{1}{T_1} \right)$$

(K_1 and K_2 are the stability constants of the complex at temperatures T_1 and T_2 , respectively), the following values of parameters at $T = 293$ K were obtained: $\Delta H = 42.9$ kJ mol⁻¹, $\Delta G = -19.9$ kJ mol⁻¹ and $\Delta S = 211$ J mol⁻¹ K⁻¹. The positive values of the enthalpy and entropy terms suggest the preferential contribution of the hydrophobic interaction between the carotenoid and glycyrrhizin molecules into the stability of the complex formed and also substantial desolvation of the glycyrrhizin molecule, which is typical of inclusion complexes.

Inclusion complexes of carotenoids with GA of a composition 1 : 2 are formed both in aqueous solutions and in polar solvents such as DMSO, acetonitrile and alcohols. It is assumed that the complex represents a carotenoid molecule placed inside a torus formed by the dimer of glycyrrhizinic acid.

Stability constants of complexes were estimated based on changes in the optical density of the solution at a fixed carotenoid concentration and variable glycyrrhizin concentration (Fig. 7). If the carotenoid concentration is much lower than that of glycyrrhizin, the stability constant of their complex can be calculated based on the Benesi–Hildebrand method.¹⁴²

$$\frac{D}{\Delta D} - 1 = \frac{1}{K} \frac{1}{[\text{GA}] [\text{GA}]^n},$$

where $\Delta D = \Delta\epsilon[\text{Car}]$, K is the stability constant of the complex

$$K = \frac{[\text{Car-GA}_n]}{[\text{Car}][\text{GA}]^n}. \quad (8)$$

This allowed Polaykov *et al.*¹⁴⁰ not only to estimate the stability constant of complex (K), but also to determine the reaction order (n) of complex formation in a single experiment.



For complexes of the composition 1 : 2, a linear dependence between the absorption changes and the GA concentration was observed on the coordinates $1/\Delta D$ vs. $1/[\text{GA}]$. The analysis of Job's diagram (see Fig. 6) showed that complexation of carotenoids with glycyrrhizin is a second-order reaction. Based on this, it was concluded that the complexation involves one carotenoid molecule and one glycyrrhizinic acid dimer.

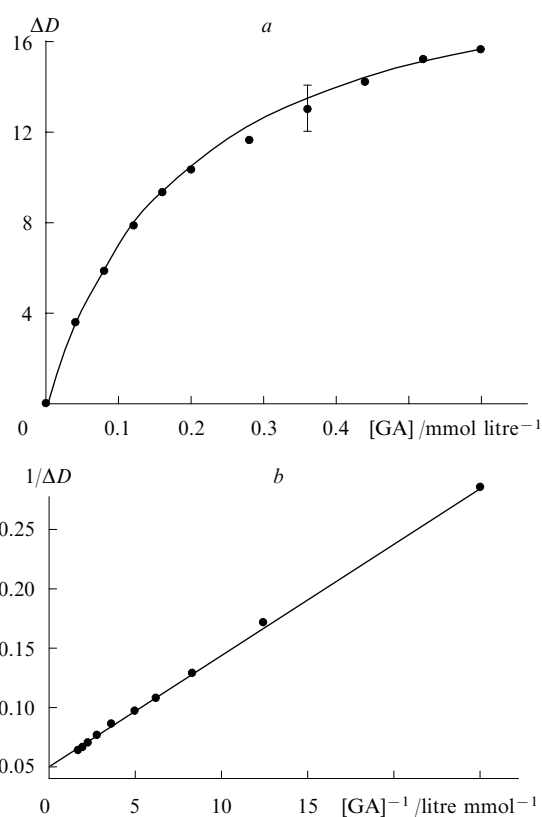
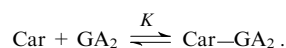


Figure 7. Changes in the optical density of a solution of β -carotene in 20% ethanol ($2.5 \mu\text{mol litre}^{-1}$) at 440 nm as a function of the concentration of glycyrrhizinic acid (a) and the Benesi–Hildebrand diagram (b).¹⁴⁰ Points correspond to experimental data, solid lines correspond to calculations for a β -carotene–GA complex with a stability constant $K = 10^4$ litre mol⁻¹.



2. Reaction of carotenoids and their complexes with FeCl₃ in polar media

The data on the effect of glycyrrhizin on the reactivity of carotenoids are of undeniable interest. As was noted above, electron transfer reactions play the key role in the chemistry of carotenoids. It was found¹⁴⁰ that electron transfer in reactions of Fe(III) salts (electron acceptors) with complexes of carotenoids with glycyrrhizin was decelerated as compared with reactions of these salts with free carotenoids and the lifetime of carotenoid radical cations in glycyrrhizin complexes in polar media increased, which resulted in the change in the ratio of reaction products. Optical methods were used for studying the reactivities of inclusion complexes of carotenoids.¹⁴⁰ The decrease in the rate of direct electron transfer from carotenoids (β -carotene and 8'-apo- β -caroten-8'-al) involved in GA complexes to Fe^{3+} was inferred from a considerable (by a factor of several dozens) decrease in the absorption of carotenoid radical cations in the presence of GA as compared with their homogeneous solutions (Fig. 8), as well as from the rate of consumption of the carotenoids during the reaction.

It is known that the second oxidation potential of β -carotene coincides with its first potential;¹⁴⁶ this is why its reaction with FeCl_3 proceeds by different mechanisms for $[\text{Car}] \geq [\text{Fe}^{3+}]$ and for $[\text{Car}] \ll [\text{Fe}^{3+}]$. In the former case, oxidation of β -carotene produces radical cation (Fig. 8a) and in the latter case, the dication (Fig. 9a). (The signal at 935 nm corresponds to the absorption of β -carotene radical cations, while the signal at 889 nm corresponds to the absorption of the dication.) When

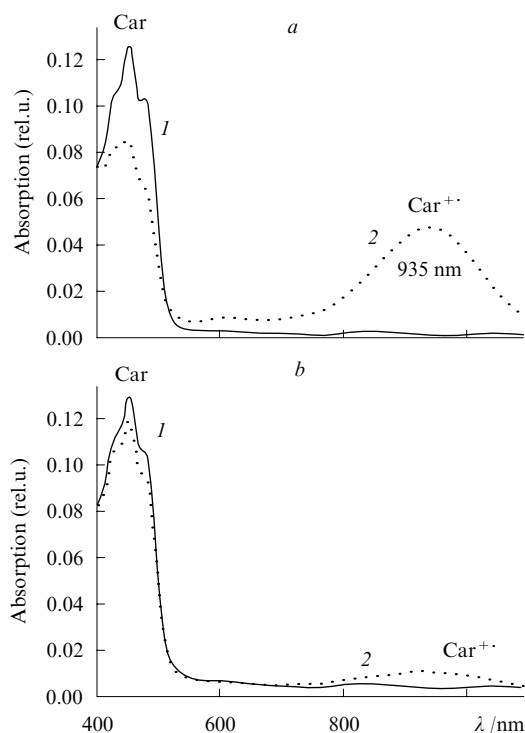


Figure 8. Absorption spectra of β -carotene recorded before (curve 1) and after (curve 2) mixing with the equivalent amount of FeCl_3 in acetonitrile at room temperature.¹⁴⁰

(a) In the absence of glycyrrhizin; (b) in the presence of $0.1 \text{ mmol litre}^{-1}$ of glycyrrhizin. $[\text{Car}] = [\text{FeCl}_3] = 1.3 \text{ }\mu\text{mol litre}^{-1}$.

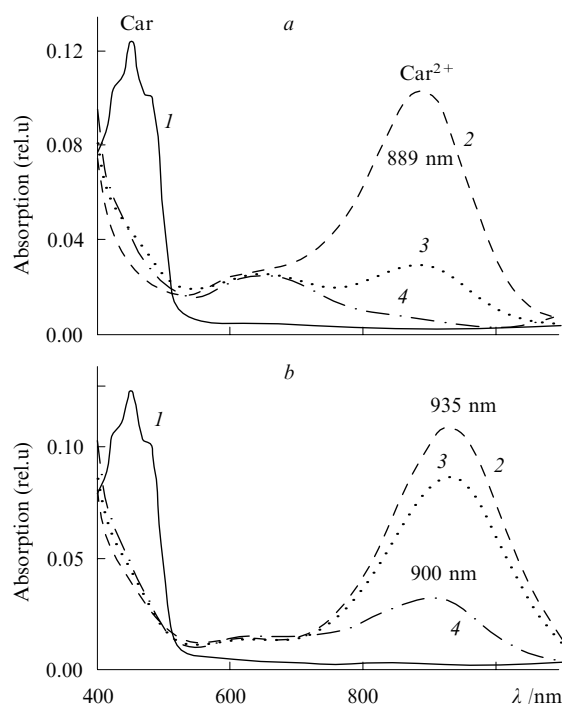


Figure 9. Absorption spectra of β -carotene recorded before (curve 1) and after (curves 2–4) mixing with an excess of FeCl_3 in acetonitrile at room temperature.¹⁴⁰

(a) In the absence of glycyrrhizin; (b) in the presence of $0.1 \text{ mmol litre}^{-1}$ of glycyrrhizin. $[\text{Car}] = 1.3 \text{ }\mu\text{mol litre}^{-1}$, $[\text{FeCl}_3] = 7 \text{ }\mu\text{mol litre}^{-1}$, (1) spectrum of β -carotene, (2) spectrum of a solution of β -carotene and FeCl_3 immediately after mixing, (3 and 4) spectra measured 6 and 20 min after the addition of FeCl_3 , respectively.

β -carotene reacted with an excess of Fe^{3+} in the presence of GA, the stabilisation of the β -carotene radical cation was observed (Fig. 9b).

Thus, the observed ¹⁴⁰ differences in the reactions of Fe^{3+} salts with carotenoids either incorporated in glycyrrhizin complexes or in the free state suggest that the changes in the reactivity of carotenoids upon the addition of glycyrrhizin are caused by the formation of complexes. The concomitant increase in the lifetime of charged forms of carotenoids (cations and dications) by a factor of dozens implies that these species do not leave the complex being stabilised inside it.

3. Reactions of carotenoids and their complexes with quinones in polar media

The reactions of carotenoids with quinones is yet another example of the effect of complexation on their reactivity. Quinones were chosen because they are important natural electron acceptors.

The system β -carotene–2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (the latter was taken because its reaction with carotenoids does not require additional photo- or thermoactivation due to its low reduction potential) was chosen as the model system for studying the reactivity of inclusion compounds.¹⁴⁰ The formation of radical cations upon the addition of the quinone to a solution of β -carotene was judged from the changes in the absorption spectrum of the latter.

A characteristic feature of this reaction is that the curves that describe the decay kinetics of β -carotene radical cations incorporated in a glycyrrhizin complex or in solution have different shapes (Fig. 10). For a free carotenoid, the radical cation signal decays exponentially (the radical lifetime is $\sim 20 \text{ s}$), whereas in the presence of glycyrrhizin, the signal decay curve demonstrates

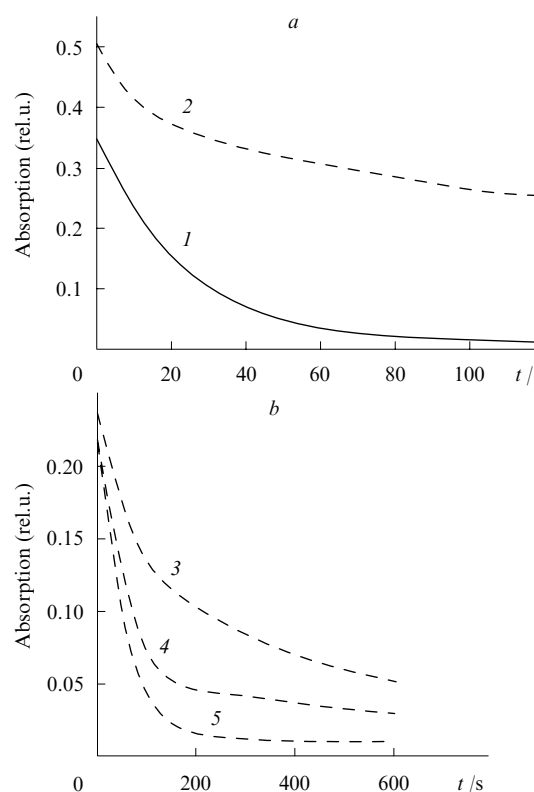


Figure 10. Decay kinetics of the absorption signal of β -carotene radical cation formed upon addition of DDQ to β -carotene in the absence (curve 1) and in the presence of different amounts of glycyrrhizin (curves 2–5).¹⁴⁰ (a) $[\text{Car}] = [\text{DDQ}] = 4 \text{ }\mu\text{mol litre}^{-1}$, (b) $[\text{Car}] = 2 \text{ }\mu\text{mol litre}^{-1}$, $[\text{DDQ}] = 5 \text{ }\mu\text{mol litre}^{-1}$; GA concentration $/\text{mmol litre}^{-1}$: 0.3 (2), 0.1 (3), 0.06 (4), 0.03 (5).

two distinct regions, which suggests the contribution of two processes, namely, a fast exponential and a slow ones (Fig. 10 b).

$$I = \frac{a}{1 + t/\tau}.$$

This two-component decay kinetics of the carotenoid radical cation made it possible to suggest that in solutions containing glycyrrhizin both the radical cations of the free carotenoid ($\tau \approx 20$ s) and the radical cations incorporated in the complex ($\tau \approx 1000$ s) are present. (Note that the contributions of these two states can be observed separately only in the absence of fast exchange between them.) The different shapes of decay curves at 935 nm for different glycyrrhizin concentrations (Fig. 10 b) point to the increase in the contribution of the slow component with the increase in the GA concentration, this contribution increasing proportionally to the square of GA concentration.¹⁴⁰ Such a square-law dependence could stem from the fact that the structure of the GA complex of the carotenoid radical cation in acetonitrile corresponds to the stoichiometry of 1 : 2. Bearing in mind that the contribution of the slow component is about 50% at the glycyrrhizin concentration of 0.1 mmol litre⁻¹, it can be concluded that for this concentration the ratio of free radical cations and their complexes is $\sim 1 : 1$. Based on expression (8), the stability constant of the carotenoid radical cation complex was estimated to be of an order of magnitude of 10⁸ litre² mol⁻².

From the aforesaid, it follows that the stabilisation of the carotenoid radical cation due to its complexation with glycyrrhizin should substantially change the yield of reaction products of carotenoids with quinones. Thus if the CTC formed in the first stage is located inside the complex, the yield of the 'in-the-cage' reaction product, *i.e.*, the adduct of the carotenoid to the quinone, is increased. Otherwise, the increase in the lifetime of the free radical cation would increase the yield of carotenoid *cis*-isomers. Analysis of the composition of reaction products of certain carotenoids (β -carotene, canthaxanthin and 7'-apo-7',7'-dicyano- β -carotene) with DDQ in the presence and in the absence of glycyrrhizin using HPLC (Ref. 140) has shown that in all cases, the yield of carotenoid-to-quinone adducts substantially increased when the reaction was carried out in the presence of glycyrrhizin.

This experiment made it possible to draw an important conclusion that glycyrrhizin forms stable associates not only with individual compounds and their ions, but also with charge-transfer complexes; moreover, the complexation can result in substantial changes in the reaction route and the ratio of products.

4. Reactions of carotenoids and their complexes with free radicals

Ultimately, let us consider how the complexation of carotenoids with glycyrrhizin affects the antioxidant activity of carotenoids. This problem has recently been studied in detail.¹⁹ The reaction rates of carotenoids with free radicals were estimated by EPR spin-trapping technique using *N-tert*-butyl- α -phenylnitron as the spin trap.

It should be noted that when dealing with traps, it is very important to correctly identify the spin adducts observed.^{19, 147, 148} Several test experiments were carried out to prove the correctness of assignment of the EPR signal observed in dimethyl sulfoxide to the adduct PBN-OOH.^{14, 19} First, it was found that the shape of the EPR spectrum changed depending on the concentration of hydrogen peroxide in solution.¹⁴ At low H₂O₂ concentrations ([H₂O₂] = [FeCl₂] = 1 mmol litre⁻¹), only the adduct PBN-CH₃ (DMSO was the origin of $\cdot$ CH₃) was formed, while at high concentrations ([H₂O₂] = 500 mmol litre⁻¹) the adduct PBN-OOH was formed and the adduct PBN-CH₃ disappeared as a result of the reaction of the $\cdot$ CH₃ radical with H₂O₂.¹⁴

The adducts of PBN with $\cdot$ OR radicals are unstable, especially in the presence of transition metals that can reduce them to $\cdot$ OR.^{147, 148} However, the majority of experimental facts that confirm this statement refer mainly to alkylperoxide radicals, whereas the adduct PBN-OOH was often observed under

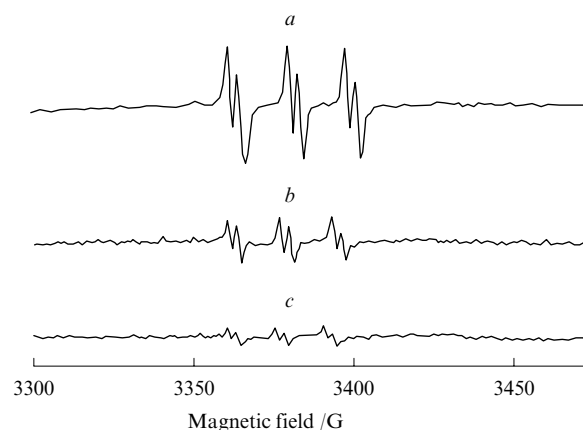


Figure 11. EPR spectra of the adduct PBN-OOH in the absence (a) and in the presence of canthaxanthin (b) and its complex with glycyrrhizin (c) in DMSO.¹⁹ [PBN] = 5 mmol litre⁻¹, [FeCl₂] = 1 mmol litre⁻¹, [H₂O₂] = 0.5 mol litre⁻¹; [Car] = [GA] = 1 mmol litre⁻¹.

normal conditions.^{149–151} The standard test for the adduct PBN-OOH is its reaction with superoxide dismutase. It was demonstrated¹⁹ that the signal of the adduct PBN-OOH completely disappeared in the presence of this enzyme, whereas no changes in the spectrum of the adduct PBN-CH₃ occurred.

Moreover, a considerable decrease in the yield of the spin adduct PBN-OOH was observed in the presence of carotenoid complexes, which followed from the EPR spectra (Fig. 11).¹⁹ Based on the experimental dependence of the yield of the spin product on the carotenoid concentration, the relative rate constant ($k_{\text{Car}}/k_{\text{ST}}$) for scavenging of the $\cdot$ OOH radical by a carotenoid was estimated according to Eqn (4). Note that one of the results of this study¹⁹ was the observation of the antioxidant activity of glycyrrhizin as such. Therefore, the ratios $k_{\text{Car}}/k_{\text{ST}}$ for different carotenoids were obtained by subtracting the contribution of glycyrrhizin to the overall rate constant for scavenging of the $\cdot$ OOH radical by a particular carotenoid (Table 1).

Table 1. Relative rate constant (k/k_{ST}) for scavenging of $\cdot$ OOH radicals by glycyrrhizic acid (GA) and GA complexes with zeaxanthin (ZX), canthaxanthin (CX) and 7'-apo-7',7'-dicyano- β -carotene (DDC).¹⁹

[GA] / mmol litre ⁻¹	k/k_{ST}^a			
	GA	CX + GA	DDC + GA	ZX + GA
0	—	2	7	4
0.5	12	59	133	4
1	12	46	116	4
2	12	6	38	4

^a Experimental error of k/k_{ST} determination is $\sim 10\%$.

Since the structures of carotenoid complexes with glycyrrhizin differ depending on whether the concentration of the latter is higher or lower than 1 mmol litre⁻¹, the rates of peroxide radical scavenging by free carotenoids and by their complexes in DMSO were compared for different concentrations of glycyrrhizin. The data listed in Table 1 show the presence of a synergistic effect, which manifests itself in the significant increase in the rate of scavenging of radicals by carotenoids [canthaxanthin (CX) and 7'-apo-7',7'-dicyano- β -carotene (DCC)] incorporated in complexes with GA. The absence of the effect for zeaxanthin (ZX) was quite unexpected. The different behaviour of these three carotenoids was explained by their different polarographic half-wave oxidation potentials $E_{1/2}$. As is shown in Fig. 2, the $k_{\text{Car}}/k_{\text{ST}}$

vs. $E_{1/2}$ dependence is hyperbolic. A segment corresponding to the rapid changes in the rate of peroxide radical scavenging by a carotenoid is located close to $E_{1/2} = 0.7$ V. The oxidation potentials of canthaxanthin ($E_{1/2} = 0.68$ V) and 7'-apo-7',7'-dicyano- β -carotene (0.72 V) fit exactly the region of 'fast changes' of scavenging rates, whereas the potential of zeaxanthin ($E_{1/2} = 0.56$ V) lies rather far in the plateau region. Bearing this in mind, the differences in the rates of radical scavenging by carotenoid complexes can be attributed to the changes in $E_{1/2}$ upon formation of the complexes. Indeed, even minor changes in the $E_{1/2}$ of CX and DCC can lead to a substantial increase in k_{Car}/k_{ST} .

To check this hypothesis, we studied the effect of complexation on the oxidation potentials of two carotenoids, namely, zeaxanthin and canthaxanthin.¹⁹ Polarographic half-wave potentials were measured in 0.1 mmol litre⁻¹ solutions of carotenoids in acetonitrile in the presence of 0.2 mmol litre⁻¹ GA at room temperature. In both cases, E was observed to increase, viz., by 0.05 V for CX and by 0.03 V for ZX. Such a change in the oxidation potential for zeaxanthin cannot cause any changes in its antioxidant activity, whereas a substantial increase in k_{Car}/k_{ST} will be observed for canthaxanthin. Yet another aspect of significance of this result is that it confirms the correctness of the earlier hypothesis on the role of electron transfer in scavenging of radical species by carotenoids.¹⁴

The results discussed above make it possible to conclude that complexation with glycyrrhizin has a substantial effect on the reactivity of carotenoids, viz., this decreases the electron transfer rate in the reaction with electron acceptors and increases the lifetime of carotenoid radical cations in complexes, which results in changes in the ratio of reaction products of carotenoids with electron acceptors. Experimental results on the rates of scavenging of peroxide radicals by different carotenoids suggest that the changes in the oxidation potentials of carotenoids in complexes are among the key factors that determine their reactivity.

VIII. Conclusion

In the present review, the following homolytic reactions of carotenoids were considered: reactions with free radicals and complexation. The choice of these processes was caused by the keen interest of scientists in the antioxidant properties of carotenoids. As was mentioned above, the antioxidant activity of carotenoids is being extensively studied. Several reviews^{14–17} on this subject have already been published; however, none of them provides the analysis of physicochemical factors responsible for this activity. Our review was intended to fill this gap.

We have demonstrated that electron transfer is typical of carotenoids not only in their transformations in photosynthetic centres or in the presence of electron donors or electron acceptors, but also in the reactions of carotenoids with free radicals and also in their *cis*–*trans* isomerisation. It can be stated that it is the tendency of carotenoids to single-electron transfer that unites the most significant biological processes involving carotenoids, from photosynthesis and photoisomerisation of retinal in visual pigment rhodopsin to their antioxidant activity.

The discussion, in this review, of carotenoid complexation processes was also associated with the studies of their antioxidant properties. At present, the development of effective pharmaceutical preparations based on inclusion complexes of natural compounds is one of the most rapidly developed fields of medicinal chemistry. However, insufficient attention is paid to the fundamental studies of the mechanism of complexation and physicochemical properties of inclusion complexes.

Particularly, the field of complexation of carotenoids with different 'host' molecules is still in its infancy. The information on the effect of complexation on the reactivity of 'guest' molecules clearly demonstrates the great prospects of this direction. In fundamental studies, these results make it possible to gain better insight into the role of weak interactions in complexation and also

into the mechanism of the effect of organised media of the reactivity of inclusion compounds, while in applied studies, a possibility appears of the purposeful choice of complexation agents for strengthening (or weakening) of one or another property of carotenoids.

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^b — *Dokl. Chem. (Engl. Transl.)*

^c — *Russ. J. Gen. Chem. (Engl. Transl.)*

^d — *Russ. J. Phys. Chem. (Engl. Transl.)*

Inorganic nanofluorides and related nanocomposites

S V Kuznetsov, V V Osiko, E A Tkatchenko, P P Fedorov

Contents

I. Introduction	1065
II. Hydrolysis of fluorides and its prevention	1066
III. Synthesis of nanoparticles	1067
IV. One-dimensional nanoobjects	1073
V. Two-dimensional nanoobjects	1073
VI. Fluoride nanocomposites	1074
VII. Nanotechnology and nanoarchitecture	1078
VIII. Conclusion	1078

Abstract. The properties and prospects of application of fluoride nanoparticles are discussed. Pyrohydrolysis is considered as the key process determining the chemistry and technology of fluorides; its role increases on going to the nanosize region. The physical and chemical methods for the synthesis of fluoride nanoparticles, one- and two-dimensional nanoobjects as well as approaches to the preparation of nanocomposites (glass ceramics, heterovalent solid solutions with defect clusters, eutectoid composites, *etc.*) are analysed. Nanotechnology techniques used to produce heterogeneous nanoobjects are outlined. The bibliography includes 238 references.

I. Introduction

In recent years, nanosized particles have attracted increasing interest due to their unique physical and chemical properties, which differ from the properties of macro- and microparticles. However, nanoparticles of inorganic fluorides have received less attention than nanoparticles of other classes of compounds such as metals, oxides and semiconductors. In particular, nanoparticles of inorganic fluorides were not mentioned in the handbook¹ and only one of 668 references in the review² refers to fluorides. Major publications on fluoride nanoparticles appeared in the last 5 years.

The synthesis and investigations of fluoride nanoparticles are of interest for the following reasons.

Laser ceramics was developed based on yttrium aluminium garnet and rare-earth oxides. The optical transmission, optical losses and spectral-generation characteristics of these ceramics are not virtually inferior to those of single crystals.^{3,4} Considerable progress in the nanoparticle preparation technology was achieved with the use of self-organisation processes of nanoparticles. The advantages of laser nanoceramics over single crystals include the

possibility of producing large objects, improved mechanical characteristics, uniform distribution and high concentrations of activating ions and the possibility of preparing a transparent optical medium where the synthesis of single crystals presents problems.

Analysis of the trends of development of modern photonics in different countries demonstrated that devices based on fluoride compounds will play a considerable role in the nearest future. This statement is supported by the following physical facts:

- transmission of fluorides in a wide spectral region (from 0.2 to 6 μm); short phonon spectra preventing the development of the adverse effect of multiphonon relaxation in electronic levels of impurity ions;

- the ease of introduction of considerable amounts of active rare-earth ions (up to concentrations of 10^{21} cm^{-3}) into fluorides;

- better mechanical properties and higher moisture resistance of fluorides compared to other classes of compounds having a wide transmission window, such as chlorides and chalcogenides;

- high thermal conductivity of fluorides.

Due to the above-mentioned advantages, fluorides, primarily as single crystals, are successfully used for the production of active and passive elements of laser systems employed in medicine, ecology and informatics, in particular, as elements of unique tunable lasers.

In the light of the above, the possibility of constructing analogous fluoride nanoceramics for photonics (lasers, scintillators, *etc.*) primarily based on alkaline-earth fluorides doped with rare-earth metals is very attractive.^{5–8}

Certain parameters of nanoparticles are improved compared to bulk crystals. The special spectroscopic properties of nanoparticles containing lanthanide ions are determined by the following circumstances:^{9–12}

- the absence of low-energy phonons and low density of phonons resulting in a radical change in the dynamics of energy transfer;

- a change in local symmetry of cations in small clusters and on the particle surface;

- small Stark splitting due to a decrease in the crystal field strength.

These features are responsible for the specific nature and prospects of development of nanophotonics. In particular, the luminescence intensity and the lifetime of the excited state for a nanocrystalline $\text{NaGdF}_4:\text{Eu}^{3+}$ powder increase with a decrease in particle size from 60 to 14 nm.¹¹ Thus, nanopowders of various

S V Kuznetsov, V V Osiko, E A Tkatchenko, P P Fedorov Laser Materials and Technologies Research Centre, A M Prokhorov General Physics Institute, Russian Academy of Sciences, ul. Vavilova 38, 119991 Moscow, Russian Federation. Fax (7-495) 135 77 44, e-mail: tez@rambler.ru (S V Kuznetsov), tel. (7-495) 135 77 44, e-mail: osiko@lst.gpi.ru (V V Osiko), e-mail: tkatchenko@ns.crys.ras.ru (E A Tkatchenko), tel. (7-499) 503 82 76, e-mail: ppf@lst.gpi.ru (P P Fedorov)

Received 19 March 2006

Uspekhi Khimii 75 (12) 1193–1211 (2006); translated by T N Safonova

fluorides doped with lanthanide ions hold promise for the production of monitor displays, optical amplifiers, lasers and phosphors.^{11, 13–15}

Sodium fluoride nanoparticles doped with uranium exhibit much higher electron emission than single crystals, due to which these nanoparticles were recommended as materials for probes for cytological, microbiological and medical studies.¹⁶

Fluoride nanoparticles, to be more precise, powders with very high specific surface area (up to $200 \text{ m}^2 \text{ g}^{-1}$ and larger) have attracted interest as materials for new types of catalysts. Due to high specific surface area, fluorides can serve as very efficient acid catalysts because coordinatively unsaturated sites of metal atoms are accumulated on the surface of such compounds.^{17, 18} Powders of fluorides AlF_3 , AlClF_2 , FeF_3 and CrF_3 with highly developed surface act as very strong Lewis acids, which are comparable in or even stronger than SbF_5 . Nanocrystalline magnesium fluoride can be used as a sorbent (support).^{17–21} The catalytic activity is particularly high if compounds are amorphous.

In some cases, the synthesis of fluoride nanoparticles is simpler, more efficient and is characterised by a higher output compared to conventional methods for the preparation of single and polycrystals (sintering or fusion of precursors at high temperature in a fluorinating atmosphere). In particular, this is true for the synthesis of complex fluorides by precipitation from solutions, which does not require complicated apparatus. The preparation of powders in the sol–gel process occurs much more rapidly than in the solid-phase synthesis, which was exemplified by BaMgF_4 and SrAlF_5 as promising nonlinear optical crystals for laser frequency conversion to the UV range.²²

Fluoride nanoparticles possess enhanced reactivity due to which the temperature of solid-phase reactions with their involvement can be lowered.

Composites containing nanocrystalline lithium fluoride and a conducting phase (carbon or metals) were patented as electrode materials for reversible lithium batteries.²³

Nanoparticles of calcium fluorophosphates favour remineralisation of tooth enamel thus preventing caries and tooth eruption and improving the quality of tooth fillings.^{24, 25} The addition of YbF_3 (as well as BaSO_4) nanoparticles to dental cements improves their mechanical characteristics.²⁶

Nanocomposites, among which are fluoride glasses and heterovalent solid solutions primarily of alkaline-earth and rare-earth fluorides, are polyfunctional materials and have wide application.

Nanotechnology enables synthesis of compounds in a highly non-equilibrium state. In particular, NaYF_4 (a high-temperature cubic modification, which is transformed into an equilibrium low-temperature modification with time)²⁷ and BaY_2F_8 (Ref. 28) were prepared as unstable crystal polymorphs. In nanotechnology, classical manifestations of the Ostwald step rule can be observed.

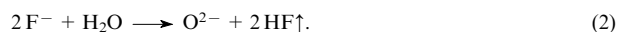
The boundary that determines the transition of a substance into the nanostate can be drawn in different ways based on different physical properties. In the present review, this concept is extended and referred to particles with size up to 100 nm; the specific surface area of spherical nanoparticles with this diameter and a density of 6 g cm^{-3} is higher than $10 \text{ m}^2 \text{ g}^{-1}$.

In addition to ensembles of nanoparticles, there are nanostructured objects with well-developed porosity and, correspondingly, with high specific surface area in which individual particles are difficult to distinguish. Amorphous fluoride catalysts belong to such objects,^{17–21} and they are also considered in the present review.

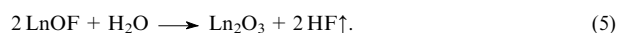
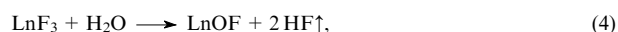
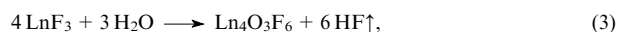
We focus our attention on procedures for the preparation of nanosized fluoride materials as powders and composites. The methods for characterisation of such materials are beyond the scope of the present review. The properties and fields of application and methods for the synthesis of one- and two-dimensional nanoobjects are briefly outlined.

II. Hydrolysis of fluorides and its prevention

Fluorides react with water with elimination of HF, which causes difficulties in the preparation of both bulk fluoride materials and nanoparticles. This process occurring at high temperature is called pyrohydrolysis.^{29–35} The first step of pyrohydrolysis involves adsorption of water molecules on the surface of fluoride particles. In the next steps, the fluoride ion is replaced by OH^- and O^{2-} anions according to the reactions



Due to the similar sizes of the fluoride ion and the hydroxyl anion, the replacement of the former by the latter occurs by a mechanism of isomorphic substitution, the single-phase state of the system being retained. Once the critical concentration is achieved, accumulation of oxygen ions in the lattice of bulk fluoride samples leads to formation of the second phase (oxide or oxofluoride). In particular, pyrohydrolysis of rare-earth trifluorides LnF_3 initially affords oxofluorides with different compositions (Ln_2OF_4 , $\text{Ln}_4\text{O}_3\text{F}_6$, LnOF , *etc.*). Oxides are the final transformation products of LnF_3



It should be noted that the replacement of the fluorine atom by the oxygen atom is thermodynamically unfavourable. Hence, fluorides are generally stable in dry air (oxygen) even on heating.

Pyrohydrolysis starts on the surface of a substance and continues in the bulk (Fig. 1a). The rate of the process depends on the diffusion coefficients of anions. In bulk samples, the oxygen diffusion rates along lattice defects (dislocations and intergrain boundaries) are substantially higher (Fig. 1b). Lattice defects can be decorated with the second oxide phase. An increase in the surface area and the passage to nanoparticles would lead to sharp acceleration of this process. The probable scheme of pyrohydrolysis of nanoparticle agglomerates is shown in Fig. 1c. Rapid and spatially complicated pyrohydrolysis processes apparently occur in the case of a fractal structure of nanoparticles.

Fluorides differ substantially in the tendency to undergo pyrohydrolysis. These compounds are characterised by such

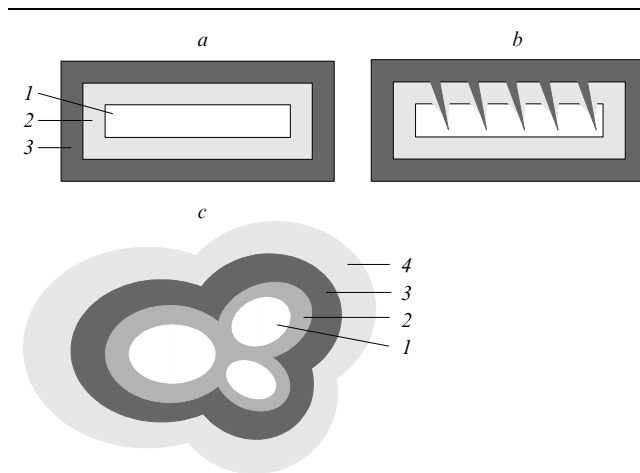


Figure 1. Scheme of pyrohydrolysis of a fluoride single crystal.

(a): (1) A single crystal, (2) an intermediate opalescent zone, (3) a non-transparent outer zone (oxide phase);³⁴ (b) the same in the presence of dislocation bundles in the crystal; (c) the same in the case of hydrolysis of a nanoparticle agglomerate: (1) fluoride, (2) hydroxofluoride, (3) oxofluoride, (4) a layer of adsorbed water.

parameters as the temperature at which hydrolysis starts or the time of completion of hydrolysis at a particular temperature, which are purely empirical. It was found³² that the stability of fluorides with respect to pyrohydrolysis decreases in the following order: $\text{NaF} > \text{SrF}_2 > \text{BaF}_2 > \text{LiF} > \text{CaF}_2 > \text{MgF}_2 > \text{LnF}_3 > \text{AlF}_3 > \text{BiF}_3 > \text{ZnF}_2 > \text{ThF}_4 > \text{UF}_4$. The time required for complete hydrolysis at 1000 °C is longer than 20 min for alkali, alkaline-earth (except for magnesium) and beryllium fluorides; the time for other fluorides is shorter than 20 min. The hydrolytic stability of LnF_3 decreases on going from light lanthanides to heavy lanthanides.^{33,35} The abnormally high pyrohydrolysis rate is observed for CeF_3 .^{33,36} According to the results of a study,³¹ fluorides can be arranged in the following series of decreasing stability to hydrolysis: $\text{BaF}_2 > \text{CaF}_2 > \text{MgF}_2 > \text{MnF}_2 > \text{PbF}_2 > \text{CdF}_2 > \text{CoF}_2 > \text{NiF}_2 > \text{ZnF}_2 > \text{FeF}_2$, $\text{CrF}_3 > \text{FeF}_3$, CuF_2 , AgF . In another study,³⁷ the following series was proposed (based on the temperature at which the reaction between a fluoride powder and a superheated water vapour starts): $\text{BaF}_2 > \text{SrF}_2 > \text{CaF}_2 > \text{MgF}_2 > \text{CdF}_2 > \text{ZnF}_2$. For strontium fluoride, this temperature is 1120 °C; for zinc fluoride, 400 °C.

Hydrolysis of some fluorides starts at room temperature. In particular, it was found³⁸ that prolonged (for several years) storage of an indium fluoride powder in air is accompanied not only by hydration but also by hydrolysis. Zirconium and hafnium fluorides behave analogously. Hydrolysis of highly hygroscopic niobium pentafluoride occurs even more readily and it is recommended to employ hydrogen fluoride liberated upon its exposure in air at room temperature for preparative purposes.³⁹

Fluorides are characterised by strong water vapour adsorption on the surface.^{40,41} An increase in the powder dispersity and passage to nanoparticles would lead to a sharp decrease in the temperature at which hydrolysis starts and an increase in the number of fluorides hydrolysable at room temperature.

Ordinary powders prepared from aqueous solutions or containing surface-adsorbed moisture are dehydrated by heating to a temperature lower than the temperature at which hydrolysis starts (for example, heating in high vacuum to 200 °C). Technological operations are also carried out in the atmosphere of anhydrous inert gas. In some cases, the use of high vacuum is insufficient to prevent pyrohydrolysis in high-temperature technological processes. An active fluorinating atmosphere (pyrolysis products of Teflon, hydrogen fluoride, tetrafluoromethane or their combinations) is used.²⁹ The efficiency of gaseous fluorinating reagents decreases in the following series: $\text{C}_2\text{F}_4 > \text{NF}_3 > \text{CF}_4 > \text{COF}_2 > \text{SF}_6$.⁴²

III. Synthesis of nanoparticles

1. Synthesis of nanoparticles by physical methods

a. Vapour phase deposition

Initial steps of the formation of thin films (formation of adatoms, critical nuclei and growth islets), including evaporation (sublimation) of a substance onto a substrate, belong to the field of nanotechnology. Nanoparticles which are formed in the vapour bulk by a mechanism of homogeneous nucleation, can be collected. Nanoparticles of PbF_2 of both cubic and orthorhombic polymorphs (21–43 nm) were synthesised by vapour condensation in ultrahigh vacuum.⁴³ Calcium fluoride nanoparticles were synthesised analogously.⁴⁴

b. Mechanical grinding

Fluoride nanoparticles can be synthesised using high-energy mills. Images of LiF particles obtained by scanning electronic and atomic force microscopy are shown in Figs. 2a,c and 2b,d, respectively. Nanoparticles of a sample ground in ethanol in an agate mortar are presented in Fig. 2a,b. An increase in the time of grinding leads to such a compact particle agglomeration that scanning electronic microscopy does not reveal details of the particle structure (Fig. 2c). However, atomic force microscopy reveals fitting of particles, each particle having an irregular shape

and, apparently, being an agglomeration product of several nanoparticles (Fig. 2d). It should be noted that there are no planar (001) faces, which are very typical of lithium fluoride micropowders due to perfect cleavage.[†]

Calcium fluoride nanoparticles with a size of 15–20 nm were prepared by grinding single crystals in an agate mortar under a layer of acetone followed by ultrasonic dispersion.⁴⁵

Nanoparticles of FeF_3 and GaF_3 were prepared^{46,47} by mechanical milling using zirconium oxide balls in a high-energy mill under argon for 16–20 h. Studies by powder X-ray diffraction, Mössbauer spectroscopy and NMR spectroscopy demonstrated that nanocrystalline grains with a size of ~15 nm held together by disordered intergrain layers were formed. The magnetic properties of FeF_3 and GaF_3 nanopowders are similar to those of amorphous phases.

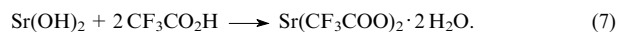
c. Laser ablation

The energy can be pumped into a substance also by laser ablation. For example, a procedure for the synthesis of nanoparticles by ablation of a sodium fluoride single crystal doped with uranium onto a molybdenum support was documented.¹⁶ The nanoparticle size was 20–30 nm.

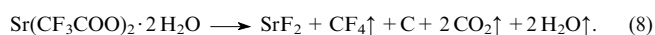
2. Synthesis of nanoparticles by chemical methods

a. Thermolysis of precursors

Salts of fluoroorganic acids, primarily, of trifluoroacetic acid can be used for the synthesis of fluorides by thermolysis. Under particular reaction conditions, highly dispersed samples with high specific surface area can be prepared. The preliminary synthesis of salts was carried out by the reactions of trifluoroacetic acid with the corresponding hydroxides or carbonates, for example, according to the reactions



Decomposition of trifluoroacetates can be accompanied by the formation of a solid carbon phase, for example, according to the reaction



Decomposition can be carried out in an inert atmosphere under dynamic vacuum, by the flux method and by chemical vapour phase deposition. Fluoroacetic acid is used as a fluorinating reagent in the sol–gel process. In this case, the synthesis of fluoroacetates is followed by their decomposition.

Decomposition of trifluoroacetates in air affords oxyfluoride phases. For example, study of pyrolysis of yttrium trifluoroacetate on a quartz glass surface in the temperature range of 400–900 °C showed⁴⁸ that the initially formed YF_3 particles are successively transformed into $\text{YO}_{0.80}\text{F}_{1.40}$ (orthorhombic system), YOF (trigonal system) and Y_2O_3 , which corresponds to pyrohydrolysis of bulk samples. Only oxofluorides were obtained⁴⁹ by decomposition of lanthanum trifluoroacetate in a SiO_2 matrix. Oxofluorides are also formed if a basic salt, for example, $\text{InOH}(\text{CF}_3\text{COO})_2$,⁵⁰ is obtained in the initial synthesis of trifluoroacetates.

Aluminium and chromium trifluoroacetates were used as precursors²¹ to give aluminium and chromium fluoride powders with specific surface area up to $50 \text{ m}^2 \text{ g}^{-1}$. Thermolysis of europium trifluoroacetate in a melt of trioctylphosphine oxide afforded⁵¹ EuF_3 nanoparticles with a size of 3–10 nm.

Alkaline-earth (barium, strontium and calcium) fluorides with highly developed specific surface were synthesised⁵² by thermolysis of trifluoroacetates of the corresponding metals in an inert

[†] P P Fedorov, S V Kuznetsov, V A Konyushkin, S V Petrov, V G Kuryavyi, V N Buznik, S V Lavrishchev, in *The XIIth National Conference on Crystal Growth (NCCG-2006) (Abstracts of Papers)* (Moscow: Institute of Crystallography of the Russian Academy of Sciences, 2006) p. 417.

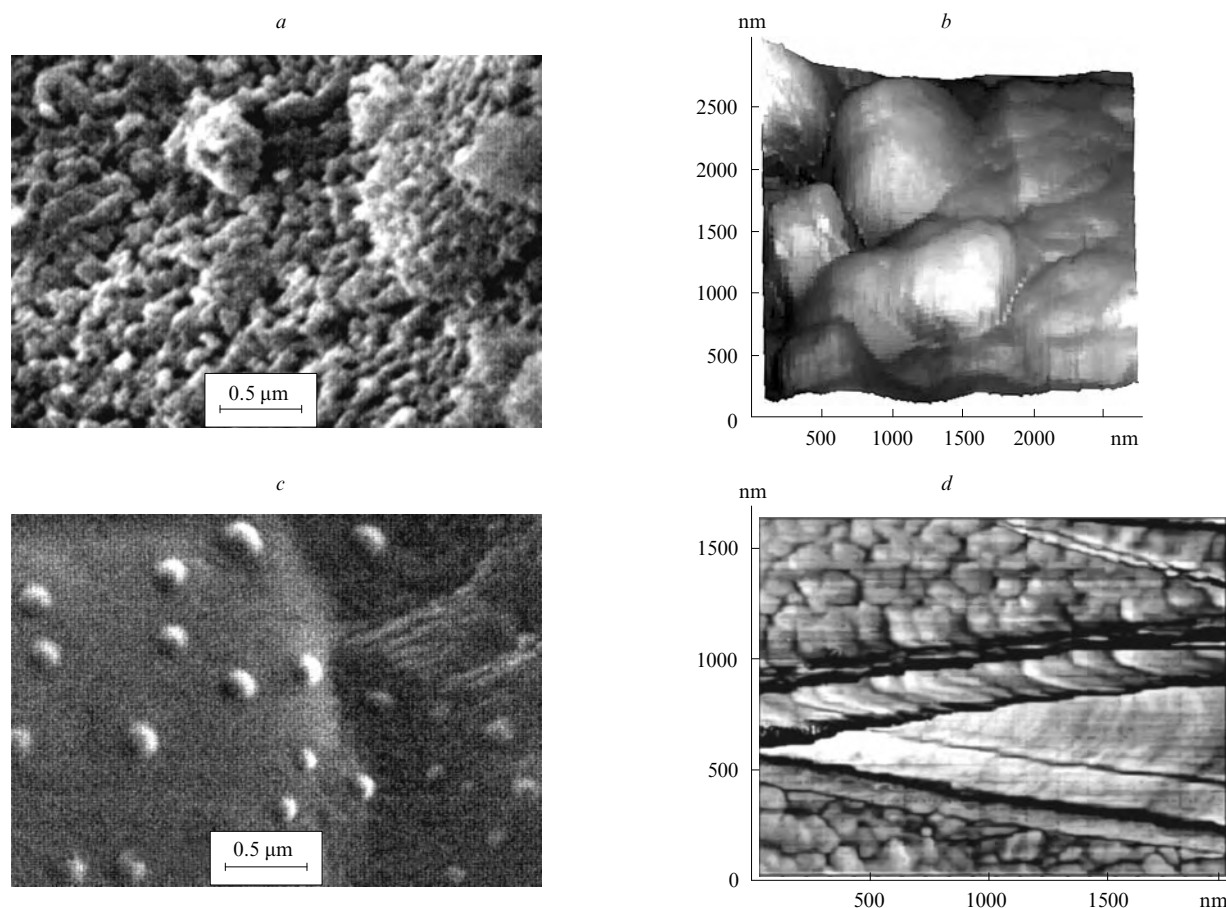


Figure 2. Photomicrographs of LiF particles after grinding of a single crystal in ethanol in an agate mortar.

(a, b) Manual grinding for 2 h (courtesy of S V Lavrishchev, the Research Centre of Fibre Optics at the A M Prokhorov General Physics Institute of the Russian Academy of Sciences); (c, d) grinding in a FRITSCH-Pulverizette 00.502 mill for 5 h (courtesy of V G Kuryavi, the Institute of Chemistry of the Far-Eastern Branch of the Russian Academy of Sciences).

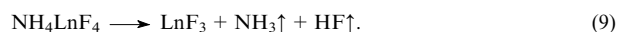
atmosphere followed by annealing under a stream of oxygen at 500 °C (to burn off carbon impurities). The specific surface areas of the resulting CaF_2 , SrF_2 and BaF_2 samples were 44, 37 and 24 $\text{m}^2 \text{g}^{-1}$, respectively. The results of studies of the SrF_2 surface by scanning electronic microscopy are presented in Fig. 3.

Fluorides can be synthesised in addition to thermolysis of trifluoroacetates by transformations of other fluoroorganic compounds. For example, four fluoroorganic compounds were studied⁵³ with the aim of preparing thin films of NaF by chemical

vapour phase deposition. The best results were obtained with the use of sodium hexafluoroisopropoxide $(\text{CF}_3)_2\text{CHONa}$. Fluoroalkoxides were used in the synthesis of fluorides by chemical vapour phase deposition.⁵⁴ Anhydrous lanthanum hexafluoroacetylacetonate served as a precursor⁵⁵ for the preparation of nanosized-thick films of LaF_3 by organometallic chemical vapour deposition. Heating of bis(trifluoromethanesulfonyl)imide, $(\text{CF}_3\text{SO}_2)_2\text{NH}$, in a SiO_2 matrix at 400 °C afforded LaF_3 .⁴⁹

Heating of a fluorine-containing gel prepared by hydrolysis of alkaline-earth and rare-earth fluoroalkoxides afforded pure fluorides, the particle size depends on the conditions of thermal treatment.⁵⁶

Different in principle precursors are documented.⁵⁷ Nanoparticles of rare-earth fluorides ($\text{Ln} = \text{Nd}, \text{Sm}, \text{Eu}, \text{Gd}$ and Tb) were synthesised by decomposition of needle-like NH_4LnF_4 particles, precipitated from methanolic solutions according to the reaction



Decomposition products retained the shape of the precursor particles.

b. Mechanochemical synthesis

In some cases, mechanical milling of a mixture of fluorides in high-energy mills is accompanied by chemical reaction producing nanoparticles.⁵⁸ In a number of publications, the formation of submicrometre-sized particles was reported. However, these particles are presumably agglomerated from smaller particles, and we include these data in the present review. Experiments^{59–62} were

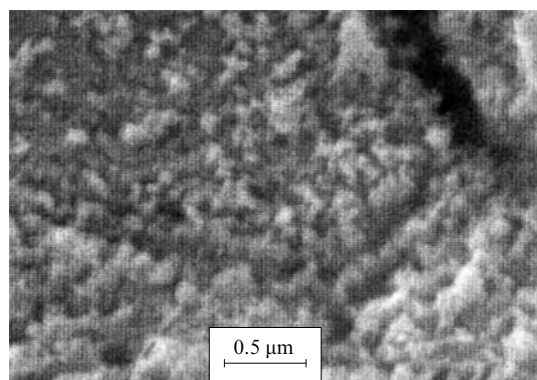


Figure 3. Electronic image of strontium fluoride after decomposition of trifluoroacetate.⁵²

The specific surface area is 37 $\text{m}^2 \text{g}^{-1}$.

performed with the use of a planetary ball mill with zirconium oxide balls 15 mm in diameter at a rotation speed of 700 rpm. Milling was carried out at room temperature.

Oxofluorides LnOF with a particle size of 15–20 nm were synthesised from a mixture of oxides and fluorides (the reaction time was 1–2 h).⁵⁹

Complex fluorides MLnF_4 (LiYF_4 , KYF_4 and NaNF_4 , where $\text{Ln} = \text{Y, Pr, Nd, Gd, Ho or Er}$) were synthesised⁵⁸ by the mechanochemical solid-phase reaction of MF and LnF_3 powders. The completeness of the reaction was determined from powder X-ray diffraction data and the amount of unconsumed MF dissolved in water. The reaction was completed in 4 h. The size of coherent scattering regions of the resulting particles estimated from line broadening in X-ray diffraction patterns was 13 nm, which is consistent with the results of scanning electron microscopy.

Cubic perovskites $\text{KM}^{\text{II}}\text{F}_3$ ($\text{M}^{\text{II}} = \text{Mg, Ca, Mn, Fe, Co, Ni}$ and Zn) were prepared by milling equimolar amounts of KF and the corresponding difluoride in a planetary mill in air.⁶¹ The synthesis was completed in 6 h. Study by scanning electron microscopy demonstrated that large agglomerates with a particle size of ~ 200 nm were obtained. The absence of the evidence of hydrolysis was unexpected taking into account high hygroscopicity of KF and the fact that transition metal fluorides are easily hydrolysed. The lattice parameters of the resulting compounds are similar to the corresponding characteristics of specimens prepared by the solid-phase synthesis. Metal–oxygen bonds were not found by X-ray photoelectron spectroscopy.

The reaction of lanthanum oxide with polytetrafluoroethylene was studied.⁶⁰ After milling for 4 h, the product consisted of oxofluoride LaOF , amorphous $\text{La}(\text{CO}_3)\text{F}$ and carbon. Heating in air to 600 °C afforded pure LaOF with a particle size of ~ 10 nm.

Nanocrystals of a non-stoichiometric fluorite phase $\text{Ca}_{1-x}\text{La}_x\text{F}_{2+x}$ were prepared by the mechanochemical synthesis from a mixture of single crystals consisting of CaF_2 with an additive of 20 (or 10) mol.% LaF_3 .⁶³ The components were ground in a planetary ball mill under argon. The reaction started after milling for 30 min. Milling for 2 h did not lead to completion of the reaction (90%–95% yield). The coherent scattering regions were 8–30 nm. After heating to 1000 °C, nanoparticles of the solid solution $\text{Ca}_{0.8}\text{La}_{0.2}\text{F}_{2.2}$ decomposed to give two fluorite phases with composition $\text{Ca}_{0.52}\text{La}_{0.48}\text{F}_{2.48}$ and $\text{Ca}_{0.94}\text{La}_{0.06}\text{F}_2$, which does not correspond to the phase diagram.

The mechanochemical synthesis of fluorine-conducting solid electrolytes ($\text{Pb}_{1-x}\text{Sn}_x\text{F}_2$ and $\text{NH}_4\text{Sn}_2\text{F}_5$) was documented.⁶⁴

Ball milling was used to introduce a small amount of a metal catalyst (iron or nickel) into magnesium hydride by the reaction with fluorides.^{65–67} The resulting substance is a promising material for hydrogen power engineering. Mixing of preground MgH_2 and FeF_3 (or NiF_2) powders followed by milling affords MgF_2 nanoparticles, which prevent hydride particle agglomeration. Both primary and secondary milling is performed in an inert atmosphere. Nanofluoride particles can also have a catalytic effect on hydrogen sorption.

c. Precipitation from solutions

Fluorides of many metals are poorly soluble in water. The synthesis of fluorides by the exchange reactions with precipitation of the product has long been known. Precipitation of rare-earth trifluorides was examined in detail.⁶⁸ Precipitation of phases formed in KF – LnF_3 systems from aqueous solutions^{69–71} and in NaF – LnF_3 systems is documented.^{69–73} Relatively recently, it has been found that nanoparticles can be synthesised according to this procedure, although the formation of, for example, colloidal solutions of $\text{NH}_4\text{Y}_3\text{F}_{10}$ and $\text{NH}_4\text{Y}_2\text{F}_7$ by the reactions of YCl_3 and NH_4HF_2 solutions was documented.⁷⁴

Compounds NaNF_4 ($\text{Ln} = \text{Y or Yb}$) doped with praseodymium ions were synthesised by mixing chloride solutions (pre-

pared by dissolution of rare-earth oxides in boiling hydrochloric acid) with stoichiometric amounts of a NaF hot solution.²⁷ The precipitate was repeatedly washed with distilled water and dried at 80 °C. The initially formed high-temperature cubic modification passed completely into the hexagonal modification ($a = 5.969$, $c = 3.53$ Å) after ageing of the precipitate for 10 days. The average grain size of these phases was ~ 900 nm.

This procedure was subject to modifications.^{11, 14, 28, 75} Spherical $\text{NaGdF}_4:\text{Eu}^{3+}$ nanoparticles of a size of 20 nm (data from transmission electron microscopy) were prepared by precipitation. Storage of the powder at 650 °C under a stream of $\text{Ar} + 10\% \text{SF}_6$ led to an increase in the particle size to 50–350 nm. No oxygen impurities were revealed by IR spectroscopy and Eu^{3+} ion spectroscopy.^{11, 75} $\text{KGdF}_4:\text{Eu}^{3+}$ nanoparticles were synthesised analogously;¹⁴ the size of coherent scattering regions of the particles was 19 nm. A metastable cubic modification was precipitated. Heating led to a complex change of structural types, and the KErF_4 -type hexagonal modification was obtained for the first time.⁷⁶ The presence of the hydroxyl ion was revealed by IR spectroscopy. The non-equilibrium polymorph $\text{BaY}_2\text{F}_8:\text{Eu}^{3+}$ (as a nanopowder) with a fluorite-type structure and the lattice parameter $a = 5.767$ Å was synthesised analogously.²⁸ This lattice parameter is substantially smaller than that of any equilibrium composition of the solid solution $\text{Ba}_{1-x}.\text{Y}_x\text{F}_{2+x}$ in the BaF_2 – YF_3 system.⁷⁷ Upon heating in a stream of $\text{Ar} + 10\% \text{SF}_6$, the sample undergoes a phase transition to the equilibrium monoclinic structure BaY_2F_8 .

In an analogous solution precipitation method,⁷⁸ aqueous solutions of $\text{Eu}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ and NaF served as the starting compounds. The reaction product that formed upon mixing of these two solutions was washed with water and ethanol and dried at 70 °C for 3 hours. Nanorods of the hexagonal phase NaEuF_4 with a diameter of 20–30 nm and a length of 60–100 nm were obtained. An increase in the $\text{Eu}^{3+}:\text{NaF}$ ratio from 1:4 to 1:10 led to the formation of a phase with a cubic fluorite-type structure (spheres ~ 200 nm in diameter) and the lattice parameter of 5.61 Å. Based on the phase diagram presented by Thoma *et al.*,⁷⁹ the composition $\text{Na}_5\text{Eu}_9\text{F}_{32}$ was assigned to this phase. In reality, the compound with this formula does not exist.⁷⁶ Based on the dependences of the lattice parameter of fluorite phases of variable composition in NaF – LnF_3 systems,⁸⁰ it can be concluded that nanoparticles have the composition $\text{Na}_{0.38}\text{Eu}_{0.62}\text{F}_{2.24}$. Chemical analysis is required to solve the problem.

Canadian researchers studied in detail precipitation of nano-sized fluorides LaF_3 , $\text{LaF}_3:\text{Eu}$ and $\text{La}_{0.45}\text{Yb}_{0.5}\text{Er}_{0.05}\text{F}_3$ and modifications of their surfaces.^{12, 13, 81–83} A solution of rare-earth nitrates was mixed with a solution of sodium fluoride to yield $\text{LaF}_3:5\% \text{LnF}_3$ nanoparticles and then fluorides were precipitated by adding ethanol. The particles were separated by centrifugation, washed with ethanol and dried *in vacuo*. The average particle size was ~ 20 nm.¹³

The $\text{KY}_{2+x}\text{F}_{7+3x}$ phase with variable composition ($0.5 < x < 1$) with a fluorite-type structure and a particle size of 17 nm was synthesised by mixing concentrated KF and $\text{Y}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ solutions followed by stirring for 30 min, centrifugation and washing with deionised water.⁸⁴ Heating to 550–850 °C leads to ordering of the crystal lattice and the appearance of lines belonging to a superstructure in X-ray diffraction patterns.

Very important results on the morphology evolution of LaF_3 nanoparticles during its precipitation from $\text{La}(\text{NO}_3)_3$ and KF solutions (including the reaction at constant pH) were obtained.^{85, 86} Successive transformations of amorphous hydroxyfluoride into crystalline LaF_3 nanoparticles of hexagonal shape, empty spheres with a diameter of several hundred nanometres consisting of agglomerates formed by small particles and the transformation of spheres into needles and ribbons were observed.

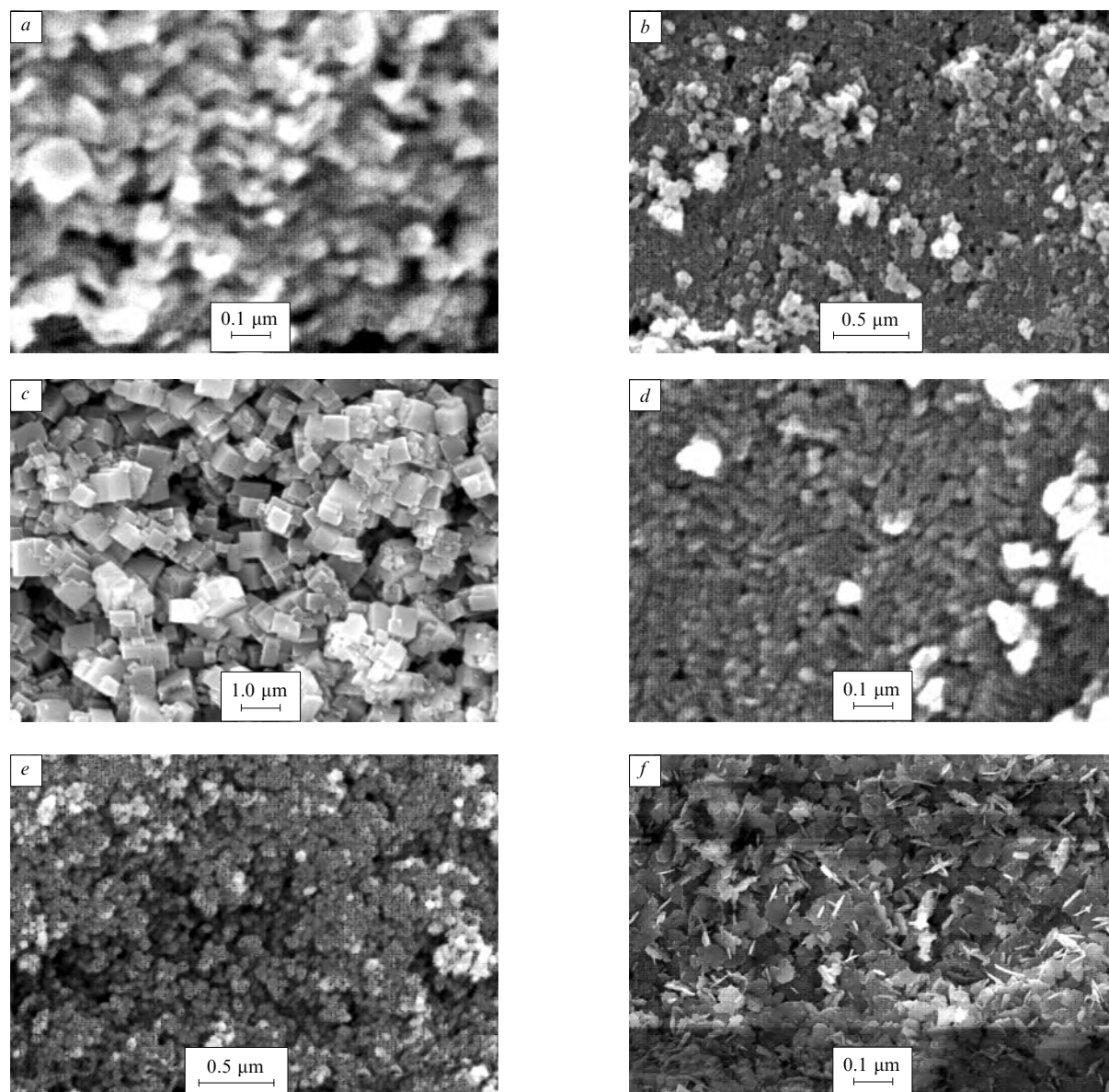


Figure 4. Electronic images of fluorides prepared by precipitation from aqueous nitrate solutions.

(a) $\text{Ca}_{0.9}\text{Er}_{0.1}\text{F}_{2.1}$ after precipitation by titration into hydrofluoric acid; (b) $\text{Ca}_{0.9}\text{Er}_{0.1}\text{F}_{2.1}$ after washing with ethanol; (c) $\text{Ca}_{0.9}\text{Er}_{0.1}\text{F}_{2.1}$ after drying at 150 °C; (d) $\text{Ca}_{1-x}\text{Yb}_x\text{F}_{2+x}$ after precipitation by titration with hydrofluoric acid; (e) $\text{Sr}_{1-x}\text{Nd}_x\text{F}_{2+x}$ after precipitation by titration with hydrofluoric acid, washing and prolonged drying at ≤ 100 °C; (f) BaF_2 after precipitation by titration with an ammonium fluoride solution.

Selected photomicrographs of fluoride particles, which we have synthesised[‡] by precipitation from aqueous solutions, are shown in Fig. 4.

Stabilisation of colloidal solutions of fluoride nanoparticles presents a special problem. The preparation of colloidal solutions of NaYF_4 (the particle size was 5–30 nm) was documented.⁸⁷ A procedure was developed¹³ for dispersion of colloidal LaF_3 nanoparticles in solution with the use of citrate ligands adsorbed on the surface of nanoparticles.⁸

Crystallisation of nanoparticles from solutions can be performed under conditions of hydrothermal synthesis. This is used

for the synthesis of many complex fluorides, for example, of NaYF_4 ;⁸⁸ $\text{NH}_4\text{Er}_3\text{F}_{10}$;⁸⁹ KMF_3 ($\text{M} = \text{Mn}, \text{Co}, \text{Ni}, \text{Zn}$ or Mg);⁹⁰ K_2LnF_5 , KLnF_4 , KLn_2F_7 , $\text{KLn}_3\text{F}_{10}$;^{91–93} LiYF_4 , KYF_4 and BaBeF_4 .⁹⁴ The particle size increases as the temperature of the synthesis and the reaction time are increased.

In some case, fluorides precipitated from solutions were subjected to additional mild (at a temperature lower than 180 °C) hydrothermal treatment. Nanocrystalline fluorides of La, Pr, Nd, Sm and Y were synthesised^{95,96} from the oxides Ln_2O_3 ($\text{Ln} = \text{Y}, \text{La}, \text{Pr}, \text{Nd}$ or Sm) dissolved in 10% nitric acid. A NH_4F solution was added to the nitrate solutions to obtain colloidal precipitates and a 10% KOH (or NaOH) solution was added to pH 4–5. Colloidal precipitates were stored in an autoclave at 80–180 °C for 12–24 h. The precipitates were filtered off, washed and dried in air at 80 °C. The resulting fullerene-like nanoparticles had a shape of empty spheres, their diameter increased from 10 to 30–50 nm as the temperature in the autoclave was increased from 120 to 180 °C.

[‡] S V Kuznetsov, T T Basiev, V V Voronov, S V Lavrishchev, V V Osiko, E A Tkatchenko, P P Fedorov, I V Yarotskaya, in *Proceedings of the Second International Siberian Seminar INTERSIBFLUORINE-2006* (Tomsk: Institute of Inorganic Chemistry, 2006) p. 135.

[§] See also F Wang, Y Zhang, X Fan, M Wang *J. Mater. Chem.* **16** 1031 (2006).

$\text{LaF}_3 : \text{Yb}^{3+}, \text{Er}^{3+}$ nanoparticles were prepared by the hydrothermal synthesis.⁹⁷

Nanoparticles can also be formed upon sonication (sonochemistry). The addition of an NaF alkaline solution to an acidic solution of rare-earth nitrates with intense sonication followed by hydrothermal treatment led to the formation of $\text{YF}_3 : \text{Ln}^{3+}$ nanoparticles.⁹⁸

The hydrothermal synthesis of nanoparticles of rare-earth oxofluorides was patented.^{99, 100}

Non-aqueous solvents can be used for the synthesis of fluorides to decrease the degree of hydration and remove hydroxyl impurities. Needle-like NH_4LnF_4 particles ($\text{Ln} = \text{Nd}, \text{Sm}, \text{Eu}, \text{Gd}$ or Tb) with nanometre cross-section were prepared from methanolic solutions.⁵⁷ Nanorods with composition $\text{PbBr}_{2-x}\text{F}_{2(1-x)}$ ($x = 0.15, 0.3$) were prepared from methanolic solutions of lead acetate, potassium fluoride and cetyltrimethylammonium bromide or potassium bromide.¹⁰¹

Particles with composition KNiF_3 as empty spheres with a diameter of 200–400 nm were synthesised by the solvothermal reaction in ethanol at 110 °C with the use of KF and NiCl_2 as the starting reagents. According to the results of transmission electron microscopy, these spheres consist of nanoparticles with the size of 10 nm (the wall thickness was 20–40 nm).¹⁰²

Nanoparticles of CeF_3 with the size of 5–10 nm were synthesised from a solution of CeCl_3 and HF in ethylene glycol at 180 °C.¹⁰³ The nanoparticles were washed with ethanol, separated from the liquid phase by centrifugation and dried.

Synthesis from solution of metal acetates and alkoxides in non-aqueous solvents (isopropyl alcohol or methanol) by treatment with anhydrous hydrogen fluoride provides the basis for one of modifications of the sol–gel process (see below).

d. Precipitation from solutions in nanoreactors

The use of the so-called nanoreactors enables one to limit mechanically the sizes of the resulting particles. Solid porous templates, such as zeolites, gels or opals, can serve as nanoreactors.⁴⁹ Optical transmission of products is essential for their use in photonics.

Silica gel was also used.^{49, 104} Borosilicate glasses with the pore size of 4 nm pressed into pellets and Al_2O_3 ceramics with the pore size of up to 0.1 μm served as porous templates.¹⁰⁵ Porous membranes were placed between aqueous solutions of $\text{Pb}(\text{NO}_3)_2$ and NH_4F with concentrations of 0.1 mol litre⁻¹. The reaction produced PbF_2 nanoparticles in pores, both the equilibrium orthorhombic modification and the high-temperature cubic modification being obtained.

The reversed microemulsion method has gained wide acceptance in the synthesis of fluoride nanoparticles. This method has been developed in detail for other classes of compounds. The history of the problem was covered in the review.² Back in 1943, it was found^{106, 107} that certain ratios of water, an organic phase and two surfactants give quasihomogeneous mixtures called quaternary microemulsions. Long-chain organic molecules containing a hydrophilic head and a lipophilic tail (for example, cetyltrimethylammonium bromide, CTAB) are miscible with both hydrocarbons and water (Fig. 5a). Due to ion-dipole interactions, surfactants form spherical aggregates encapsulating water, the polar (ionic) ends of surfactant molecules being oriented inward (Fig. 5b). The orientation of molecules in microemulsions leads to minimisation of the surface tension thus providing stability, including thermodynamic stability, as opposed to usual macroemulsions. Such emulsions are called reversed emulsions because water in such emulsions is dispersed in an organic matrix.

It was suggested that quaternary reversed microemulsions were used for the preparation of colloidal non-charged particles.¹⁰⁸ The method consists of preparing two solutions of emulsions with required anions and cations, respectively, followed by mixing of these solutions to prepare the target compound (Fig. 5c–e). Emulsions with different volumes of an aqueous

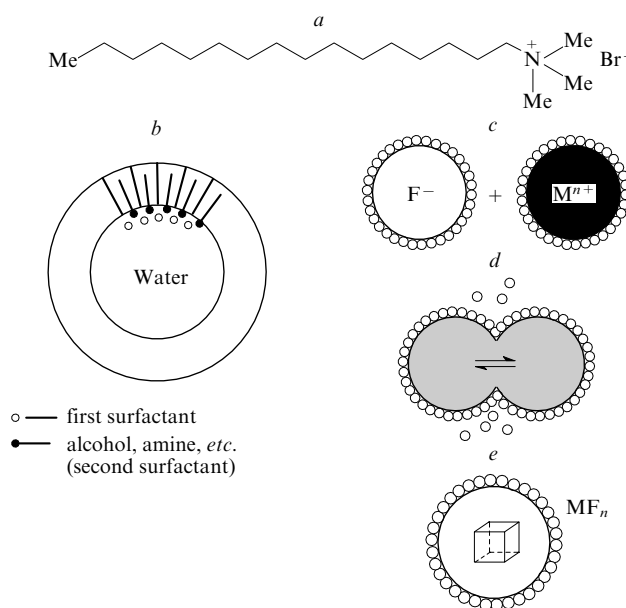
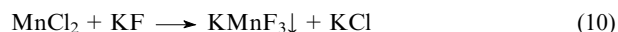


Figure 5. The CTAB molecule (a) and schemes of the structure of a microemulsion (b) and the synthesis of nanofluorides MF_n by the reverse a microemulsion method (c–e).

phase (a nanoreactor) can be prepared by varying the ratio of the aqueous and organic phases and the amount of a surfactant, which allows one to obtain nanoparticles of the desired size. The resulting particles are subjected to either coagulation (for example, by adding acetone) or centrifugation until a precipitate is formed, and the precipitate is washed, for example, with methanol. A classical microemulsion quaternary system has the following composition: n-butanol/CTAB, n-octanol/water. This approach is applicable to compounds poorly soluble in water ($\sim 10^{-5}$ mol litre⁻¹) and is used for the synthesis of fluoride nanoparticles. In some cases, ternary microemulsions, in which the second surfactant is absent, are used instead of quaternary microemulsions.

The synthesis of NH_4MnF_3 nanoparticles with sizes of 10–60 nm with the use of n-heptane/ NH_4AOT /water microemulsions [AOT is bis(2-ethylhexyl)sulfosuccinic acid] and concentrated aqueous NH_4F and $\text{Mn}(\text{OAc})_2$ solutions was documented.¹⁰⁹ An increase in the reaction time, a decrease in the salt concentration, an increase in the percentage of the aqueous phase and increase in temperature lead to enlargement of crystallites.

Fluoromanganates (KMnF_3 and NaMnF_3) exhibiting magnetic properties were synthesised¹¹⁰ according to the reaction



with the use of the following microemulsion system: n-octane/CTAB, n-butanol/water. The particle size depends on the volume of nanoreactors. Particles of the same compounds with the size of 30 nm were synthesised by Carpenter¹¹¹ with the use of an emulsion system containing dioctyl sulfosuccinate, isooctane and water.

The synthesis of BaF_2 nanoparticles containing up to 65 mol.% NdF_3 was documented.¹¹² Emulsion systems consisted of cyclohexane, Igepal CO-520, ethanol and aqueous solutions of salts of the target cations and hydrofluoric acid. An increase in the concentration of the precursor leads to an increase in the size of the resulting crystallites. Powder X-ray diffraction study demonstrated that nanoparticles are heterogeneous and consisted virtually of pure BaF_2 and solid solutions $\text{Ba}_{1-x}\text{Nd}_x\text{F}_{2+x}$ with different concentrations. It was hypothesised that BaF_2 is repeat-

edly precipitated on the surface of nanoparticles enriched in neodymium. The resulting samples were tested for the presence of impurities. An IR spectroscopic study demonstrated that up to 3 mass %–5 mass % of precursor ions, as well as hydroxyl groups, are present in samples prepared starting from nitrate and acetate salts. If precursors are readily soluble salts, the amount of impurities in samples is smaller.

The synthesis of BaF_2 nanoparticles and a solid solution $\text{Ba}_{1-x}\text{Ce}_x\text{F}_{2+x}$ ($x = 0.033$) with the use of an octan-2-ol/CTAB/water microemulsion system was documented.¹¹³ It was found that the particle size decreases as the fraction of water in the system and the reaction time decrease. After washing of nanoparticles with ethanol, the final product contained traces of nitrate ions and hydroxyl groups (IR spectroscopic data).

The synthesis of CeF_3 nanoparticles from a polyisobutane–butanediimide/cyclohexane/water emulsion system was performed.¹¹⁴ An increase in the percentage of water and the precursor concentration strongly influences the size and morphology of the resulting particles. The crystal structure was described as cubic face-centred, which does not correspond to the structure of bulk samples of CeF_3 .

Nanoparticles of CeF_3 and the solid solution $\text{Ce}_{1-x}\text{Lu}_x\text{F}_3$ ($x \leq 0.5$) were synthesised by the microemulsion method.¹¹⁵ The hexagonal structure typical of CeF_3 was found for all samples. The maximum luminescence intensity at ~ 325 nm is observed for $x = 0.3$.

An n-octane/CTAB, n-butanol/water microemulsion system was used in the synthesis of BaF_2 nanoparticles, including those activated with 6 mol.% europium and erbium.^{116–118} It was found that only cubic nanoparticles grow until the critical size of the growing nanoparticle is smaller than the volume of the elementary reaction zone. As soon as the size becomes larger than this volume, the growth of dendrites begins. The edge lengths of cubic particles without dendrites were 100–200 nm. In the presence of dendrites (data from transmission electron microscopy), the aggregate size was 400–450 nm. Self-organisation of BaF_2 nanoparticles, which were synthesised by the reversed microemulsion method, giving rise apparently to dissipative structures was described.¹¹⁹

The use of microemulsions in the synthesis of particles of solid solutions of the general formula $\text{K}(\text{Y},\text{Ln})_{2+x}\text{F}_{7+3x}$ ($0.5 < x < 1$) with a size of 14 nm was documented.⁸⁴

e. Variations of the sol–gel method

Crystallisation techniques used for the synthesis of bulk crystals in gels^{120,121} make it possible to decrease substantially the rate of chemical reactions due to an increase in the path length of the ion counter diffusion resulting in the formation of a new poorly soluble phase. This situation is ideal for the preparation of nanoparticles characterised by a low degree of agglomeration and investigation of the mechanism of their crystallisation. However, the output of this process is low, and other modifications of the sol–gel technology were used for the synthesis of fluoride nanoparticles.

According to one version, a porous homogeneous hydroxyl sol–gel is prepared and subjected to low-temperature treatment with a fluorinating agent giving rise to a highly dispersed amorphous powder, which becomes more compact on heating. This approach was developed for the synthesis of fluoride glasses.^{39,122,123} A sol of nanocrystalline MgF_2 was synthesised by the reaction of hydrofluoric acid with the sol prepared from a methanolic solution of H_2O_2 and $\text{Mg}(\text{OMe})_2$.¹²⁴

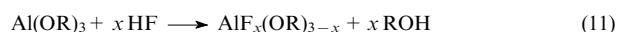
In another version, a fluorinating agent (generally, trifluoroacetic acid) is directly used as one of the starting compounds along with metal acetates and alkoxides for the preparation of gels.^{22,27,125–127}

BaMgF_4 doped with Eu^{2+} was synthesised from a solution of a mixture of barium, magnesium and europium acetates in isopropyl alcohol.¹²⁸ Trifluoroacetic acid and water were added to the solution to give a trifluoroacetate gel; its heating to 500 °C led to crystallisation of BaF_2 from the amorphous state (data from powder X-ray diffraction). At 550–600 °C, BaMgF_4 particles appeared.

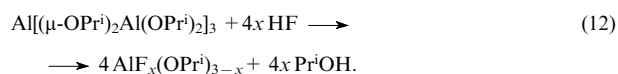
An attempt was made to synthesise analogously KGd_2F_7 .¹²⁹ Gadolinium and potassium acetates were dissolved in a stoichiometric ratio in isopropyl alcohol under argon in a Teflon reactor. Trifluoroacetic acid was added to the solution and the mixture was stirred for 3 h. Then a quartz substrate was coated with this solution and heated at 650 °C for 40 min under a stream of dry argon. The resulting product consisted of submicrometre-sized particles and contained oxygen as an admixture. Its composition corresponds to the formula $\text{K}_{0.31}\text{Gd}_{0.69}\text{F}_{1.84}\text{O}_{0.27}$. The monoclinic lattice parameters are similar to the lattice parameters of anhydrous KGd_2F_7 .

In the third version of the sol–gel method, a silicate gel containing fluoride nanoparticles is prepared. Mixing of a silicate sol and a MgF_2 sol affords nanoparticles dispersed in an amorphous matrix. Heating results in a composite MgF_2 – SiO_2 .¹²⁴ An improved modification of this process was patented.¹³⁰ Nanocrystals of LaF_3 (10–30 nm) in a silicate gel were synthesised by the sol–gel method starting from trifluoroacetic acid, lanthanum acetate, tetramethyl orthosilicate, methanol and dimethylformamide followed by heating of the gel to 300 °C. At 800 °C, pyrohydrolysis of LaF_3 started.¹⁰⁴ Glass ceramics can be prepared analogously.¹³¹ For example, nanocrystallites of LaF_3 in transparent SiO_2 -based glass ceramics were synthesised by the sol–gel method.¹³²

A special modification of the sol–gel process was developed^{17,18,20,133,134} with the aim of synthesising fluoride catalysts with highly developed surface. In the first step, solutions of metal alkoxides in a non-aqueous solvent (for example, aluminium isopropoxide in isopropyl alcohol) are treated with anhydrous hydrogen fluoride to yield an amorphous catalytically inactive solid as a precursor of the fluoride. The F:Al ratio in this precursor of AlF_3 was approximately equal to 2:1, the carbon content was 31%, and the specific surface area was 430 m² g^{−1} (Ref. 17). In the general form, the reaction equation is as follows:



($x = 0–3$); for aluminium isopropoxide existing as a tetramer, the equation is as follows:



Treatment of the products with a fluorinating reagent (CCl_2F_2) at 350 °C affords an amorphous AlF_3 powder with a specific surface area of 206 m² g^{−1} and the carbon content of 0.4 mass%, which is characterised by very high catalytic activity. Heating leads to crystallisation accompanied by an exothermic effect at 540–570 °C, which corresponds to the formation of $\alpha\text{-AlF}_3$.

Magnesium fluoride with a specific surface area of 190 m² g^{−1} and mixed catalytically active fluorides with highly developed surface [$\text{MgF}_2\text{:FeF}_3$ (Ref. 18) and $\text{MgF}_2\text{:CrF}_3$ (Ref. 20)], in which magnesium fluoride serves as a sorbent (support), were synthesised analogously. The scheme of the process is shown in Fig. 6. It was hypothesised that the true sol–gel process occurs to give a three-dimensional random network analogous to networks of classical gels (in particular, of a silicate gel). Random binding of fluoroaluminate octahedra postulated in the fluoride gel corresponds to the network in fluoroaluminate glasses.

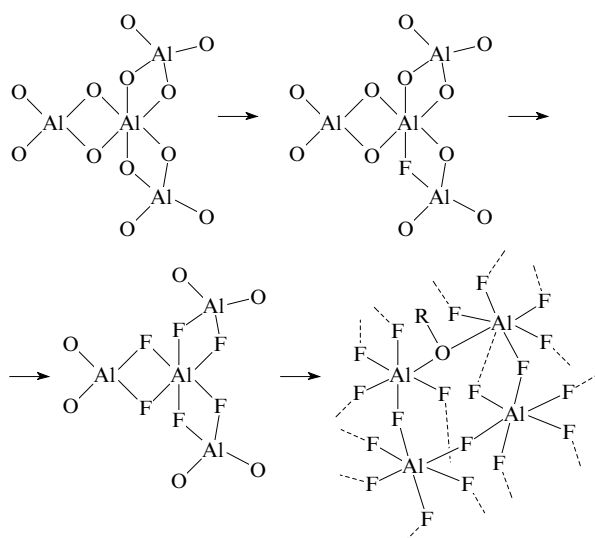


Figure 6. Scheme of the formation of a random network in different steps of the sol-gel process with the successive replacement of oxygen atoms by fluorine in bridging bonds.¹³⁴

f. Miscellaneous methods of synthesis

Nanoparticles of potassium, barium and strontium fluorides and sodium chloride were prepared⁶ by the flame synthesis. The corresponding precursor (metal 2-ethylhexanoate) was mixed with a stoichiometric amount of fluoro- or chlorobenzene, and the mixture was nebulised in a methane-oxygen flame. The resulting product was collected on a heated filter to prevent water condensation. The particle size of CaF_2 was 20 nm.

UF_5 nanoparticles were synthesised by laser photolysis of gaseous UF_6 in a supersonic nozzle reactor for isotope separation.^{135–137}

A study¹³⁸ on the synthesis of single-crystalline PbF_2 nanoparticles by selective chemical dissolution of bulk nanocomposite oxyfluoride glass ceramics is of interest. Impurity-free lead fluoride nanoparticles with the size of 15 nm doped with Eu^{3+} ions show intense fluorescence (green and blue) after IR excitation.

Fluoride nanoparticles can be prepared by gas-phase fluorination of dispersed systems.

IV. One-dimensional nanoobjects

Unique physical properties of one-dimensional (or 1D) nanoobjects and the possibility of producing functional materials based on these nanoobjects have attracted considerable attention.

Whisker crystals characterised by exceptional mechanical properties are typical 1D objects.^{139,140} The main mechanism for their growth is the so-called vapour-liquid-crystal mechanism according to which growth occurs from the vapour phase through a melt drop. The diameter of whisker crystals is determined by the size of the starting drop and is generally of a micrometre size. A decrease in the drop diameter leads to a decrease in the growth rate (due to a change in the vapour pressure over the drop). Nevertheless, it is possible to grow such thin whiskers. Whisker crystals were prepared from the vapour phase for such fluorides as LiF , NaF (Refs 121 and 139) (Fig. 7) and CdF_2 .¹⁴¹

Another procedure for the preparation of 1D nanoobjects is based on crystallisation from solution.¹³⁹ Nanorods of the hexagonal phase NaEuF_4 20–30 nm in diameter and 60–100 nm in length were prepared from aqueous solutions of europium nitrate and sodium fluoride.⁷⁸ Whisker crystals of BaF_2 oriented along the [111] direction with a length of 50 μm and a size ratio of 1000 : 1 were synthesised by the hydrothermal method with the use of a microemulsion.¹⁴² The crystal thickness was determined by the drop size.

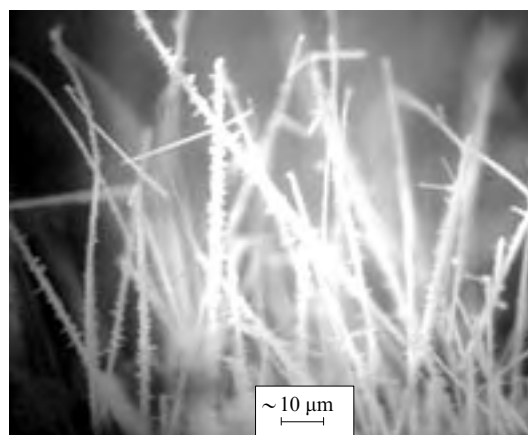


Figure 7. Whisker NaF crystals grown from a vapour phase with the use of BaFCl as a transport reagent.

Precipitation of compounds $\text{PbBr}_x\text{F}_{2-x}$ ($x \leq 0.3$) from methanolic solutions afforded needle-like nanoparticles 30–50 nm in diameter and 500–1000 nm in length;⁵⁷ NH_4LnF_4 particles ($\text{Ln} = \text{Nd}, \text{Sm}, \text{Eu}, \text{Gd}$ or Tb) were synthesised by solvothermal treatment of the precipitate at 150 °C.¹⁰¹ Thermolysis of the fluoroammonium complexes NH_4LnF_4 produced rare-earth trifluorides. The shape memory effect, *i.e.*, the retention of the particle shape, was observed. The resulting 1D nanoobjects were characterised by high concentration of structural defects.

One-dimensional nanoobjects correspond to one of steps of evolution of LaF_3 nanoparticles as the F:La ratio increases during titration in an aqueous solution.⁸⁶

V. Two-dimensional nanoobjects

Films are typical two-dimensional (2D) nanoobjects. Islet films, which represent nanoparticle ensembles on a substrate, are natural and one of the simplest elements of the nanocrystalline architecture.

The formation of fluoride films was studied in detail. In addition to fundamental problems, there are several practical applications due to which these objects have attracted interest: antireflection coatings,^{143–146} epitaxial dielectric films on semiconductors¹⁴⁷ and luminescent coatings.^{129,148–152}

The lattice parameters of calcium and cadmium fluorides ($a = 5.463$ and 5.388 Å, respectively) are similar to the silicon lattice parameter ($a = 5.4305$ Å). Layers, that are similar in the characteristic geometric sizes to the $\text{Si}(111)$, $\text{Ge}(111)$ and $\text{GaAs}(111)$ planes are present in the structures of rare-earth trifluorides (in particular, [001] in the tysonite structure). This fact has stimulated interest in the preparation and investigation of the corresponding epitaxial layers.^{147,153,154}

The cubic lattice parameter can be varied in a wide range (from 5.388 to 6.20 Å), and coatings for lead chalcogenides can be adjusted based on this parameter with the use of the solid solutions $\text{Ca}_{1-x}\text{Sr}_x\text{F}_2$ and $\text{Sr}_{1-x}\text{Ba}_x\text{F}_2$ as well as by the introduction of rare-earth metals into the fluorite structure (giving rise to the solid solutions $\text{M}_{1-x}\text{Ln}_x\text{F}_{2+x}$).^{149,155}

However, the difference in the thermal expansion coefficients, which are 3–7 times larger for fluorides than for semiconductors, is a serious problem.

A small difference in the lattice parameters of deposited layers makes it possible to construct heterostructures.¹⁵⁶ Dielectric fluoride layers are used for the construction of more complex structures, for example, of metal-insulator-semiconductor systems.¹⁵⁷

In addition to molecular beam epitaxy,^{148,149,151} spray coating,^{145,158} chemical vapour phase deposition,^{53,55} magnetron spraying,¹⁵⁹ deposition of fluoride films by soft chemistry

methods has been developed in recent years (Refs 125, 128, 160–163 as well as[†]).

VI. Fluoride nanocomposites

1. Glass ceramics

In recent years, the properties and procedures for the preparation of glass ceramics, such as the generation of a micro- or nano-dispersed crystalline phase in a glass matrix, have been extensively studied.¹⁶⁴ As a rule, such materials are prepared by crystallisation of glasses, *i.e.*, by thermal treatment at near-crystallisation temperature. One of the aims is to prepare transparent glass ceramics for nanophotonics.^{165–167} Such materials have a series of novel properties and are free from many drawbacks of glasses and single-crystalline materials. These materials are processable, they are suitable for the preparation of fibres characterised by a high capacity for activating ions and the isotropicity and homogeneity of properties and activator concentrations.

In practice, there is often a need for functional materials in which the distribution coefficients of activator ions between the matrix and nanoparticles are substantially different. The transfer of an activating additive in the crystalline environment leads to narrowing of luminescence linewidths and an increase in luminescence intensity compared to the intensity of the analogous luminescence of glasses. In particular, this can be achieved by preparing fluoride nanoparticles in a silicate or aluminosilicate matrix.

LaF_3 ,^{168–172} PbF_2 (Refs 173 and 174 as well as[†]), $\text{Pb}_{1-x}\text{Cd}_x\text{F}_2$ (Refs 165–167 and 175–177) and CaF_2 (Ref. 178) can serve as fluoride particles accumulating rare-earth ions. In some cases, nanoparticles of solid solutions $\text{M}_{1-x}\text{Ln}_x\text{F}_{2+x}$ at high concentrations were obtained.

Crystallisation of the glass with composition $16.5 \text{ Al}_2\text{O}_3 \cdot 1.6 \text{ AlF}_3 \cdot 12.7 \text{ LaF}_3 \cdot 4.3 \text{ Na}_2\text{CO}_3 \cdot 64.9 \text{ SiO}_2$ afforded the LaF_3 phase where rare-earth elements were incorporated in a different proportions: Er^{3+} , 2%–3% of the total amount of the introduced erbium fluoride; Pr^{3+} , up to 70%.¹⁶⁹

The preparation of a transparent glass-crystalline material based on the glass with composition $30 \text{ SiO}_2 \cdot 15 \text{ AlO}_{3/2} \cdot 29 \text{ CdF}_2 \cdot 17 \text{ PbF}_2 \cdot 5 \text{ ZnF}_2 \cdot 4 \text{ YF}_3$ was documented.^{166,167} The glass transition temperature and the crystallisation temperature of the starting glass are 395 and 475 °C, respectively. Thermal treatment with the aim of preparing glass ceramics was carried out in the temperature range of 440–470 °C for 30–60 min. The crystallite size was 6–8 nm.

Glass ceramics with similar composition, $30 \text{ SiO}_2 \cdot 15 \text{ AlO}_{1.5} \cdot 28 \text{ PbF}_2 \cdot 22 \text{ CdF}_2 \cdot (4.8-y) \text{ GdF}_3 \cdot 0.1 \text{ NdF}_3 \cdot y \text{ YbF}_3 \cdot 0.1 \text{ TmF}_3$ ($y = 0, 0.1, 0.2, 0.5, 1.0, 2.0, 3.0, 4.0$ and 4.8), were prepared.¹⁷⁹ The crystallite sizes in this system are virtually independent of the annealing time (Fig. 8a). Therefore, thermal treatment did not lead to growth of fluoride particles, which were already present in the glass.

In addition to crystallisation of cast glasses, sol–gel methods are used.^{131,132,180} The glass ceramic with composition $0.1 \text{ ErF}_3 \cdot 0.1 \text{ YbF}_3 \cdot 5 \text{ LaF}_3 \cdot 94.8 \text{ SiO}_2$ was prepared by Fujihara's method.¹³² Tetraethoxysilane (TEOS), which was dissolved in an equimolar amount of ethanol, was hydrolysed with water in the presence of acetic acid as the catalyst. The $\text{TEOS}:\text{H}_2\text{O}:\text{AcOH}$ ratio was 1:10:0.5. Rare-earth acetates were dissolved in trifluoroacetic acid ($\text{M}^{3+}:\text{F}^- = 1:10$). A small amount of water was added to accelerate dissolution. The trifluoroacetate solution was slowly stirred with silica sol. The gel formation occurred at room temperature for two weeks. Drying was performed at 40–70 °C for one week. The dry gel was heated to 1000 °C in air

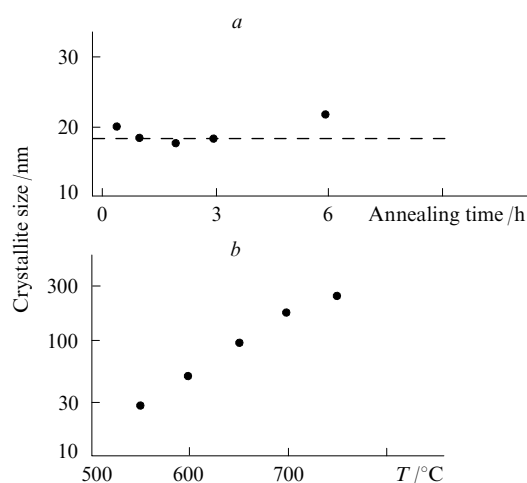


Figure 8. Plots of the crystallite size vs the parameters of thermal treatment.

(a) The particle size of $\text{Pb}_{1-x}\text{Cd}_x\text{F}_2$ in the $30 \text{ SiO}_2 \cdot 15 \text{ AlO}_{1.5} \cdot 28 \text{ PbF}_2 \cdot 22 \text{ CdF}_2 \cdot (4.8-y) \text{ GdF}_3 \cdot 0.1 \text{ NdF}_3 \cdot y \text{ YbF}_3 \cdot 0.1 \text{ TmF}_3$ glass vs the annealing time;¹⁷⁹ (b) the particle size of LaF_3 in the $53 \text{ SiO}_2 \cdot 11 \text{ Na}_2\text{O} \cdot 27 \text{ Al}_2\text{O}_3 \cdot \text{Al}_2\text{F}_6 \cdot 7 \text{ La}_2\text{F}_6 \cdot 0.07 \text{ Er}_2\text{F}_6$ glass vs the temperature of thermal treatment for 12 h.¹⁷³

at a rate of 75 K h⁻¹, after which the sample became more compact and transparent glass ceramics involving fluoride nanoparticles was obtained. Lanthanum fluoride nanoparticles doped with erbium were dispersed as a colloidal solution in a silica sol that is formed upon hydrolysis of tetraethoxysilane. The disperse system was coated onto a substrate to prepare thin films.¹⁸⁰

According to the commonly accepted Gleiter concept, glasses (as opposed to composite materials) are considered as uniform homogeneous media.¹⁸¹ However, this concept is doubtful as referred to nanomaterials. Not only short-range but also medium-range order regions tens of ångströms in size were found in glasses by different methods. A crystallite model of glasses, which was proposed by Lebedev more than 80 years ago¹⁸² and was considered as an antithesis to the Zachariasen–Warren theory of continuous random networks,^{183–185} has been confirmed and defined more specifically in recent years (due to the use of modern methods of investigation),^{186–188} including the model of strained mixed clusters¹⁸⁹ (Fig. 9). Therefore, contrary to the opinion of Gleiter,¹⁸¹ in some cases glasses can be considered as true nanocomposites where nanometre-size crystalline regions (they can have different compositions and structures) are surrounded by an amorphous strained defect shell. This is also true for fluoride glasses, which are promising materials for optical information transmission. A vast diversity of fluoride glasses includes the following main classes: fluorozirconate, fluoro-hafnate, fluoroaluminate, fluoroindate and fluoroberyllate glasses.^{190–194}

In the light of the above, the crystallisation process can be considered as either an increase in the size of crystallites, which are already present in the glass, or as the appearance and growth of crystallites the structures of which differ from those present in the glass. Therefore, in some cases, structural difference between glasses and glass ceramics is rather quantitative than qualitative in essence.

The crystallisation processes of fluoride glasses, including those giving rise to transparent glass ceramics, were considered.^{195–200} It was shown²⁰¹ that the optical transmission retained upon crystallisation of 90% of a fluorozirconate glass.

The plots of the crystallite size vs. the parameters of thermal treatment of oxofluoride glasses shown in Fig. 8 illustrate two different situations: (1) thermal treatment does not lead to growth of fluoride particles that are already present in the glass; (2) a rise

[¶] B-Ch Hong, K Kawano *J. Alloys Compd.* **408–412** 898 (2006); P Jia, J Lin, M Yu *J. Lumin.* **122–123** 134 (2007).

[†] G Dantelle, M Mortier, D Vivien, G Patriarche *Opt. Mater. (Amsterdam)* **28** 638 (2006).

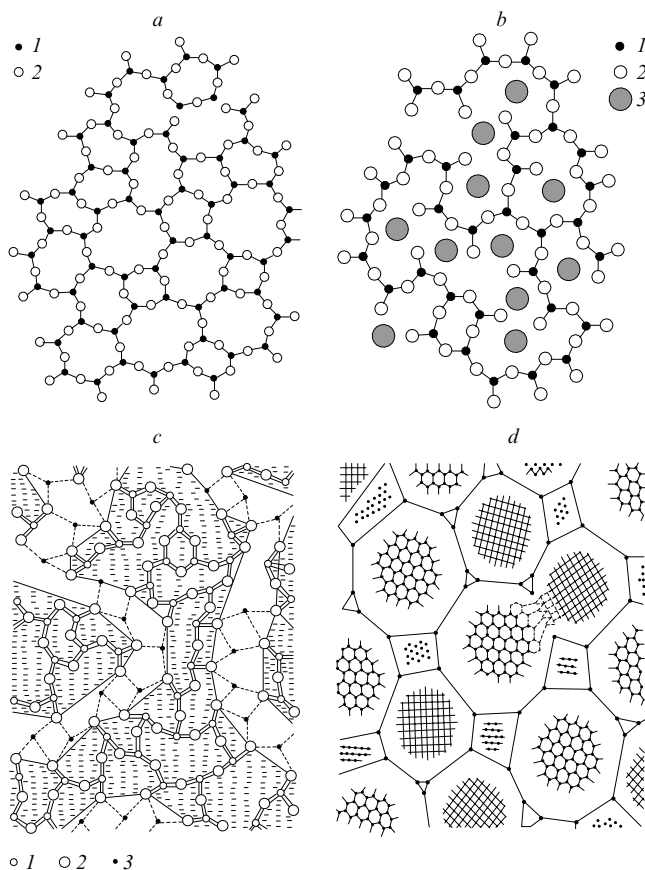


Figure 9. Models of glass structures.

(a) The Zachariasen model,¹⁸³ (b) the Warren model,^{184, 185} (c) the Greaves model,¹⁸⁷ (d) the Goodman model (the model of strained mixed clusters).¹⁸⁹

(1) Network-forming atoms, (2) bridging atoms, (3) network-modifying ions.

of the temperature leads to an increase in the particle size. In the latter case, glass ceramics with a particle size smaller than 60 nm (calculated from the line broadening in X-ray diffraction patterns) retain optical transmission.

The question of whether it is correct to consider glasses as nanocomposites requires additional studies, including the use of atomic force²⁰² and transmission electron microscopy.

2. Single crystals of heterovalent solid solutions

Association of point defects in crystals gives rise to various complex defects the size of which together with the relaxation region of the matrix is equal to several unit cells, *i.e.*, corresponds to nanoobjects. On the whole, crystals containing defects at rather high concentration can be considered as nanocomposites (Fig. 10).

For fluoride systems, the solid solutions $M_{1-x}Ln_xF_{2+x}$ with a fluorite structure formed in MF_2-LnF_3 systems ($M = Ca, Sr, Ba, Cd$ or Pb ; $Ln = La-Lu, Y$ or Sc) are typical examples of such nanocomposites.²⁰⁴ Phase equilibria in these systems were studied in detail.^{68, 155} The width of the solid solution regions reaches 50 mol.% ($x \leq 0.5$). At lower temperatures, solid solutions are thermodynamically unstable and either decompose or undergo ordering. However, these processes are hindered and single crystals grown from a melt retain optical transmission for decades.

The formation of such solid solutions is a typical example of heterovalent isomorphism with a variable number of atoms per unit cell.²⁰⁵ Cations have different charges. Hence, the insertion of additional fluoride ions into the lattice of dilute solid solutions is necessary for electrostatic compensation (Goldschmidt's scheme)

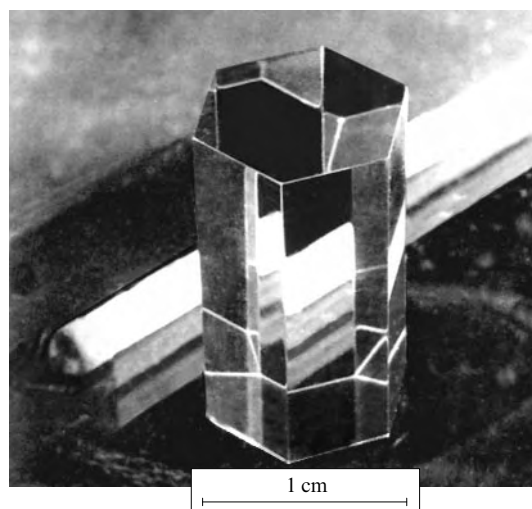


Figure 10. Nanocomposite as an artificially faceted single crystal of the solid solution $Sr_{0.69}La_{0.31}F_{3.31}$ corresponding to the maximum in melting curves of the solid solution with a fluorite structure in the SrF_2-LaF_3 system.²⁰³

Most refractory inorganic fluoride ($T_m = 1570^\circ C$).



Thus, there are two types of point defects in the fluorite lattice. Electrostatic interactions between these defects lead to their association to form dipoles ($Ln^{3+} - F_{int}^-$), which can have different crystallographic orientations. An increase in the concentration of rare-earth fluorides leads to further association of dipoles to form $(Ln^{3+} - F_{int}^-)_2$ dimers and more complex associates (clusters).^{206, 207} More than two dozens of cluster models were proposed based on data from various experiments and calculations.^{204, 208, 209}

In solid solutions, the presence of Ln_6F_{37} clusters (Fig. 11) was reliably established.^{210, 211} In these clusters, the coordination polyhedra of rare-earth metals are tetragonal antiprisms. An additional anion occupies the cuboctahedral cavity in the centre of the cluster. The existence of such clusters was revealed, in particular, by X-ray diffraction study of ordered fluorite-like phases in these systems. Such clusters are naturally incorporated into the fluorite lattice (see Fig. 11). Since the geometric sizes of associates differ from the size of the matrix lattice regions, which are replaced by these associates, the corresponding composites have local internal strains and deformations. The charge of the cluster differs from the charge of the fragment of the fluorite lattice. Hence, the formation of clusters is accompanied by elimination of an equal amount of additional anions into the matrix according to the equation

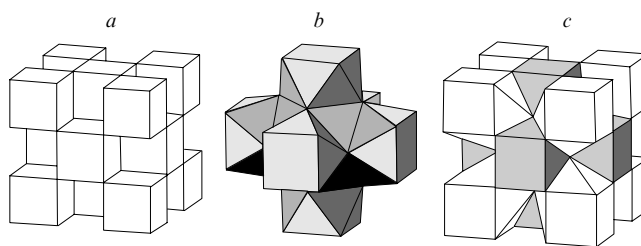
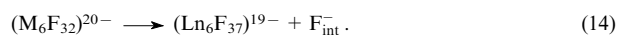


Figure 11. Fragment of the fluorite lattice (a), the Ln_6F_{37} cluster (b) and the Ln_6F_{37} cluster incorporated into the fluorite lattice (c).

Both an increase in the concentration of charge carriers and the presence of a deformed zone in the cluster shell lead to a sharp increase in the ionic conductivity.^{212,213}

The formation of the solid solutions $M_{1-x}Ln_xF_{2+x}$ corresponds to the so-called block isomorphism. In this case, the long-range order in the packing of cations is retained, although the anion sublattice undergoes very strong local deformations.

The concentration of clusters increases with an increase in concentration of solid solutions. In the range of 6 mol.%–8 mol.%, percolation occurs, *i.e.*, clusters get in contact with each other to form superclusters in which rare-earth elements are accumulated. The sizes of such superclusters can be as large as several micrometres.

The scheme of successive defect association in the fluorite structure is shown in Fig. 12. The concentration boundaries of the regions vary with temperature and depend on the chemical composition of the systems. The concentration range corresponding to individual clusters containing several rare-earth ions mainly belongs to the region of nanomaterials.

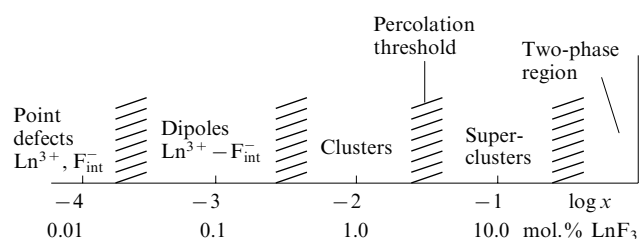


Figure 12. Regions of defect association in the solid solutions $M_{1-x}Ln_xF_{2+x}$ with a fluorite structure.

The structures of clusters in the solid solutions $M_{1-x}Ln_xF_{2+x}$ radically differ from the structures of rare-earth fluorides. Therefore, clusters cannot serve as nuclei of the LnF_3 phase. It is this fact that is responsible for stability of solid solutions against decomposition and the possibility of their use as photonic materials.

An analogous defect structure (poorly studied) is also typical of heterovalent solid solutions having a fluorite structure in the MF_2-XF_4 ($X = Zr, Hf, U$ or Th), $NaF-LnF_3$ and, to a lesser degree, $KF-LnF_3$ systems, as well as of phases with variable composition with a tysonite structure formed in the MF_2-LnF_3 systems. There is also high similarity with fianites, which are solid solutions with a fluorite structure in the $Ln_2O_3-(Zr,Hf)O_2$ systems.²⁰⁶ Coherent submicrometre-size zones of the second phase are well known in metal alloys.

The term ‘antiglass’ was introduced²¹⁴ for the description of crystalline disordered phases characterised by essential local disorder in the presence of a long-range order (in usual glasses, the long-range order is absent, but they have a short- and medium-range order). The heterovalent solid solutions under consideration are typical antiglasses. The similarity of the physical properties of glasses and antiglasses is an example of the principle of equivalence of disorder sources proposed by Tretyakov.²¹⁵

Taking into account the difference in principle between glasses (chaos with islets of order) and antiglasses (order with islets of chaos), antiglasses cannot be considered as an intermediate between crystals and glasses. It is more probable that antiglasses are antipodes of glasses. This main difference leads to a series of additional essential differences. Since solid solutions (antiglasses) are highly defect, they are characterised by a low entropy of melting and, correspondingly, have a low activation barrier to nucleation, and their melts solidify virtually without supercooling. To the contrary, glass-forming melts are characterised by strong supercooling. The appearance of antiglasses as strongly disordered crystalline phases with variable composition, the presence of clusters (defects) and the absence of supercooling are factors limiting the glass formation.

Glasses [for example, $ZrF_4-BaF_2-LaF_3-AlF_3-NaF$ (ZBLAN)] and antiglasses [for example, the solid solutions $Ba_{1-x}Ln_xF_{2+x}$ (Ln are rare-earth metals, $x \leq 0.5$) with a fluorite structure] have the following similar features:

- nanoheterogeneity, the cluster (crystallite) character of the structure;
- a high degree of disorder, high entropy;
- broad multicentre luminescence spectra, broadening, which does not disappear at lower temperatures;
- abnormal low-temperature thermal conductivity, the absence of maxima in the temperature dependence of thermal conductivity;
- fragility, the absence of cleavage;
- high ionic conductivity, the absence of a conductivity jump on melting;
- thermodynamic instability under standard conditions; an increase in the cooling rate expands the region of existence;
- variable chemical composition and high isomorph capacity;
- dependence of physical properties (density, refraction index and conductivity) on the conditions of thermal treatment;
- characteristic features of vibrational spectra;
- percolation phenomena;
- polyfunctionality of materials based on these substances;

and the following differences:²⁰⁵
glasses are characterised by the presence of only a short- and medium-range order, a network structure, fusible composites, high entropy of melting, strong supercooling of melts, which depends on the cooling rate; antiglasses are characterised by a long-range order, a framework structure, refractory, maxima in the melting curves, slight supercooling of melts.²¹⁶

3. Eutectic and eutectoid nanocomposites

Let us consider the possibility of preparing nanocrystalline composites by eutectic crystallisation. Steady-state crystallisation can afford rather ordered plate- or rod-like structures (the transition of one type into another is determined by the volume fraction of the crystallising phases).²¹⁷ An electronic image of the $LiF-LiCdF_4$ eutectic system with a fibre diameter of $\sim 1 \mu m$ is shown in Fig. 13.²¹⁸

For steady-state eutectic crystallisation, the following formula is true

$$\lambda^2 R = \text{const},$$

where λ is the characteristic linear size (for example, the rod diameter) and R is the crystallisation rate. Therefore, to decrease

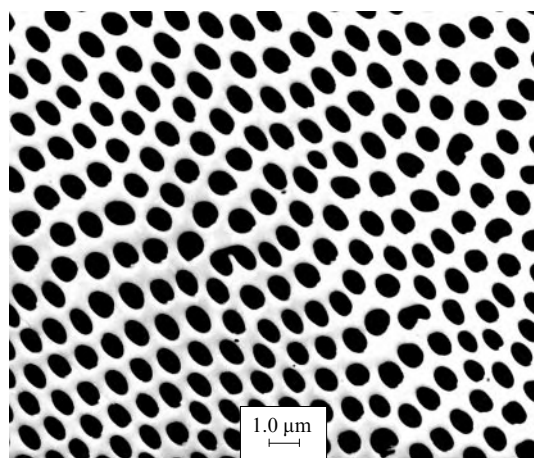


Figure 13. Electronic image of the eutectic composite $LiF-LiGdF_4$. Directed crystallisation at a rate of 10 mm h^{-1} , the temperature gradient was 70 K min^{-1} .

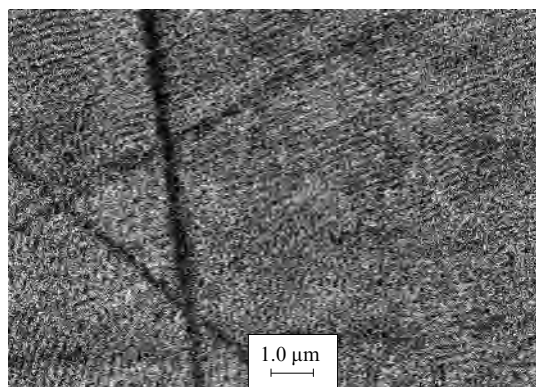


Figure 14. Image of the product of eutectoid decomposition of a solid solution in the BaF_2 – CaF_2 system.²¹⁹ Cooling at a rate of 100 K min^{-1} ; straight dark lines correspond to scratches on the surface.

the rod diameter by a factor of 10, it is necessary to increase the rate by a factor of 100, which is difficult to perform technically for a steady-state process.

Eutectoid composites hold more promise. The microstructure of an alloy after eutectoid decomposition in a system consisting of calcium and barium fluorides is shown in Fig. 14. In this system, three phases having fluorite structures (solid solutions based on the components and an intermediate high-temperature phase) exist in equilibrium at 870°C .²¹⁹ The sample is characterised by high ionic conductivity comparable with the conductivity of a specially formed composite prepared by successive deposition of nanolayers of calcium and barium fluorides.²²⁰

4. Oxide nanoparticles in fluoride matrices

Fluoride matrices are used for the insertion of nanoparticles with another chemical composition. For example, ZnO and ZnGa_2O_4 nanoparticles dispersed in MgF_2 or LaF_3 films were prepared by the sol–gel method.^{221, 222}

It is known that dispersion in an ionic matrix, including a fluoride matrix, of nanoparticles of dielectric materials, such as SiO_2 and Al_2O_3 , causes an increase in ionic conductivity. This approach is known under the name ‘heterogeneous doping’. The maximum conductivity is observed for a certain volume fraction of dispersed submicrometre-size particles. The theoretical aspects of heterogeneous doping were considered in the publications.^{223–225} A substantial increase in the fluoride-ionic conductivity was observed in such heterogeneous systems as $\text{CaF}_2 : \text{Al}_2\text{O}_3$, $\text{BaF}_2 : \text{Al}_2\text{O}_3$,²²⁶ $\text{Ca}_{0.995}\text{Na}_{0.005}\text{F}_{1.995} : \text{CeO}_{2-x}$ and $\text{Ca}_{0.992}\text{Y}_{0.008}\text{F}_{2.008} : \text{CeO}_{2-x}$.²²⁷

5. Other fluoride nanomaterials

In addition to inorganic fluorides, other compounds also belong to nanocrystalline materials. Evidently, crystalline fluoroorganic polymers,²²⁸ like usual polymers, are nanoparticles (with an ordered arrangement of molecules), which are present in a matrix with a lesser degree of order, in a wide temperature range. These materials are analogues of glass ceramics.

Ultradispersed polytetrafluoroethylene (UDPTFE) powders were synthesised.²²⁹ The technology of the preparation of this material is based on nucleation and condensation of gaseous products of thermal decomposition of industrial polytetrafluoroethylene (Fluoroplast-4). The sizes of particles formed in the gas medium are in the range of 25–50 nm.^{229, 230} Particles of an UDPTFE powder, the sizes of which vary from 100 to 1200 nm (the average size is 550 nm), consist of nanoblocks. A photomicrograph of an individual particle is shown in Fig. 15. The particles consist of blocks up to 100 nm in size. The blocks are held together by low-molecular-weight polytetrafluoroethylene

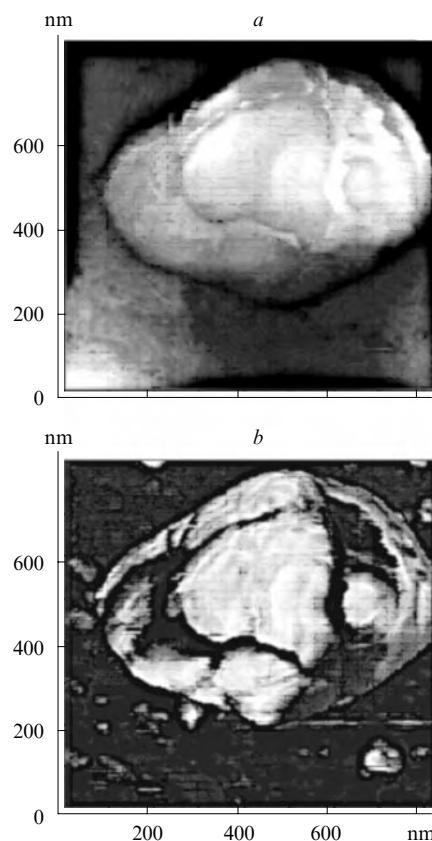


Figure 15. Images of a nanoparticle of ultradispersed polytetrafluoroethylene taken with the use of an atomic force microscope (courtesy of V M Buznik). (a, b) Different measurement modes.

(PTFE), the structure and properties of which differ from those of the usual high-molecular-weight compound. Some particles are coated by this material. Low-molecular-weight PTFE is characterised by solubility in some solvents and supercritical carbon dioxide, which made it possible to prepare 2–4 nm thick polymeric coatings.²³⁰

A family of new nanomaterials, including magnetic materials, was synthesised by deposition of metal nanoparticles (Fe, Co, Ni, Cu or Pd) on the surface of ultradispersed PTFE granules. Deposition is accompanied by a chemical reaction. In some cases, nanoparticles have a complex composition. Defluorination of PTFE giving rise to a fluoride interlayer and a carbide layer was observed.^{230–232} The structural model of an iron nanoparticle on the surface of an UDPTFE nanogranule is shown in Fig. 16.

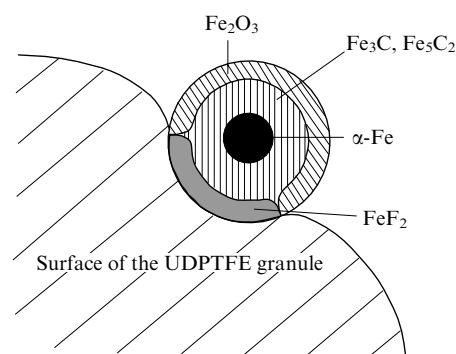


Figure 16. Structural model of an iron nanoparticle on the surface of an ultradispersed polytetrafluoroethylene nanogranule.²³²

VII. Nanotechnology and nanoarchitecture

As a rule, the synthesis of nanoparticles is merely the first step of the construction of materials. Fluoride nanoparticles are used in intermediate steps and for the construction of more complex structures of functional importance, *i.e.*, in the design of nano-objects.

It was demonstrated¹⁵⁸ that decomposition of a CoF₂ film in a transmission electron microscope afforded cobalt nanoparticles with a size of 5–10 nm.

The introduction of YF₃ nanoparticles into a shell of polyelectrolyte multilayer capsules was found to improve their mechanical characteristics.²³³ The scheme of this multistep process is shown in Fig. 17.

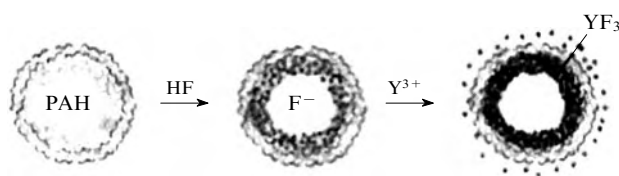


Figure 17. Scheme of the modification of polyelectrolyte capsules with yttrium fluoride nanoparticles.²³³ PAH is poly(allylamine hydrochloride).

One of operations in nanotechnology is coating of nanoparticles. Taking into account the luminescence properties of lanthanide compounds, interactions between active metal ions and OH⁻ ions, which are efficient luminescence quenchers, present a serious problem. The surface of nanoparticles of fluorides Gd_{0.9}Er_{0.1}F₃, which are present in a porous SiO₂ matrix, was coated with Gd₂O₃.⁴⁹ The suspension was placed in an aqueous solution containing Gd³⁺ and urotropine. Heating at 80 °C for 2 h led to deposition of a Gd(OH)₃ layer. Upon further heating to 500 °C, the hydroxide coating is transformed into the oxide coating. Decomposition of europium trifluoroacetate in a triethylphosphine oxide (TOPO) melt afforded EuF₃ nanoparticles coated with TOPO, which prevents pyrohydrolysis and leads to the efficient energy transfer of europium radiation outwards.⁵¹

A more complicated nanotechnological process was employed¹³ for the preparation of luminescent silica films containing LaF₃ nanoparticles doped with Er³⁺, Nd³⁺ and Ho³⁺ (5% each) by the sol–gel method. The authors solved two problems: insulation of luminescent ions against OH groups (for this purpose, nanoparticles were coated with undoped LaF₃) and dispersion of colloidal nanoparticles in solution with the aim of their homogeneous inclusion into the sol–gel matrix (for this purpose, citrate ions adsorbed on the surface of nanoparticles were used). The following operations were performed successively: precipitation of nanoparticle nuclei, their coating, stabilisation in a colloidal solution, introduction of particles into a gel and film formation.

Studies on the synthesis of hybrid organic/inorganic systems based on fluoride nanoparticles were started (see, for example, Refs 25, 82, 234 and 235).

Coating of multilayer carbon nanotubes by EuF₃ and TbF₃ nanoparticles using intermediate hydrophobic interactions between the surface of carbon nanotubes and sodium dodecyl sulfate was documented.²³⁶ The nanoparticle size was at most 10 nm.

VIII. Conclusion

In recent years, extensive studies in the field of nanotechnology of fluorides have been performed. However, it is obvious that these investigations are in their infancy and will be further developed, in particular, with the use of methods for the synthesis of nano-

particles (the aerosol method, thermolysis of fluoroammonium salts, *etc.*).

Further investigations of the influence of the dispersity on hydrolysis of fluorides and particularly studies of the first step, *viz.*, adsorption of water and other substances on the surface of fluoride particles, as well as the development of procedures for the preparation of protective coatings on the surface of fluoride nanoparticles, are required. Taking into account the similar sizes of the F⁻ and OH⁻ ions, it can be assumed that in many cases, where fluoride nanoparticles are synthesised from an aqueous solution or in air, these particles would contain a particular fraction of OH groups, which increases as the surface is approached (*i.e.*, nanoparticles are hydroxofluorides). According to the results of chemical analysis, the oxygen content increases with increasing amount of rare-earth metals in single crystals prepared by the hydrothermal method. The lattice parameters and the phase transition temperatures are in satisfactory agreement with the corresponding parameters of samples synthesised under anhydrous conditions. The available data (see, for example, Refs 11, 14 and 75) demonstrate that the degree of hydrolysis in the synthesis of nanoparticles increases when potassium is used instead of sodium, which is obvious taking into account substantially higher hygroscopicity of KF compared to NaF. In the case of precipitation of sodium–rare-earth element compounds, OH⁻ ions are virtually absent. For potassium compounds, substantial hydrolysis is observed. It should be noted that according to earlier data (see Refs 69, 70 and 72), the degree of hydration in the case of precipitation with sodium fluoride and potassium fluoride from aqueous solutions of rare-earth salts of cubic double fluorides M_{0.5–x}Ln_{0.5+x}F_{2+2x}·*n*H₂O (*x* = 0.05–0.17) is smaller for M = Na (*n* = 0.2–0.5) than for M = K (*n* = 1–3).

It seems paradoxical that no hydrolysis was observed after completion of the mechanochemical synthesis, where hygroscopic potassium fluoride was mixed with easily hydrolysable transition metal fluorides in air.⁶¹

In many photographs, fluoride nanoobjects look like clouds and pieces of cotton without pronounced boundaries. This is a characteristic feature of a fractal structure.^{237, 238} The self-similarity of the particle shape at several structural levels was noted.⁸⁶ This problem calls for further investigation. It should be noted that the term ‘surface area’ for fractals is ambiguous (can be determined in different ways) and depends on the measurement procedure. In particular, different values of the specific surface area, which is the practically important parameter (for example, for catalysts), can be obtained by the adsorption method with the use of different adsorbed gases.

The random arrangement of fluoroaluminate octahedra postulated in a fluoride gel (see Fig. 6) corresponds to a network in fluoroaluminate glasses. Therefore, one would expect that analogous gels would be prepared for other groups of fluoride glasses, such as fluoroberyllate, fluorohafnate, fluorozirconate and fluoroindate glasses. Amorphous fluoride powders prepared by the sol–gel technology hold considerable promise for the synthesis of different types of fluoride glasses.

Nanofluorides are promising materials for the synthesis of single crystals, particularly, if the components of compounds are substantially different in volatility. An example is SrAlF₅ single crystals of which are promising nonlinear optical materials for laser frequency conversion to the UV range.²²

High mobility of fluoride ions, which is probable in fluoride nanoparticles, may be of practical importance.⁶⁴ It should be noted that ¹⁹F NMR spectroscopy is the method of choice for studying this phenomenon.⁴⁴

It is also necessary to examine the dependence of the toxic effect of fluorides on the particle size.

We thank J Ballato, A Bednarkiewicz, A I Boltalin, J Botta, D Boyer, I I Buchinskaya, V M Buznik, E E Carpenter, Y Chunhua, M Dejneka, A Fery, W Filho, S Fumio, T I Glazunova, R N Grass, C L Griffiths, M G Ivanov, Ishizawa Hitoshi, E Kemnitz, R N Kostoff, Y D Li, J L Light,

M Lezhnina, R Mahiou, J-M Nedelec, O B Petrova, L Prentice, B P Sobolev, W J Stark, N Stubicar, M Tyas, F van Veggel, Xianping Fan, Xianwen Wei, Yuhua Wang, Qiwu Zhang, Jishuang Zhang and P Zipper for providing information. We thank E V Chernova for technical help in preparing the manuscript.

This review has been written with the financial support of the Government Contract of the Ministry of Education and Sciences (No 02.435.11.2011, 15 July 2005).

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^d — *Crystallogr. Rep. (Engl. Transl.)*

^e — *Dokl. Chem. (Engl. Transl.)*

^f — *Inorg. Mater. (Engl. Transl.)*

^g — *Mendeleev Chem. J. (Engl. Transl.)*

The kinetic ordering and growth dissymmetrisation in crystalline solid solutions

A G Shtukenberg, Yu O Punin, O V Frank-Kamenetskaya

Contents

I. Introduction	1083
II. Experimental techniques for the elucidation of the growth dissymmetrisation of crystals	1086
III. The symmetry aspects of the dissymmetrisation and the structural inhomogeneity of crystals	1090
IV. Dissymmetrisation-induced changes in the crystal structure	1093
V. The metastability of the kinetic ordering	1095
VI. The kinetic ordering and the atomic structures of growing faces	1096
VII. The diffusion relaxation	1097
VIII. Control factors of the kinetic ordering	1099
IX. Conclusion	1103

Abstract. The review concerns the order–disorder kinetic (growth) phase transitions, which are characteristic of inorganic crystalline solid solutions. The emphasis is placed on the emergence of metastable low-symmetry phases (*i.e.*, the dissymmetrisation of crystals), which can occur due to the drastic difference between the atomic structures of growing faces and the bulk crystal. The experimental techniques for the elucidation of this phenomenon, possible crystal symmetries and structures induced by the dissymmetrisation as well as the effects of crystal composition, growth medium composition, growth temperature and growth rate are analysed. The bibliography includes 177 references.

I. Introduction

The order–disorder transitions are equally typical of naturally occurring and artificial crystals. The phase diagram of a compound can reveal areas of the thermodynamic stability and instability of its ordered and disordered phases in specific ranges of thermodynamic parameters, *e.g.*, temperature and pressure. A change in the thermodynamic parameters can induce a transition from an ordered into a disordered phase or *vice versa*. Such classical phase transitions have been known for a long time and are beyond the scope of the present review. This review concerns the kinetic (or growth) order–disorder phase transitions.^{1,2}

A kinetic phase transition implies the emergence of a phase of a particular compound (with either constant or variable stoichiometry) within the stability range of another phase of the same compound driven by kinetic factors.^{3–5} The term ‘kinetic phase transitions’ emphasises that it is kinetic rather than thermodynamic factors that act as the control parameters for such transitions. Kinetic transitions in crystals with variable stoichiometry (*i.e.*, solid solutions), which is a particular case of this general phenomenon, can be classified into two groups, *viz.*, ordering and disordering transitions. The former ones occur due to the selective incorporation of solid solution components into different crystallographic sites of a growing crystal face. The latter ones occur due to a poorer statistical selection of different atoms at high crystal growth rates (atoms in the surface layer do not have enough time to settle themselves in the sites corresponding to an ordered state before a next layer is deposited).¹ We limit ourselves to only kinetic ordering processes, since quite extensive experimental data on this subject became available over the recent years.

At the first glance, the kinetic ordering phase transitions look exotic among numerous ordinary equilibrium phase transitions. However, a careful consideration of the issue indicates that these transitions are not so rare, especially, in the case of solution-grown crystals. Presently, this phenomenon has been well documented for ~30 compounds (Table 1–3), but we believe that the actual range of its occurrence is far broader and it is characteristic of the majority of solid solutions.

Investigations into the kinetic phase transitions are encouraged by the interest in unusual behaviour of crystals and processes responsible for the formation of crystalline solid solutions. The underlying regulations can be applied to reconstruct conditions of the mineral formation in nature.

Atoms, vacancies and their groups can be a subject of either positional or rotational ordering. The presence of partial occupancies of crystallographic sites statistically occupied by different atoms and vacancies in the crystal structure is a prerequisite to the kinetic positional ordering. This phenomenon can be observed both in the case of complete miscibility of isomorphous components [*e.g.*, the ordering of trivalent cations in garnets of the grossularite–andradite series, $\text{Ca}_3(\text{Al,Fe})_2(\text{SiO}_4)_3$] and limited isomorphism (as in the case of the ordering of the Al^{3+} cations substituting for the Si^{4+} ions in quartz, SiO_2). The kinetic ordering can take place when a respective ordinary thermodynamic phase transition is both known [*e.g.*, orthorhombic–hexagonal cordierite $\text{Mg}_2\text{Al}_3(\text{AlSi}_5\text{O}_{18})$] and unknown [*e.g.*, orthorhombic–triclinic topaz $\text{Al}_2\text{SiO}_4(\text{OH},\text{F})_2$].

The known cases of the orientational kinetic ordering are rather scarce. In particular, such an ordering in the distribution of the OH groups was described in apophyllite $\text{KCa}_4(\text{Si}_4\text{O}_{10})_2 \cdot (\text{F},\text{OH}) \cdot 8\text{H}_2\text{O}$ crystals.³⁸ Probably, a similar effect is typical of grossularite garnet $\text{Ca}_3\text{Al}_2[\text{SiO}_4,(\text{OH})_4]_3$ crystals.^{87,120} Yet

A G Shtukenberg, Yu O Punin, O V Frank-Kamenetskaya Department of Geology, St Petersburg State University, Universitetskaya nab. 7/9, 199034 St Petersburg, Russian Federation. Fax (7-812) 328 44 18, tel. (7-812) 328 96 47, e-mail: sasha@as3607.spb.edu (A G Shtukenberg), crystgen@geology.pu.ru (Yu O Punin), olga@OF3102.spb.edu (O V Frank-Kamenetskaya)

Received 5 October 2005

Uspekhi Khimii 75 (12) 1212–1236 (2006); translated by Ya V Zubavichus

another example is given by the orientational ordering in the distribution of the SO_4^{2-} groups revealed for the dissymmetrisation of crystals of aluminium chromium potassium alum, $\text{K}(\text{Al},\text{Cr})(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}$.³⁴ However, these three cases virtually encompass all available information on the orientational kinetic ordering. Therefore, we shall further discuss the positional ordering only.

The early history of investigations into the kinetic ordering of atoms, often also referred to as the growth dissymmetrisation of crystals, dates back to the 1960s, when several compounds featuring the ordered distribution of dopant atoms over specific crystallographic sites equivalent in the parent high-symmetry structure [in particular, the ordering of the Gd^{3+} ions in synthetic

corundum Al_2O_3 (Ref. 84) and of the Fe^{3+} ions in calcite CaCO_3 (Ref. 85) and amethyst, a purple quartz modification^{74, 75]} were discovered. In all these cases, the growth processes were suggested to be the driving factor for the ordering (in particular, the non-equivalence of different sites with respect to the crystal growth front was noted) although no detailed mechanism of this phenomenon was then formulated. The general idea of the growth ordering mechanism was proposed by Shubnikov¹²¹ based on theoretical arguments. For the first time, this mechanism has been elaborated in detail by Tsinober and Samoilovich⁷⁹ for quartz and by Nizamutdinov *et al.*⁸¹ for zinc selenate and sodium kröhnkite $\text{Na}_2\text{Cd}(\text{SO}_4)_2 \cdot 2\text{H}_2\text{O}$ (Ref. 80) and somewhat later by Akizuki and Sunagawa⁶³ for adularia (which is a low-temperature

Table 1. Examples of the growth dissymmetrisation in crystalline solid solutions according to diffraction methods.

Solid solution, chemical formula	Growth sector ^a	Ideal space group	Real space groups	Optical anomalies ^b	Signatures in diffraction ^c			Ordering type, maximum degree	Number of structures studied ^d	Ref.
					1	2	3			
Isotropic crystals										
Garnets										
Ca ₃ (Al,Fe) ₂ (SiO ₄) ₃	{110}	<i>Ia</i> $\bar{3}$ <i>d</i>	<i>Fddd</i> , <i>I</i> $\bar{1}$	$\Delta n = 0.015$	+	+	+	Al/Fe, 0.74	9	6–16
Ca ₃ (Al,Cr,V) ₂ (SiO ₄) ₃	{110}	<i>Ia</i> $\bar{3}$ <i>d</i>	<i>Fddd</i> , <i>I</i> $\bar{1}$	$\Delta n = 0.007$	+	+	+	Al/Cr, 0.66	7	17, 18, our data
(Y,Nd) ₃ Ga ₅ O ₁₂	{110}	<i>Ia</i> $\bar{3}$ <i>d</i>	?	$\Delta n = 0.0004$	+	?	?	Y/Nd (see ^a)	—	19–21
Analcimes-pollucites	?	<i>Ia</i> $\bar{3}$ <i>d</i>	<i>I4</i> ₁ / <i>acd</i> , <i>Ibca</i> , <i>I2</i> ₁ <i>2</i> ₁ <i>2</i> ₁	$\Delta n > 0$	+	+	+	Al/Si, 0.92 Na/ $\square$, 0.23 Cs/H ₂ O, 0.30	8	22–25
Cs _{<i>x</i>} Na _{1–<i>x</i>} AlSi ₂ O ₆ · (1 – <i>x</i>) H ₂ O										
Na(ClO ₃ ,BrO ₃)	{100}, {111}, { $\bar{1}\bar{1}\bar{1}$ }	<i>P2</i> ₁ <i>3</i>	<i>P1</i> , <i>R3</i>	$\Delta n = 0.02$	+	+	+	ClO ₃ /BrO ₃ , 0.75	20	26–28
Alum										
K(Al,Cr)(SO ₄) ₂ · 12 H ₂ O, (K,NH ₄)Al(SO ₄) ₂ · 12 H ₂ O, other isomorphous series	{111}	<i>Pa</i> $\bar{3}$	<i>R</i> $\bar{3}$, <i>P</i> $\bar{1}$	$\Delta n = 0.0001$	—	+	—	Al/Cr, 0.10 NH ₄ /K, 0.05	4	29–34, our data
(Pb,Ba)(NO ₃) ₂ , (Pb,Sr)(NO ₃) ₂	{111}	<i>Pa</i> $\bar{3}$	<i>R</i> $\bar{3}$, <i>R3</i>	$\Delta n > 0$	—	+	+	Pb/Ba, 0.22 Pb/Sr, 0.09	6	35, 36, our data
Uniaxial crystals										
Apophyllite ^e KCa ₄ (Si ₄ O ₁₀) ₂ (F,OH) · 8 H ₂ O	{101}, {110}	<i>P4</i> / <i>mnc</i>	?	$2V = 88^\circ$	?	?	?	OH [–]	6	37–39
Vesuvianite Ca ₁₉ (Mg,Fe,Al) ₁₃ Si ₁₈ O ₆₈ · (O,OH,F) ₁₀	{110}, {111}	<i>P4</i> / <i>mnc</i>	<i>P2</i> / <i>n</i>	$2V = 45^\circ$	+	?	+	Al/Fe, 0.85	6	40–42
Cordierite Mg ₂ Al ₃ (AlSi ₅ O ₁₈)	{10 $\bar{1}$ 0}, {0001}	<i>P6</i> / <i>mcc</i>	<i>Cccm</i>	$2V = 90^\circ$	+	+	+	Al/Si, 1	∞	43–54
Tourmaline (elbaite-liddicoatite) (Ca,Na)(Al,Li) ₃ · Al ₆ (Si ₆ O ₁₈)(BO ₃) ₃ (OH) ₃ F	{10 $\bar{1}$ 1}, {02 $\bar{2}$ 1}, {11 $\bar{2}$ 0}, {10 $\bar{1}$ 0}	<i>R3m</i>	<i>Cm</i> , <i>C1</i>	$2V = 30^\circ$	+	+	+	Al/Li, 0.33	3	55, 56, our data
Edingtonite BaAl ₂ Si ₃ O ₁₀ · 4 H ₂ O	{110}, {001}	<i>P</i> $\bar{4}$ ₂ <i>m</i> , <i>P2</i> ₁ <i>2</i> ₁ <i>2</i>	<i>P1</i>	$2V = 54^\circ$	+	?	?	Al/Si	—	57, 58
bis(11-Bromoundecanoyl) peroxide	{100}	<i>P4</i> ₃ <i>2</i> ₁ <i>2</i> ₁ <i>P2</i> ₁ <i>2</i> ₁ <i>2</i> ₁	<i>P1</i>	$2V > 0$	?	?	?	molecules	1	39, 59–61
1,5-Dichloro-2,3-dinitrobenzene	{100}	<i>P4</i> ₃ <i>2</i> ₁ <i>2</i> ₁ <i>P2</i> ₁ <i>2</i> ₁ <i>2</i> ₁	<i>P1</i>	$2V > 0$	?	?	?	molecules, 0.68	2	39
Biaxial crystals										
Adularia KAlSi ₃ O ₈	{110}, {1 $\bar{1}$ 0}	<i>C2</i> / <i>m</i>	<i>C</i> $\bar{1}$	+	+	+	+	Al/Si	∞	43, 47 62–64
Asparagine-aspartic acid	{010}	<i>P2</i> ₁ <i>2</i> ₁ <i>2</i> ₁	<i>P12</i> ₁ <i>1</i>	—	?	+	?	molecules, 0.13	1	60, 61, 65, 66
Brewsterite (Sr,Ba) ₂ Al ₂ Si ₁₂ O ₃₂ · 10H ₂ O	{011}, {610}, {010}	<i>P2</i> ₁ / <i>m</i>	<i>P</i> $\bar{1}$	+	+	?	?	Al/Si	3	67, 68

Table 1 (continued).

Solid solution, chemical formula	Growth sector ^a	Ideal space group	Real space groups	Optical anomalies ^b	Signatures in diffrac- tion ^c			Ordering type, maximum degree	Number of structures studied ^d	Ref.
					1	2	3			
Biaxial crystals										
Topaz Al ₂ SiO ₄ (OH,F) ₂	{ <i>hkl</i> }, { <i>hk0</i> }	<i>Pbnm</i>	<i>P1</i>	+	—	?	+	OH/F	1	69–72
Yugawaralite CaAl ₂ Si ₆ O ₁₆ ·4H ₂ O	{011}, {120}	<i>C2/m</i>	<i>Pc</i> , <i>P1</i>	+	+	?	?	Al/Si	2	58, 73
Cinnamamide-2-thienyl- acryl amide	{001}, {011}	<i>P2</i> ₁ / <i>m</i>	<i>Pc</i> , <i>P1</i>	—	+	?	+	molecules, 0.73	3	61, 65

Notes. ‘Our data’ stands for unpublished crystal structure data by the authors of the present review.

^a Only the growth sectors that have been characterised by X-ray diffraction or spectroscopic techniques are included; ^b Δn is the maximum birefringence (*i.e.*, the difference between principal values of the refraction index of the crystal), $2V$ is the maximum angle between the optical axes; the presence of optical anomalies (+) in a biaxial crystal can be revealed according to one of the following criteria: the sector zoning in the distribution of optical parameters, a non-typical optical indicatrix, variations of optical properties over the crystal not related to stoichiometry variations; ^c 1 are distortions of the ideal unit cell parameters, 2 are different intensities of reflections, which were symmetry-equivalents in the parent structure, 3 is the appearance of forbidden reflections. The symbols ‘+’ and ‘—’ denote the presence and the absence of the dissymmetrisation signature, respectively, the symbol ‘?’ means that no information is available; ^d the number of independent crystal structure refinements for a compound in low-symmetry space groups is given; the dash symbol in this column means that no crystal structure refinement has been accomplished and the conclusions on the real symmetry have been derived based on a qualitative analysis of the experimental diffraction pattern; the symbol ‘ ∞ ’ indicates that the number of independent refinements is large due to the possibility of equilibrium phase transitions; ^e the orientational ordering of the OH groups have been detected with IR spectroscopy and the growth origin of the ordering has been confirmed by the observation of optical anomalies.

modification of potash feldspar, KAlSi_3O_8) and for a series of other compounds, including apatite $\text{Ca}_5(\text{PO}_4)_3(\text{OH},\text{F})$,⁹⁷ garnets,⁷ apophyllite,³⁸ topaz,⁶⁹ analcime $\text{NaAlSi}_2\text{O}_6 \cdot \text{H}_2\text{O}$ (Ref. 23), *etc.*

According to these results, the mechanism of the dissymmetrisation can be described as follows. Crystallographic sites statistically occupied by different atoms and vacancies are strictly equivalent only in the bulk of the crystal. They can well become geometrically and energetically non-equivalent on the crystal surface, which enables their regular occupation by different structural units. The ordered state emerged on the surface can further drift towards the bulk of the crystal. Although this state is metastable, it can be preserved in the crystal for a long time due to very low diffusion rates typical of solids. As a result, the structure of a crystal becomes distorted and its symmetry decreases.

It is known¹²² that the crystal growth proceeds as the attachment of atoms, molecules or other building blocks to the crystal surface. The crystal surface can be either atomically smooth or rough at the molecular level. The attachment of atoms to a smooth

surface is difficult and thus the growth can be realised only as a tangential movement (*i.e.*, parallel to the face surface) of growth steps (which is the layer-by-layer, or tangential growth), since the attachment of an atom to a step end is much more favourable energetically than that to the flat surface. In the case of a rough surface, atoms can attach to any its point, which gives rise to a uniform movement of the face as a whole (which is the normal growth). Schemes of the emergence of site non-equivalence for the cases of the normal and tangential growth modes are shown in Fig. 1. It is clear that atoms having identical environments in the bulk of the crystal, can occupy sites that are non-equivalent with respect to a face or a face step of the crystal. These two cases give rise to the normal and tangential selectivity of the component incorporation, respectively.

The growth dissymmetrisation is a rather interesting phenomenon from the thermodynamic viewpoint. It is manifested most prominently upon the crystallisation under conditions close to the equilibrium, in particular, at low growth rates. This results in an apparent contradiction to the laws of non-equilibrium thermo-

Table 2. Examples of the growth dissymmetrisation in crystalline solid solutions according to electron spin resonance data.

Compound, chemical formula	Tracedopant	Growth sector	Ideal space group	Real space group	$I_1 : I_2 : I_3 \dots$	Optical anomalies	Ref.
Quartz, SiO_2	Al^{3+} , Fe^{3+}	$\{0001\}$, $\{\bar{1}\bar{1}20\}$, $\{01\bar{1}1\}$	$P3_121$	$P3_121$ $P2$ $P1$	1 : 1 : 1 1 : 0.2 : 0.2 1 : 0.2 : 0.1	$2V = 25^\circ$	43, 74–79
$\text{ZnSeO}_4 \cdot 6\text{H}_2\text{O}$	Cu^{2+}	$\{102\}$, $\{112\}$, $\{110\}$, $\{001\}$	$P4_12_12$	$P1$	2 : 1 : 3 : 2.5	$2V > 0$	80–83
$\text{Na}_2\text{Cd}(\text{SO}_4)_2 \cdot 2\text{H}_2\text{O}$	Cu^{2+} , Gd^{3+} , V^{4+}	$\{010\}$	$P2_1/c$	—	8 : 1	?	80, 82, 83
Corundum Al_2O_3	Gd^{3+}	—	$R\bar{3}c$	—	—	?	84
Calcite CaCO_3	Fe^{3+} , Mn^{2+}	—	$R\bar{3}c$	—	—	?	85

Notes. Similar patterns of ordering of paramagnetic defects were also observed in herderite, phenacite and beryl;⁸⁶ however, the growth nature of the ordering therein was not elucidated. $I_1 : I_2 : I_3$ is the maximum experimentally measured intensity ratio of the ESR spectral signals that are equivalent in the parent crystal structure.

Table 3. Examples of crystals, for which the growth dissymmetrisation is suspected based on indirect methods.

Compound	Formula	Symmetry class	Ref.
Isotropic crystals			
Garnets grossularite – hydro-grossularite	$\text{Ca}_3\text{Al}_2[\text{SiO}_4, (\text{OH})_4]_3$	$m\bar{3}m$	87
Ralstonite	$\text{Na}_x\text{Mg}_x\text{Al}_{2-x}(\text{OH}, \text{F})_6 \cdot \text{H}_2\text{O}$	$m\bar{3}m$	88
Strontium titanate	SrTiO_3	$m\bar{3}m$	89
Uniaxial crystals			
Apatite	$\text{Ca}_5(\text{PO}_4)_3(\text{OH}, \text{F})$	$6/m$	90–98
Eremeyevite	$\text{Al}_6(\text{BO}_3)_5(\text{OH})_3$	$6mm$	93, 99–102
Calcite	CaCO_3	$\bar{3}m$	103
Dolomite	$\text{CaMg}(\text{CO}_3)_2$	$\bar{3}$	103
Milarite	$\text{K}_2\text{Ca}_4\text{Be}_4\text{Al}_2\text{Si}_{24}\text{O}_{60} \cdot \text{H}_2\text{O}$	$6/mmm$	90, 92, 104
Osumilite	$(\text{K}, \text{Na})_2(\text{Fe}, \text{Mg})_4 \cdot (\text{Al}, \text{Fe})_3\text{Si}_{24}\text{O}_{60} \cdot 2 \text{H}_2\text{O}$	$6/mmm$	105, 106
Tourmaline	$\text{Na}(\text{Al}, \text{Li}, \text{Mg}, \text{Fe})_3 \cdot \text{Al}_6(\text{Si}_6\text{O}_{18})(\text{BO}_3)_3 \cdot (\text{OH}, \text{O})_3(\text{OH}, \text{F})$	$3m$	90, 93, 107
Chabazite (including herschelite, phacolite)	$\text{Ca}_2\text{Al}_4\text{Si}_8\text{O}_{24} \cdot 13 \text{H}_2\text{O}$	$\bar{3}m$	90, 108–110
Biaxial crystals			
Brookite	TiO_2	mmm	111
Harmotome	$\text{Ba}_2\text{Al}_4\text{Si}_{12}\text{O}_{32} \cdot 12 \text{H}_2\text{O}$	$2/m$	112
Mesolite	$\text{Na}_{16}\text{Ca}_{16}\text{Al}_{48}\text{Si}_{72}\text{O}_{240} \cdot 64 \text{H}_2\text{O}$	2	113
Natrolite	$\text{Na}_{16}\text{Al}_{16}\text{Si}_{24}\text{O}_{80} \cdot 16 \text{H}_2\text{O}$	$mm2$	113
Prenite	$\text{Ca}_2\text{Al}_2\text{Si}_3\text{O}_{10}(\text{OH})_2$	$mm2$	90, 114
Scolecite	$\text{Ca}_8\text{Al}_{16}\text{Si}_{24}\text{O}_{80} \cdot 24 \text{H}_2\text{O}$	m	113
Staurolite	$\text{Fe}_2\text{Al}_9\text{O}_7(\text{OH})(\text{SiO}_4)_4$	$2/m$	115
Stilbite	$\text{Na}_2\text{Ca}_4\text{Al}_{10}\text{Si}_{26}\text{O}_{72} \cdot 34 \text{H}_2\text{O}$	$2/m$	116, 117
Epidote	$\text{Ca}_4(\text{Al}, \text{Fe})_6\text{O}_2(\text{SiO}_4)(\text{Si}_2\text{O}_7)\text{OH}$	$2/m$	118
Epistilbite	$\text{Ca}_3\text{Al}_6\text{Si}_{18}\text{O}_{48} \cdot 16 \text{H}_2\text{O}$	$2/m$	119

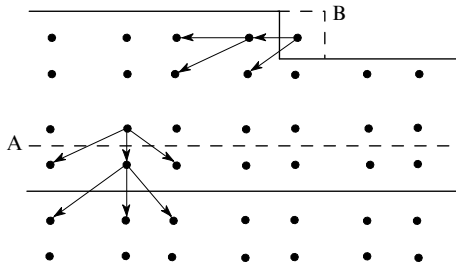


Figure 1. Scheme illustrating the non-equivalence of atoms, which are equivalent in the bulk of a crystal, with respect to the growth front. A is the normal selectivity case, B is the tangential selectivity case. The solid and dashed lines correspond to two consecutive positions of the crystal growth front; the arrows mark the geometric environment of an atoms at the moment of its incorporation into the crystal (adapted from Ref. 80).

dynamics stating that non-equilibrium structures should emerge far from the equilibrium.^{123–125} Actually there is no contradiction, since the emergence of non-equilibrium structures concerns the non-linearity of physical and chemical processes related to the deviation from the equilibrium rather than the mere fact of a deviation. Provided that the non-linearity is the strongest at small deviations from the equilibrium (exactly as it occurs upon the specific adsorption of atoms on the surface of a growing crystal), the probability of the emergence of non-equilibrium structures will increase with an approach to the equilibrium.

Over the whole history of investigations into the growth ordering, a large body of information on both the mechanism of the phenomenon and its influence on the symmetry and structure of the resultant crystalline solid solutions has been gathered.

The present review aims at the generalisation and critical analysis of the available data on all aspects of the growth ordering and experimental techniques for its elucidation. The emphasis is placed onto the crystallochemical origins of the growth dissymmetrisation.

II. Experimental techniques for the elucidation of the growth dissymmetrisation of crystals

1. Crystal optics

According to the Neumann’s principle, a decrease in the symmetry of a crystal should be reflected in the symmetry of its physical properties. In particular, this is valid for crystal optical parameters described by the dielectric impermeability tensor. The dielectric impermeability ψ represents reciprocal dielectric permeability and relates to the refraction index as¹²⁶

$$\psi = n^{-2}.$$

The shape and the orientation of the optical indicatrix, which is the representation surface of this tensor, have to reflect properly the real symmetry of the crystal. The growth dissymmetrisation is accompanied by a change in the optical properties of the crystal, which is manifested in the appearance of characteristic ‘optical anomalies’. For instance, the optical indicatrix of a cubic crystal can transform from a sphere to a uniaxial or biaxial ellipsoid, and the initially optically isotropic crystal will become birefringent. The degree of distortion of the optical indicatrix is described by the birefringence, which is the difference between the maximum and the minimum refraction indices.

Crystal optical methods have several evident advantages over alternative methods for the elucidation of the growth ordering. These include the high sensitivity to minute distortions of the crystal structure induced by ordering of structural units; the possibility of simultaneous monitoring of crystal optical parameters over a large number of the crystals under study; the straightforwardness and affordability of the analysis: the analysis of a large amount of samples does not require long time and expensive instrumentation. Thus the crystal optics is indispensable at preliminary stages of the investigation, *i.e.*, for the detection of the dissymmetrisation and for the quantification of the degree of this effect within a number of samples from the same isomorphous series. Overall, the method does not allow one to establish what types of crystal structure distortions are responsible for the observed distortions of the optical indicatrix. However, some robust algorithms for rather accurate calculations of the optical indicatrix based on the crystal structure have been elaborated recently.^{127–134} By performing calculations and comparing theoretical optical parameters with the experimental ones for a series of models one can analyse the origin of the optical anomalies with their relation to the ordering of structural units. In particular, such calculations were performed for garnets of the grossularite – andradite $\text{Ca}_3(\text{Al}, \text{Fe})_2(\text{SiO}_4)_3$ (Refs 14–16) and grossularite – uvarovite $\text{Ca}_3(\text{Al}, \text{Cr})_2(\text{SiO}_4)_3$ series (Refs 15 and 16) and for sodium chlorate bromate²⁸ (Fig. 2).

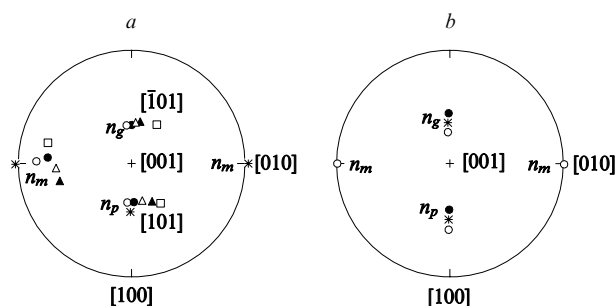


Figure 2. Theoretical (dots) and experimental (asterisks) orientations of the optical indicatrix for garnets of the grossularite–uvarovite isomorphous series (a) and sodium chlorate bromate crystals²⁸ (b); n_m , n_p and n_g are the principal values of the refraction index of a crystal; different data points correspond to different samples; the experimental crystal optical parameters and atomic coordinates used in the calculations were taken from the Refs 17 and 28 for a and b, respectively.

2. Electron spin resonance

The kinetic ordering of atoms in a crystal has been detected for the first time using electron spin resonance (ESR). This method is extremely sensitive and makes it possible to reliably measure the concentration of dopant atoms in any specific site of a regular system of points. The major limitations of the method are as follows: the substituting ion should be paramagnetic (or should form a paramagnetic centre); the concentration of the ion should be sufficiently low (below %); no other paramagnetic ions should be present in the crystal in high concentrations.

Let us consider a few examples of the application of this method to studies of the dissymmetrisation (see Table 2). Upon

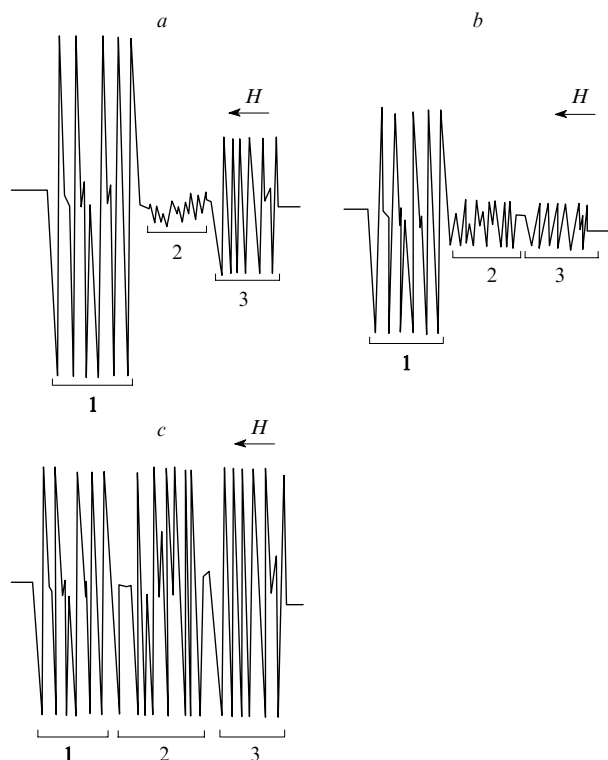


Figure 3. ESR spectra of hole centres in smoky quartz.⁷⁹ The growth sectors: $\{01\bar{1}1\}$ (a), $\{\bar{1}\bar{1}20\}$ (b) and $\{0001\}$ (c). Groups of signals which have identical intensities in the parent trigonal crystal structure of quartz are denoted with numbers from 1 to 3.

the aluminium substitution for the silicon atoms in the crystal structure of quartz (the point symmetry group 32), the $[\text{AlO}_4]^{5-}$ complex can lose an electron giving rise to a hole centre, which can easily be detected with ESR. The concentration of the hole centres is directly proportional to the aluminium concentration (and that of respective counter-ions), so that signal intensities in the ESR spectra give information on the fraction of aluminium atoms in various silicon sites. In an ESR study of crystals of artificial smoky quartz, it was found that groups of signals corresponding to the oxygen atoms of different SiO_4 tetrahedra are characterised by different intensities⁷⁹ (Fig. 3). For the growth sectors of rhombohedral faces (face symmetry 1), all three groups of signals have different intensities; for the growth sectors of prismatic faces (face symmetry 2), only two groups of signals have identical intensities; and for the growth sectors of pinacoidal faces (face symmetry 3), all three groups of signals have identical intensities. Since the intensity of lines in ESR spectra is directly proportional to the concentration of hole centres, the ordering of the hole centres revealed in this way confirms the dissymmetrisation.

3. Infrared and Raman spectroscopy

Infrared (IR) spectroscopy was successfully applied to the analysis of ordered distribution of the fluoride and hydroxide anions in topaz,^{71,72} the silicon and aluminium cations in adularia⁶³ and of the orientational ordering of the OH groups in grossularite¹²⁰ and apophyllite.³⁸ Typically, site occupancies cannot be determined by this method, however, it gives information on the presence and the degree of ordering of atoms or atomic groups in the structure.

Unfortunately, the sensitivity of IR spectroscopy is rather low. In particular, several attempts at the detection of the ordering of the Al/Fe atoms in garnets of the grossularite–andradite isomorphous series using this method failed,^{11,12} although it was reliably established using X-ray crystallography by several authors.^{6,16} It is of note that one of the samples studied by X-ray crystallography⁶ was studied later by IR and no ordering was revealed.¹² Nevertheless, inclusions of a substantially ordered phase dispersed in a disordered matrix can be efficiently revealed by IR (at sizes far below the detection limit of diffraction techniques).¹³⁵

4. Electron microscopy

High-resolution transmission electron microscopy (HRTEM) as well as other modifications of electron microscopy (e.g., TEM, SEM) can reveal the growth ordering in crystals provided that it is significant and gives rise to strong structural distortions or the appearance of superstructures. The detection of Al/Si ordering in cordierite¹³⁵ and prenite $\text{Ca}_2\text{Al}_2\text{Si}_3\text{O}_{10}(\text{OH})_2$,¹¹⁴ Ca/Mg ordering in calcite CaCO_3 and dolomite $\text{CaMg}(\text{CO}_3)_2$ (Ref. 103) can be given as examples of successful applications of electron microscopy.

5. Diffraction methods

It is X-ray, electron and neutron diffraction studies on single crystals (see Table 1) that provide the highest efficiency in the analysis of the nature of the kinetic ordering of atoms in crystals revealing detailed information on the occupancies of crystallographic sites and interatomic distances. In some cases, changes in the ordering can also be tracked by powder X-ray diffraction by monitoring shifts, splitting or broadening of diffraction reflections or the appearance of additional superstructure reflections in the diffraction patterns. In particular, dissymmetrisation-induced changes in the powder diffraction patterns were observed for cordierite $\text{Mg}_2\text{Al}_3(\text{AlSi}_5\text{O}_{18})$ ^{45,46} and edingtonite $\text{BaAl}_2\cdot\text{Si}_3\text{O}_{10}\cdot 4\text{H}_2\text{O}$.⁵⁷

As a rule, the degree of the growth ordering of atoms is low and the lower-symmetry structure subject to refinement is close to the parent high-symmetry one and thus it is difficult to unambiguously establish the fact of a symmetry lowering based on a routine experiment. To provide reliable conclusions on the man-

ifestation and the nature of the dissymmetrisation, it is necessary to collect an accurate set of intensities of diffraction reflections, then carefully analyse the experimental diffraction pattern and refine the crystal structure first in the parent high-symmetry group and then in some of its subgroups selected according to the results of the diffraction pattern analysis.

Recommendations on the accurate measurement of intensities of X-ray diffraction reflections are given elsewhere.^{25, 136} In particular, it is advisable to use nearly spherical crystals and collect the whole set of intensities over the entire Ewald sphere rather than only in its symmetry-independent part.

The following signatures of the dissymmetrisation can be observed in a diffraction pattern: distortions of the unit cell dimensions (typically, insignificant ones); differing intensities of reflections equivalent in the ideal space group; the emergence of reflections forbidden in the ideal space group. The logic of an analysis of the crystal dissymmetrisation based on the diffraction pattern can be demonstrated using garnets of the grossularite–andradite isomorphous series (grandites) with a common stoichiometry $X_3Y_2(SiO_4)_3$ ($X = Ca, Y = Al, Fe$, the ideal space group is $Ia\bar{3}d$). The anomalous birefringence in these crystals is well known.^{7, 13, 90} The idea that the optical anomalies in garnets originate in the atomic ordering has been formulated for the first time by Yoder.¹³⁷ However, the questions on the presence and the nature of the ordering in garnets remained unanswered until recent years, despite numerous attempts at revealing this ordering using X-ray crystallography undertaken over the last 25–30 years.^{6, 8–10, 14–17, 138, 139}

Let us illustrate this approach by the example of a study of three natural grandite crystals (the growth sector of rhombododecahedral faces {110}). The parameters of these crystals and the structure refinement results obtained for them by means of X-ray crystallography are summarised in Tables 4 and 5 (for details, see Ref. 16).

Significant deviations from cubic symmetry are observed for two out of three samples. These are manifested in a deviation of one of the angles (β) from 90° (see Table 4), which indicates that the actual symmetry of the crystals is orthorhombic or lower.

For a comparative analysis of the reflection intensities, all reflections equivalent in the ideal cubic diffraction class $m\bar{3}m$ were subdivided into groups according to the symmetry elements of this class. A symmetry element was considered to be violated, if the difference $I_{\max} - I_{\min}$ between the strongest and the weakest reflections within the respective group exceeded a preset threshold value [in this particular case, it was twice the difference between the intensities of the Friedel equivalents $2(I_{hkl} - I_{\bar{h}\bar{k}\bar{l}})_{\max}$].

In this way, the fractions P of reflections violating specific symmetry elements of the cubic structure were determined for

Table 5. Parameters of X-ray diffraction measurements and structure refinement for the three birefringent grandites.

Parameter	Bazh1	Bazh2	Mali
Radius of the spherical sample /mm	0.100	0.135	0.150
$\rho_{\text{exp}} / \text{g cm}^{-3}$	3.597(4)	3.703(2)	3.698(4)
Diffractometer	Nicolet P3/R3	Nicolet P3/R3	Syntex P2 ₁
$\left(\frac{\sin \theta}{\lambda}\right)_{\max}$	0.807	0.807	0.994
μ / cm^{-1}	27.91	42.54	33.94
Number of observed reflections ($I > 2\sigma_I$)	8065	10 619	9238
Number of independent reflections ($F > 4\sigma_F$)			
space group $Ia\bar{3}d$	314	325	482
space group $Fddd$	1853	1904	2193
space group $\bar{I}$	—	7002	6773
R (%)			
space group $Ia\bar{3}d$	2.81	2.64	4.49
space group $Fddd$	4.36	2.74	3.44
space group $\bar{I}$	—	3.70	3.26
R_w (%) (see ^a)			
space group $Ia\bar{3}d$	4.97	4.94	6.02
space group $Fddd$	5.16	4.63	3.82
space group $\bar{I}$	—	5.07	3.80

^a The weighting scheme utilised: $w = 1/[\sigma_F^2 + kF_{\text{obs}}^2]$, $k = 0.0010 - 0.0068$.

each group (Fig. 4). It is evident that for the crystal Bazh1, all symmetry elements of the parent point symmetry group are violated to a small virtually constant extent. These violations can be regarded as a background level induced by multiple scattering events, non-ideal spherical shape of the sample and resultant anisotropic absorption of X-rays in the crystal, *etc.* Meanwhile, the symmetry element violations are more prominent for other two crystals. And it is important that different symmetry elements are violated to different extents. In particular, the symmetry planes (010), (101) and ($\bar{1}01$) are violated not as significantly as symmetry axes. This trend is especially prominent for the crystal Bazh2: the symmetry planes therein are violated insignificantly, to an extent comparable to that in Bazh1 with simultaneous substantial violation of the remaining symmetry elements. This gives strong evidence that the crystal Bazh2 is actually orthorhombic. In the case of the crystal Mali, the violation of the symmetry planes is more pronounced, which indicates that the actual symmetry of the crystal is lowered further to triclinic.

An analysis of the systematic absences revealed 12, 391 and 196 reflections forbidden in the ideal space group $Ia\bar{3}d$ for the crystals Bazh1, Bazh2 and Mali, respectively (Table 6). Further-

Table 4. Parameters of three birefringent grandites (Bazh1, Bazh2 and Mali) studied with single-crystal X-ray diffraction.

Parameter	Bazh1	Bazh2	Mali
Fe/(Fe + Al)	0.078	0.58	0.23
Colour	light pink	brown	puce
Δn (see ^a)	0.0002(1)	0.0089(1)	0.0066(1)
Refined triclinic unit cell parameters			
$a_{\text{tr}} / \text{\AA}$	11.856(4)	11.984(2)	11.892(2)
$b_{\text{tr}} / \text{\AA}$	11.853(4)	11.979(2)	11.889(2)
$c_{\text{tr}} / \text{\AA}$	11.857(4)	11.980(2)	11.892(2)
α / deg	90.00(0)	90.00(2)	90.00(2)
β / deg	90.00(3)	90.29(2)	90.12(2)
γ / deg	90.00(0)	89.99(2)	90.03(2)
$\langle a \rangle / \text{\AA}$	11.855	11.981	11.891

^a Birefringence value.

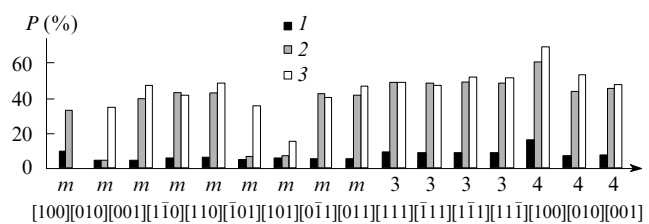


Figure 4. Fractions of diffraction reflections with $I > 4\sigma_I$ violating the symmetry elements of the point symmetry group $m\bar{3}m$ for the three grandite crystals.¹⁵ (1) Bazh1, (2) Bazh2, (3) Mali.

Table 6. Reflections violating the systematic absences for the space group $Ia\bar{3}d$ observed in the grandite crystals.

Group of reflections	Reflection conditions in the space group $Ia\bar{3}d$	Bazh2			Mali
		total	verified by ψ -scans	approved by ψ -scans [fraction (%)]	
hkl	$h + k + l = 2n$	0	—	—	0
$0kl$	$k = 2n, l = 2n$	105	22	19 (86%) ^a	36
$h0l$	$h = 2n, l = 2n$	5	5	0	7
$hk0$	$h = 2n, k = 2n$	107	11	9 (82%) ^a	49
hhl	$2h + l = 2n$	81	22	13 (59%) ^a	41
hkh	$2h + k = 2n$	12	12	0	28
hkk	$2k + h = 2n$	81	16	10 (63%) ^a	35
Total		391 (4%) ^b	88	51	196 (2%) ^b

^a With respect to the number of verified reflections. ^b With respect to the total number of reflections.

more, it was shown that the vast majority of the forbidden reflections originate from the structure dissymmetrisation rather than in multiple scattering effects for the latter samples, Bazh2 and Mali.^{16, 140} To the contrary, all 12 forbidden reflections in the crystal Bazh1 were shown to be related to multiple scattering, which means that the crystal structure remains cubic.

The preliminary conclusions on the dissymmetrisation of the crystals derived from the analysis of the diffraction patterns can be further proven by the refinements of the crystal structure in all possible space groups, including the ideal one. As a result of this laborious analysis not only the crystal symmetry can be reliably established, but also the nature of the dissymmetrisation can be revealed based on the information on occupancies of crystallographic sites and respective interatomic distances.

The crystal structure refinements were performed according to the standard procedure. The structure was refined by the least-squares method based on an analysis of the difference Fourier maps. A particular attention should be paid to the refinement of site occupancies, since severe errors can appear due to mutual correlations between the occupancies and other variables (primarily, thermal parameters). In order to suppress the effects of these correlations, the following techniques can be applied:²⁵ the average stoichiometry of the crystal can be constrained; a series of models with fixed occupancies set at several systematically varying values can be refined and compared; the occupancies can be refined against a part of the reflection array including the reflections observed at smaller diffraction angles 2θ , which are less sensitive to uncertainties in the thermal factors. Furthermore, it is often advisable first to place only one of the principal elements into the site with suspected ordering and refine its occupancy without any constraints.

The retrieval of accurate and reliable site occupancies for crystals of solid solutions from experimental diffraction data is a non-trivial task, which can be solved in a correct way not in all cases [see also a discussion of this problem elsewhere^{141–144} for the case of the determination of magnesium and iron occupancies in sites M1 and M2 from the crystal structure refinement of olivines (Mg,Fe)₂(SiO₄)]. A survey of the experimental data on a number of inorganic compounds indicates²⁵ that a change in the site occupancy can be reliably detected by means of X-ray crystallography only provided that $\Delta e / \sum e > 0.004$, where Δe is the change in the electron count upon the change in the occupancy of a site taking into account its multiplicity, and $\sum e$ is the total number of electrons in a unit cell.

Table 7. Mean bond lengths and occupancies of the octahedral sites YO₆ in the crystal structures of the non-cubic garnets.

Octahedral site	Sample Bazh2		Sample Mali	
	$\langle Y-O \rangle / \text{\AA}$	x_{Fe}	$\langle Y-O \rangle / \text{\AA}$	x_{Fe}
Space group $Fddd$				
Y1	2.003(2)	0.861(5)	1.956(5)	0.344(6)
Y2	1.962(2)	0.308(5)	1.935(5)	0.052(6)
Y1–Y2	0.041	0.557	0.021	0.292
Space group $I\bar{1}$				
Y11	2.004(3)	0.830(5)	1.964(5)	0.471(5)
Y12	2.002(3)	0.830(5)	1.946(5)	0.241(5)
Y13	2.003(3)	0.868(5)	1.951(5)	0.258(5)
Y14	2.004(3)	0.878(5)	1.961(5)	0.340(5)
(Y1i) _{av}	2.003	0.852	1.956	0.328
(Y1i–Y1j) _{max}	0.002	0.048	0.018	0.230
Y5	1.962(3)	0.277(5)	1.934(5)	0.073(5)
Y6	1.959(3)	0.279(5)	1.938(5)	0.126(5)
Y7	1.960(3)	0.308(5)	1.935(5)	0.032(5)
Y8	1.962(3)	0.320(5)	1.933(5)	0.00(1)
(Y2i) _{av}	1.961	0.296	1.935	0.058
(Y2i–Y2j) _{max}	0.003	0.043	0.005	0.126

For the example under consideration, the symmetry lowering for the crystals Bazh2 and Mali was shown to be related to the ordering of the iron and aluminium cations in the octahedral sites Y, which is accompanied by a change in the respective mean cation–oxygen bond lengths $\langle Y-O \rangle$ (Table 7). Only one symmetry-independent Y site is present in the parent cubic garnet (space group $Ia\bar{3}d$), whereas this number increases to two and eight in the orthorhombic (space group $Fddd$) and triclinic (space group $I\bar{1}$) structures, respectively.

In general, the more thorough crystal structure refinement confirms the preliminary conclusions derived from the aforementioned analysis of the diffraction pattern. According to the results of X-ray diffraction (Table 8), the crystal Bazh1 is characterised by the cubic symmetry (space group $Ia\bar{3}d$). Small distortions of the cubic symmetry revealed by crystal optical studies lie beyond the detection limit of X-ray crystallography. The crystal Bazh2 is characterised by the orthorhombic symmetry (space group $Fddd$), whereas the sample Mali is triclinic (or pseudoorthorhombic, space group $I\bar{1}$ or $I1$).

Table 8. Symmetry parameters of the grandite crystals.

Parameter	Bazh1	Bazh2	Mali
System			
optical indicatrix	orthorhombic	orthorhombic	orthorhombic
orientation	or lower	or lower	or lower
unit cell	cubic	the same	the same
Diffraction class ^a	cubic $m\bar{3}m$	orthorhombic mmm	triclinic $I\bar{1}$
Space group			
according to systematic absences	$Ia\bar{3}d$	$Fddd$	$I\bar{1}$ or $I1$
according to crystal structure refinement	$Ia\bar{3}d$	$Fddd$	$I\bar{1}$

^a An analysis of intensities of reflections equivalent in the diffraction class $m\bar{3}m$.

III. The symmetry aspects of the dissymmetrisation and the structural inhomogeneity of crystals

According to the Curie's principle,¹²⁶ the symmetry of a crystal during dissymmetrisation should be determined by the symmetry of a growing face (normal selectivity of component incorporation) and(or) face step (tangential selectivity of component incorporation). The intersection of the point symmetry group of a crystal with the point symmetry group of the matter flow normal to the face of a growing crystal (which is the cone symmetry, *i.e.*, the limiting symmetry class ∞mm) gives 10 groups possible for the normal selectivity in the component distribution (for the case of the normal growth mode by the movement of faces), *viz.*, 1, 2, 3, 4, 6, m , $2mm$, $3m$, $4mm$ and $6mm$. The respective intersection of the point symmetry group of a crystal with the point symmetry group of the planar matter flow towards a face step (the symmetry class m) gives only two point groups possible for the growth mode by the tangential movement of face steps, *viz.*, 1 and m .¹²¹

This simple (and thus rather useful) approach to the description of the crystal symmetries was applied to analyse the dissymmetrisation in many minerals, including analcime $\text{NaAl} \cdot \text{Si}_2\text{O}_6 \cdot \text{H}_2\text{O}$,²³ grossularite $\text{Ca}_3\text{Al}_2[\text{SiO}_4(\text{OH})_4]_3$,⁸⁷ chabazite $\text{Ca}_2\text{Al}_4\text{Si}_8\text{O}_{24} \cdot 13 \text{H}_2\text{O}$,¹⁰⁸ sodium chlorate bromate²⁶ and others. In particular, it was established⁶⁹ that upon the dissymmetrisation of topaz crystals (the symmetry class mmm), the growth sectors of the pinacoidal faces $\{010\}$ remain orthorhombic (the 2D symmetry group of these faces is $2mm$), the growth sectors of the rhombic prismatic faces $\{hk0\}$ become monoclinic (the symmetry group of the faces is m), whereas the growth sectors of the rhombic bipyramidal faces $\{hkl\}$ become triclinic (the symmetry group of the faces is 1). Hereinafter, the indices h , k and l in the notations of simple forms,[†] growth sectors and faces define the inclination of the faces with respect to the coordinate axes X , Y and Z and thus should be small integers.

It has to be noted that the theoretically suggested symmetry lowering is not realised in all cases, since this approach does not take into account the intrinsic symmetry of the atomic sites subject to ordering. There can be no growth ordering, but if it is actually realised, it obeys the above scheme. For instance, under the conditions of the normal selectivity for the cubic faces $\{100\}$ of alum crystals (the symmetry class $m\bar{3}$), the symmetry of the growth sector formed by this face should be lowered to orthorhombic $2mm$, however, this growth sector remains cubic in reality (see below).

† A simple form is a set of faces related to each other through the symmetry operations of the point symmetry group,¹⁴⁵ a growth sector (or growth pyramid) of a face is the area within a crystal formed by the growth of this crystal face.

The crystal dissymmetrisation effects can be strictly addressed within the formalism of the Wittke–Garrido colour symmetry groups. Such an approach has been used for the first time by Vinokurov *et al.*^{80, 82, 83, 86, 146} to describe the dissymmetrisation in zinc selenate and sodium kröhnkite $\text{Na}_2\text{Cd}(\text{SO}_4)_3 \cdot 2 \text{H}_2\text{O}$. The group properties are analysed at a point group level with the explicit consideration of the intrinsic symmetry of the sites involved. The post-dissymmetrisation symmetry of the crystal and the crystallographic sites subject to variable occupancies with isomorphous atoms are obtained as a result of this theoretical analysis.

Such an approach can be illustrated with an analysis of the symmetry of mixed alum crystals $\text{A}^+\text{M}^{3+}(\text{SO}_4)_2 \cdot 12 \text{H}_2\text{O}$ ($\text{A} = \text{K}, \text{NH}_4, \text{Rb}, \dots$; $\text{M} = \text{Al}, \text{Fe}, \text{Cr}, \dots$) (Table 9). Ideally, alum crystals are crystallised in the cubic system with the point symmetry group $m\bar{3}$ but they exhibit optical anomalies originated from the kinetic atomic ordering. Let us consider the ordering of isomorphous atoms in the A^+ or M^{3+} cationic sites [which are the special Wyckoff positions 4(b) and 4(a), respectively]. It is clear that the actual symmetry of the optical indicatrix is compatible with a symmetry lowering due to the growth ordering of the A^+ or M^{3+} cations. Furthermore, it can be seen that in the majority of cases, the theory group analysis predicts the same optical symmetry as does the analysis of the symmetry of a growing face or a face step. In particular, the normal growth of octahedral faces (the 2D symmetry group of this face is 3 within the symmetry class $m\bar{3}$) gives rise to the trigonal symmetry. Meanwhile, the tangential growth of steps on octahedral faces (the step symmetry group is 1) results in the triclinic symmetry. Notwithstanding, as has been mentioned above, the two approaches make sometimes different predictions. For instance, the growth sector of cubic faces should be characterised by the orthorhombic symmetry $2mm$ according to the 2D symmetry group of this face but the group theory analysis predicts the retention of the cubic symmetry for the case of the normal selectivity, and the actual optical indicatrix remains spherical (*i.e.*, no dissymmetrisation occurs).

Therefore, the symmetry of the growth front (*i.e.*, of a crystal face or a face step in the cases of the normal and tangential growth modes, respectively) strongly affects the symmetry of the resultant crystal. The vast majority of crystals are shaped by a set of faces belonging to one or a few regular forms, which enables the spatially inhomogeneous distribution of areas corresponding to different symmetries and structures over a crystal. Possible types of the spatial inhomogeneity commonly evidenced by optical anomalies are considered in detail below.

1. Sector zoning

During the crystal growth, every face forms its own growth pyramid (or sector) and, ideally, any crystal can be represented as a set of pyramids with a common vertex in the centre of the

Table 9. Occupancies of systems of translationally related sites (x_i , $i = 1, 2, \dots, 4$) and the real symmetry of different growth sectors of alum crystals (symmetry class $m\bar{3}$) according to optical investigations.

Growth sector	Normal selectivity			Tangential selectivity			Observed optical indicatrix symmetry
	site occupancies	face symmetry	assumed optical symmetry	site occupancies	face step symmetry	assumed optical symmetry	
$\{111\}$	$x_1 \neq x_2 = x_3 = x_4$	3	uniaxial, normal to $\{111\}$	$x_1 \neq x_2 \neq x_3 \neq x_4$	1	triclinic	biaxial, close to uniaxial
$\{110\}$	$x_1 = x_2 \neq x_3 = x_4$	m	monoclinic	$x_1 = x_2 \neq x_3 = x_4$ (see ^a)	m	monoclinic or triclinic	biaxial
$\{100\}$	$x_1 = x_2 = x_3 = x_4$	$2mm$	cubic	$x_1 = x_2 \neq x_3 = x_4$	m	monoclinic	often isotropic, sometimes biaxial

^a In the present case, the resultant symmetry depends on the orientation of growth steps: if a step is not perpendicular to the symmetry plane, then all the occupancies are different, and the point symmetry group is $\bar{1}$.

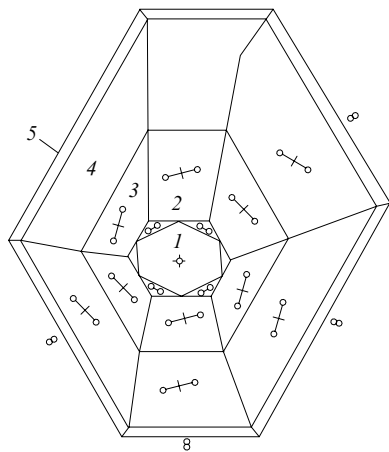


Figure 5. Optical sector zoning in a plate of an eremeyevite $\text{Al}_6(\text{BO}_3)_5(\text{OH})_3$ crystal cut parallel to the (0001) crystallographic plane.¹⁰²

The growth sectors: (1) pinacoid (the angle $2V = 0^\circ$), (2–4) hexagonal bipyramids (the angle $2V = 3^\circ$), (5) hexagonal prism (the angle $2V = 10\text{--}18^\circ$).

crystal and bases coinciding with the crystal external faces. Every growth sector features its own symmetry and crystal structure. The sector growth of different simple forms can be characterised by totally different structures, whereas the structures of different faces belonging to the same regular form can be identical but differently oriented with respect to the common coordinate system, which is similar in some aspects to the twinning texture. This type of the spatial inhomogeneity is a very common signature of the growth dissymmetrisation and, in a sense, can be regarded as its visiting card (for details, see elsewhere^{7, 14, 33, 69, 73, 79}). As an illustration, Fig. 5 depicts different orientations of the optical indicatrix for various growth sectors of an eremeyevite crystal.¹⁰² Table 10 lists data on the distribution of optical anomalies over different growth sectors in garnet $\text{Ca}_3(\text{Al,Fe,Cr})_2(\text{SiO}_4)_3$ crystals.

2. Subsector zoning

The optical sector zoning is often complicated by additional inhomogeneity of the crystal at a subsector level. The term ‘subsector zoning’ means that several subsectors can be recognised within every growth sector, which are specific areas characterised by their own structures and physical properties. Subsectorial ordering changes are a finer effect as regards the sectorial inhomogeneity, thus its manifestation has only been registered with crystal optical techniques. The reason for the emergence of the subsector zoning is as follows. Growth steps spread out over a crystal face from point sources, *viz.*, surface ends of screw dislocations. This is accompanied by the formation of growth (or vicinal) hillocks on the initially flat crystal faces, while the exact shape of the hillocks depends on the anisotropy of the crystal growth rates along the respective steps. The majority of crystals prone to the dissymmetrisation grow from mother liquors following the spiral dislocation mechanism. Since the steps originating from different sides of a vicinal hillock are differently oriented, the crystal areas derived from them under the conditions of the tangential selectivity in the incorporation of isomorphous atoms will appear differently ordered. As a consequence, the distribution of the growth ordering over subsectors formed by differently oriented steps within a sector will reflect the shape of the vicinal hillock.

In particular, typically, vicinal hillocks on the octahedral faces {111} of alum crystals (the symmetry class $m\bar{3}$) have a shape of a trigonal pyramid. As a result, every hillock gives rise to three equivalent subsectors, since the octahedral faces within this symmetry class are characterised by the point symmetry 3. Indeed, the growth sector of the octahedral faces {111} often appears subdivided into three subsectors (derived from one growth hillock) or several triplets of subsectors (derived from different growth hillocks) with different orientations of the optical indicatrix, as can be seen in crystal cuts parallel to the respective growth face. Normally, the subsectors converge in a single point corresponding to the top of the vicinal hillock³³ (Fig. 6). Similar subsector zoning patterns are observed in apatite⁹⁷ (Fig. 7), garnets of the grossularite–andradite series,⁷ analcime $\text{NaAl}_2\text{Si}_2\text{O}_6 \cdot 2\text{H}_2\text{O}$,²³ chabazite $\text{Ca}_2\text{Al}_4\text{Si}_8\text{O}_{24} \cdot 13\text{H}_2\text{O}$,¹⁰⁸ edingtonite $\text{BaAl}_2\text{Si}_3\text{O}_{10} \cdot 4\text{H}_2\text{O}$ ⁵⁷ and in other crystals. In all these cases,

Table 10. Experimental parameters of the optical indicatrix in different growth sectors for garnet crystals of the $\text{Ca}_3(\text{Al,Fe,Cr})_2(\text{SiO}_4)_3$ series (the ideal symmetry class is $m\bar{3}m$). Data from Refs 13, 15, 18, 90, 139, 147.

Growth sector	Point symmetry group	Observed optical indicatrix	Theoretical optical indicatrix	Distribution of occupancies of the octahedral sites
Cube {100}	$4mm$	sphere	sphere	$x_1 = x_2 = x_3 = x_4 = x_5 = x_6 = x_7 = x_8$
Octahedron {111}	$3mm$	uniaxial ellipsoid, the optical axis is normal to the (111) face	uniaxial ellipsoid, the optical axis is normal to the (111) face	$x_1 = x_5 \neq x_2 = x_3 = x_4 = x_6 = x_7 = x_8$
Rhombo-dodecahedron {110}	$2mm$	biaxial ellipsoid, $n_g \parallel [101]$; $n_m \parallel [010]$; $n_p \parallel [101]$ (face normal)	biaxial ellipsoid, the principal axes are parallel to [010] and $[101]$ and normal to (101)	$x_1 = x_4 = x_5 = x_6 \neq x_2 = x_3 = x_7 = x_8$
Tetragontri-octahedron {211}	m	biaxial ellipsoid, $n_p \parallel [211]$ (face normal); the plane defined by the optical axes is parallel to the symmetry plane m	biaxial ellipsoid, one of the principal indicatrix cross-sections is parallel to the symmetry plane m	$x_1 = x_5 \neq x_2 = x_8 \neq x_3 = x_7 \neq x_4 = x_6$
Tetrahexa-hedron {210}	m	biaxial ellipsoid, the principal axes are oblique to the face; the plane defined by the optical axes is parallel to the symmetry plane m	biaxial ellipsoid, one of the principal indicatrix cross-sections is parallel to the symmetry plane m	$x_1 = x_5 \neq x_2 = x_8 \neq x_3 = x_7 \neq x_4 = x_6$
Hexaocta-hedron {321}	1	biaxial ellipsoid, the orientation of the optical indicatrix is oblique	biaxial ellipsoid, the orientation of the optical indicatrix is oblique	$x_1 \neq x_2 \neq x_3 \neq x_4 \neq x_5 \neq x_6 \neq x_7 \neq x_8$

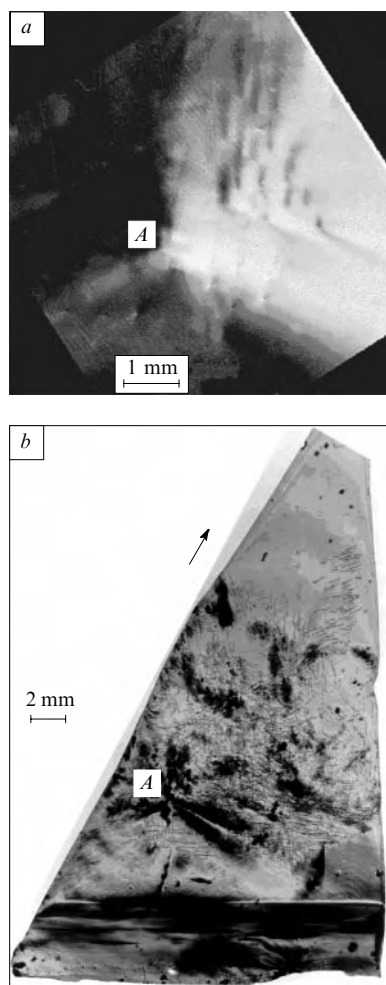


Figure 6. Subsector zoning in an alum $[K_{0.5}(NH_4)_{0.5}] \cdot Al(SO_4)_2 \cdot 12 H_2O$ crystal. The cut is parallel to the (111) growth plane.³³ (a) Anomalous birefringence around the top of a vicinal hillock (A); (b) an X-ray topogram of the cut, the arrow indicates the diffraction vector g direction for reflection 220.

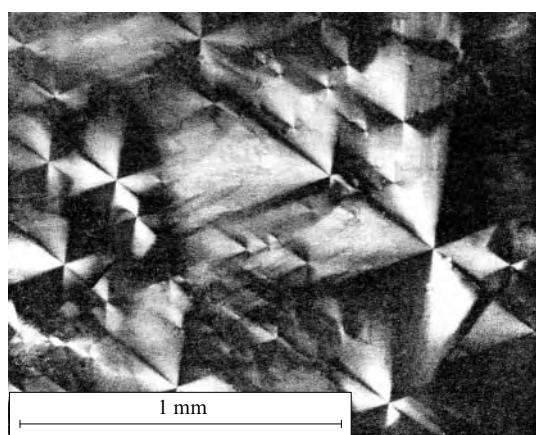


Figure 7. Optical subsector zoning in cuts of apatite crystals perpendicular to the $[0001]$ crystallographic axis.⁹⁷ The observed optical patterns correlate with the positions of vicinal hillock on the crystal face, although the correlation is ambiguous.

the resultant optical subsector zoning correlates with the vicinal face topography; and the symmetry of optical structures correspond to the symmetry of the face defined by the vicinal hillocks present on it.

Boundaries between different subsectors, *i.e.*, domains of a sector originated from different sides of a vicinal hillock, can be visualised in cuts parallel to the crystal growth direction. For instance, two vicinal hillocks formed by two dislocation bundles are clearly seen in the growth sector of the octahedral faces $(\bar{1}\bar{1}1)$ for an alum crystal (Fig. 8). The crystal domains derived from different vicinal hillocks are characterised by differently oriented optical indicatrix, such that the interdomain boundaries can readily be seen in crossed polarisers (see Fig. 8).

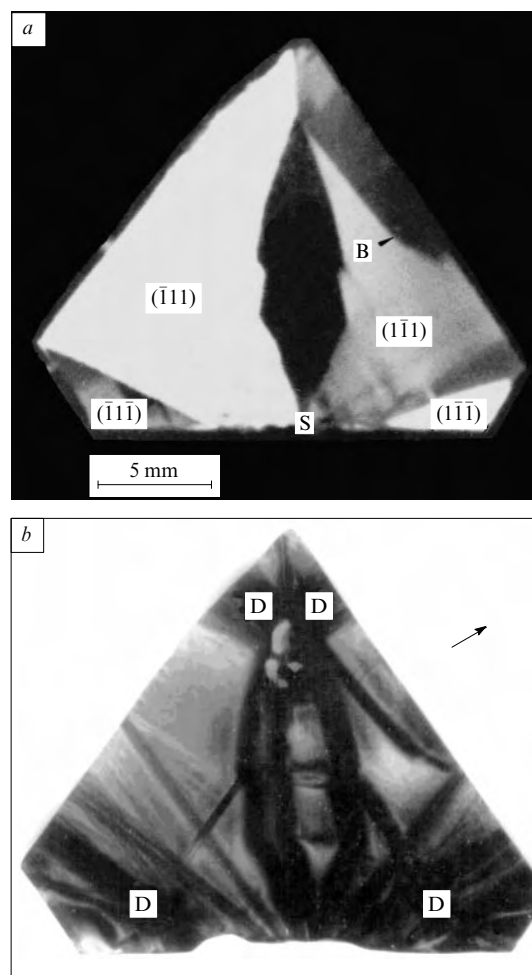


Figure 8. Subsector zoning in an alum $K(Al_{0.5}Cr_{0.5}) \cdot (SO_4)_2 \cdot 12 H_2O$ crystal.³³

(a) Anomalous birefringence in a plate, S is the seed crystal, B is the subsector zoning boundary between domains formed by growth steps from two vicinal hillocks; (b) X-ray topogram; the arrow indicates the diffraction vector g direction for reflection 333, D is a bundle of dislocations originated in the seed crystal S and a liquid inclusion.

3. The correlation between sector zoning and subsector zoning

Optical studies of crystals with the growth dissymmetrisation always reveal their prominent sectorial structure. The experimentally observed indicatrix fully agrees with the normal selectivity in the incorporation of isomorphous components. The optical subsector zoning resulted from the tangential selectivity in the incorporation of isomorphous components is often but not always the case. Typically, this is manifested weakly (minor variations in the systematic absences or a relatively small change in the birefringence). And it is rather surprising. Such crystals grow from mother liquors by the spiral dislocation mechanism, which implies that the faces grow through the movement of steps. Thus a

very distinct subsector zoning in the distribution of optical anomalies is anticipated in the majority of cases, which is not actually the case. This gives rise to an apparent contradiction: a crystal grows through the movement of steps, whereas the distribution of optical anomalies therein is better described by the normal mechanism of the crystal growth.

Several suggestions have been made to reconcile this controversy. According to one of them, the indicatrix strictly corresponding to the face symmetry, *i.e.*, to the case of the normal selectivity, is merely a net result of averaging of effects produced by numerous arbitrarily oriented steps forming this face. A modification of this hypothesis was elaborated by Gali.¹⁴⁸ Nevertheless, the growth of the vast majority of crystals proceed from a few (1–3) quite stable vicinal hillocks, which gives rise to a situation when rather large areas of a crystal are derived from identically oriented steps (see, for instance, Fig. 8), which contradicts the above mechanism. Another hypothesis assumes that the structural distortions occurring under the conditions of the tangential selectivity are close to those in the case of the normal selectivity, *i.e.*, the major energy difference between the sites results from their non-equivalence with respect to the crystal face. Additional non-equivalence due to the face step is negligible. In other words, although the tangential selectivity remains in effect, the ordering is apparently governed by the normal selectivity and the tangential selectivity effects can be revealed only in high-precision studies. We believe that this suggestion is very reasonable. According to another hypothesis, it is the diffusion relaxation that transforms the tangential selectivity ordering into the normal selectivity ordering.

4. Concentric zoning

Frequently, crystals grow under unsteady conditions, *i.e.*, temperature, growth rate, hydrodynamic regime, mother liquor composition can vary over time. Furthermore, the growing face morphology can undergo substantial changes in the course of the growth. All these factors affect the degree of ordering of isomorphous atoms and give rise to the concentric zoning in the distribution of optical parameters (which is often characterised by a very complex pattern). In this case, different extent of the dissymmetrisation under different growth conditions and at variable crystal composition acts as the key factor. The concentric zoning is observed in many crystals, in particular, in mixed alum crystals²⁹ and in garnets of the grossularite–andradite isomorphous series.¹⁵ A special case of the continuous concentric zoning (also referred to as trend) not related to variations in the crystal composition and growth conditions, which has been reliably registered in mixed alum crystals,¹⁴⁹ is of particular interest. In that case, the birefringence and, consequently, the extent of the atomic ordering increased from the centre of the crystal towards its periphery first abruptly, then more smoothly finally approaching a plateau. It might be assumed that this pattern occurs due to the succession of relatively poor initial ordering (caused by the regeneration of the seed) in the growth under conditions providing a higher degree of the atomic ordering.

IV. Dissymmetrisation-induced changes in the crystal structure

As follows from the structural data gathered to date (see Table 1), the growth dissymmetrisation gives rise to insignificant changes in the topology of the crystal structure. This is due to the partial ordering of structural units (*i.e.*, atoms, ions, molecules or vacancies) in available crystallographic sites. The maximum degree of the growth ordering η of 0.84 (see below) was revealed in vesuvianite $\text{Ca}_{19}(\text{Mg}, \text{Fe}, \text{Al})_{13} \cdot \text{Si}_{18}\text{O}_{68}(\text{O}, \text{OH}, \text{F})_{10}$ crystals.

Typically, the degree of distortion of unit cell parameters is small, but it continuously increases with perfection of the ordering in the distribution of structural units. This trend can be illustrated by a linear increase in the monoclinic angle β in initially cubic structures of garnets $\text{Ca}_3(\text{Al}, \text{Fe}, \text{Cr})_2(\text{SiO}_4)_3$ and sodium chlorate

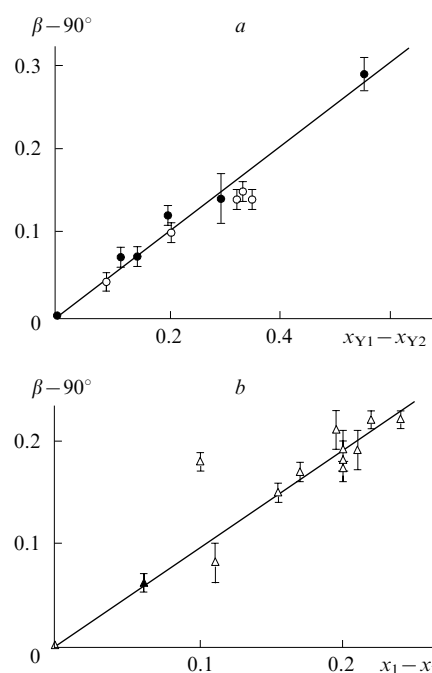


Figure 9. Monoclinic angle as a function of the difference in site occupancies.

(a) Garnets of the grossularite–andradite (plain symbols, data taken from Refs 6, 14–16) and grossularite–uvarovite (shaded symbols, data taken from Ref. 17) isomorphous series, the growth sector {110}; (b) sodium chlorate bromate solid solutions, the growth sector {100}; plain symbols are from Ref. 27, two superimposed shaded symbols are from Ref. 25.

bromate $\text{Na}(\text{ClO}_3, \text{BrO}_3)$ with an increase in the difference between the occupancies of initially equivalent sites (*i.e.*, Al and ClO_3^- occupancies x_1 and x_2 in the two available trivalent cationic and anionic sites for the former and latter compounds, respectively, Fig. 9).

Typically, the atomic ordering does not lead to the appearance of a superstructure. However, there are some exceptions to this rule. In particular, a superstructure due to the ordering of calcium and magnesium atoms was revealed in calcite and dolomite crystals using high-resolution transmission electron microscopy.¹⁰³ Unfortunately, the growth origin of the superstructure has not been confirmed so far.

According to studies of a series of solid solutions belonging to one structural type [*e.g.*, garnets^{6, 14–17} and minerals of the pollucite–analcime series $\text{Cs}_x\text{Na}_{1-x}\text{AlSi}_2\text{O}_6 \cdot (1-x)\text{H}_2\text{O}$ (Refs 22–25)], a variety of solid solutions with different symmetries and occupancies of crystallographic sites can be derived from the same isomorphous series owing to the dissymmetrisation. Frequently, the normal selectivity in the distribution of the occupancies is suggested based on a preliminary analysis, whereas a more thorough analysis yields a lower space group corresponding to the tangential selectivity (see above).

In particular, the dissymmetrisation of garnets of the grossularite–andradite and grossularite–uvarovite isomorphous series (the growth sector {110}, ideal space group $Ia\bar{3}d$) should give rise to the splitting of one octahedral cationic site Y to two sites, Y1 and Y2, with the respective symmetry lowering to orthorhombic, in the case of the normal selectivity in the incorporation of trivalent cations. Under the conditions of the tangential selectivity, each of the two sites is further split into four ones (Y1*i*, Y2*i*, $i = 1–4$), which corresponds to the triclinic symmetry. X-ray diffraction studies of eleven garnet crystals of these isomorphous series manifesting optical anomalies^{6, 14–17} showed that the symmetry of seven crystals lowered to triclinic, whereas the symmetry of remaining four crystals was orthorhombic. Moreover, the triclinic crystals were distinctly pseudoorthorhombic,

i.e., it was possible to subdivide the eight octahedral cationic sites therein into two tetrads of sites in such a way that differences in the site occupancies within a tetrad were significantly less pronounced than those between the tetrads. Formally, this pseudoorthorhombicity can be quantified with a 'triclinicity factor'

$$\xi = \frac{\max(|x_{1i} - x_{1j}|, |x_{2i} - x_{2j}|)}{|x_1 - x_2|}, \quad i, j = 1-4,$$

where x_1 and x_2 are the occupancies of the sites Y1 and Y2, respectively; x_{1i} and x_{2i} are the occupancies of the sites Y1*i* and Y2*i*, respectively.

Based on the orthorhombic or pseudoorthorhombic lattice, the degree of the cation ordering in the two sites can be calculated as

$$\eta = \frac{x_1 - x_2}{1 - |x_1 - x_2|}.$$

A comparative analysis of the experimental data on all eleven crystals indicated that both parameters vary over wide ranges: ξ is ranged between 0.045 and 0.74, whereas η varies from 0.065 to 0.79.¹⁶

Another example considers the dissymmetrisation of the growth sectors {100} in sodium chlorate bromate Na(ClO₃,BrO₃) crystals (ideal space group $P2_13$), where the normal selectivity leads to the splitting of a single site statistically occupied by chlorine and bromine atoms into two ones, which is accompanied by a decrease in the symmetry to monoclinic (space group $P2_1$). Under the conditions of the tangential selectivity, all four sites appear differently occupied, which corresponds to the triclinic symmetry (space group $P1$). Such a symmetry lowering to monoclinic or triclinic (pseudomonoclinic) was indeed observed in thirteen crystals studied using X-ray diffraction.^{26–28} As in the case of garnets discussed above, the ordering degree and the triclinicity factor varied in a wide range from one crystal to another.

The correlation between ordering of atoms in different structural sites is yet another specific feature of the growth dissymmetrisation. It is driven by the requirement to keep the local charge balance. This effect is very distinctly manifested in analcimes²² and pollucite–analcime solid solutions CsAlSi₂O₆ (pollucite)–NaAlSi₂O₆·H₂O (analcime).^{24,25} In the case of analcimes, the decrease in the symmetry from cubic (space group $Ia\bar{3}d$) to tetragonal (space group $I4_1acd$) or orthorhombic (space group $Ibca$) is caused by the ordering of the aluminium and silicon cations in the tetrahedral sites and of the sodium cations and vacancies in the octahedral sites. A linear correlation between the fraction of the aluminium in a tetrahedral site and the fraction of sodium in the closest octahedral site was established (Fig. 10). The symmetry of pollucite–analcime solid solutions decreases to orthorhombic (space group $I2_12_12_1$) due to the same reasons

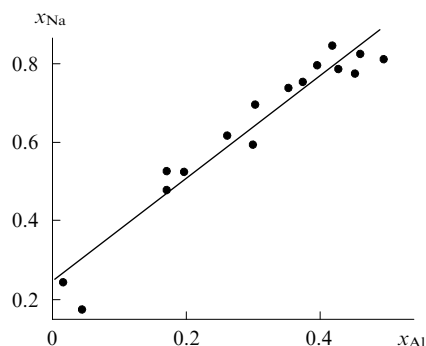


Figure 10. Sodium occupancy x_{Na} as a function of Al occupancy in the nearest tetrahedral site x_{Al} for birefringent analcime crystals.²²

and, in addition, due to the partial ordering in the distribution of the caesium cations and water molecules in channels of the Al/Si framework. Respectively, there is an apparent trend towards a linear correlation between the aluminium occupancy in a tetrahedral site and the content of monovalent cations (Cs + Na) in the closest positions.²⁵

The simultaneous ordering of cations in sites X and Y can also take place in the crystal structures of naturally occurring garnets $X_3Y_2(\text{SiO}_4)_3$ [$X = \text{Ca}, \text{Fe(II)}, \text{Mg}, \text{Mn(II)}$; $Y = \text{Al}, \text{Fe(III)}$].⁸ The kinetic ordering in ugrandite garnets $\text{Ca}_3Y_2(\text{SiO}_4)_3$ is well known (see above); however, no dissymmetrisation has been observed in related pyralpsite garnets $X_3\text{Al}_2(\text{SiO}_4)_3$.^{150–153} This implies that the ordering in the sites X of the garnet crystals occurs simultaneously with the ordering in the sites Y. The isomorphous isovalent substitution in the sites X and Y does not violate the charge balance, which assumes that the correlation in this case is driven by the necessity to compensate for local structural stresses emerging due to different sizes of the atoms subject to ordering.¹⁷

The kinetic ordering-induced dissymmetrisation of a crystal structure, which typically retains the structural type, is usually manifested in significant mutually correlated deformations of different coordination polyhedra. For instance, the ordering in the distribution of the Al and Cr/Fe cations in the octahedral sites Y of the crystal structures of ugrandite garnets gives rise not only to substantial changes in the Y–O and O–O bond lengths (Fig. 11) but also to variations in the O–Si–O bond angles in the SiO₄ tetrahedra that link the octahedra through shared vertices, which results in the respective tilt of the tetrahedra (Fig. 12).^{6,17}

Dissymmetrisation-induced changes in the crystal structures can be efficiently described with cluster models.^{17,24,25} For

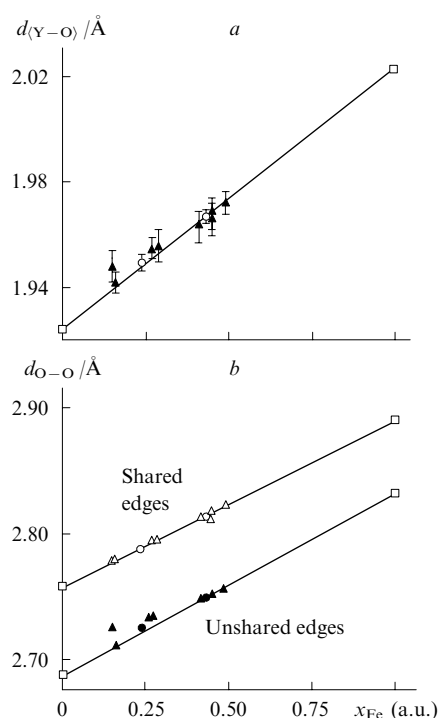


Figure 11. Change in the size of the YO₆ octahedra as a function of the iron occupancy in the site Y for a garnet $\text{Ca}_3(\text{Al}_{0.68}\text{Fe}_{0.32})_2(\text{SiO}_4)_3$ crystal (the sample Munam from Ref. 6).

(a) The Y–O bond lengths, (b) the O–O edge lengths (the shared and isolated edges are plotted as plain and shaded symbols, respectively). The crystal structure was refined in the orthorhombic space group $Fddd$ (1) and the triclinic space group $\bar{1}$ (2), the straight lines are drawn through the data points corresponding to the end members of the series (3).

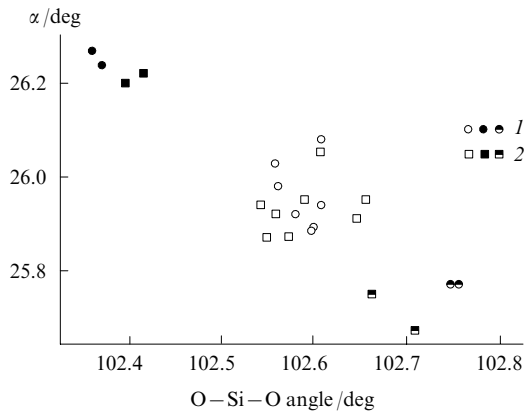


Figure 12. The tilting angle of the SiO_4 tetrahedra α as a function of the O–Si–O angle formed by the O–O edge shared with the CaO_8 polyhedron for two low-symmetry garnet $\text{Ca}_3(\text{Al,Cr})_2(\text{SiO}_4)_3$ samples (symbols 1 and 2).¹⁷

The tetrahedral edges that link two neighbouring octahedra preferably occupied by Cr (both octahedra), Al (both octahedra) and Cr (the first octahedron) and Al (the second octahedron) are marked with the shaded, half-shaded and plain symbols, respectively.

instance, in the structure of low-symmetry ugrandite garnets $\text{Ca}_3\text{Y}_2(\text{SiO}_4)_3$ ($\text{Y} = \text{Al}, \text{Cr}, \text{Fe}$), chromium/iron-rich and chromium/iron-poor $\text{CaY}_4\text{O}_{24}$ clusters can be distinguished, which alternate along the [010] axis (in the pseudocubic setting, see Table 10) and are linked with each other with SiO_4 tetrahedra (Fig. 13).¹⁷ The clusters include octahedra of the same type or those belonging to one tetrad in orthorhombic and triclinic garnets, respectively.

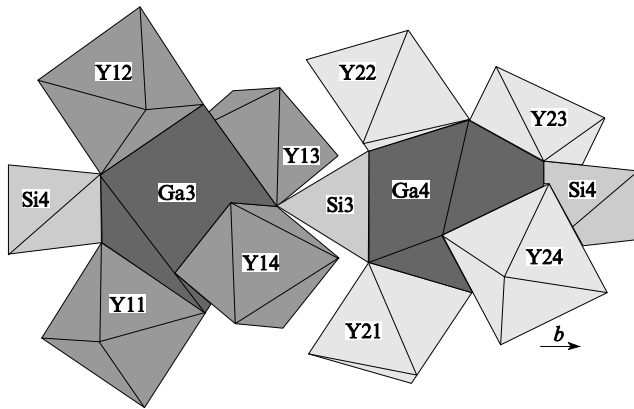


Figure 13. Cr-rich and Cr-poor $\text{CaY}_4\text{O}_{24}$ clusters alternating along the [010] crystallographic axis (in the pseudocubic setting) in the crystal structure of low-symmetry garnet $\text{Ca}_3(\text{Al,Cr})_2(\text{SiO}_4)_3$ crystals.¹⁷

V. The metastability of the kinetic ordering

The ordered state, which is equilibrium with respect to the crystal surface, becomes metastable upon transition to the bulk. This initiates the process of the diffusion equilibration of the site occupancies. As a rule, this process is characterised by a negligibly low rate at room temperature due to the very slow diffusion in solids. However, such a diffusion relaxation in the bulk of the crystal decreasing the dissymmetrisation degree should proceed much faster upon the high-temperature annealing ($T > 0.8 T_{\text{mp}}$). This effect was indeed observed for a number of crystalline

compounds, including quartz,^{78,79} brookite TiO_2 ,¹¹¹ topaz,⁶⁹ analcime,¹⁵⁴ ralstonite $\text{Na}_x\text{Mg}_x\text{Al}_{2-x}(\text{OH,F})_6 \cdot \text{H}_2\text{O}$,⁸⁸ sodium chlorate bromate,^{26,27} garnets of the grossularite–andradite isomorphous series,^{6,8,15,155} synthetic garnets $(\text{Y}_{0.53}\text{Nd}_{0.47})_3\text{Ga}_5\text{O}_{12}$,²⁰ alum,¹⁵⁶ lead strontium nitrate,³⁶ etc. It is of note that the term ‘high-temperature annealing’ is ambiguous. Alum solid solutions $(\text{K,NH}_4)\text{Al}(\text{SO}_4)_2 \cdot 12 \text{H}_2\text{O}$ ($T_{\text{mp}} \approx 90^\circ \text{C}$) undergo the annealing already at room temperature, which gives rise to the spontaneous attenuation of the birefringence upon prolonged storage. The initial crystal structures of a garnet and sodium chlorate bromate crystals manifesting the anomalous birefringence were refined and compared to those after the complete relief of the optical anomalies by a high-temperature treatment.^{8,26,27} It was demonstrated that the annealing results in the equilibration of the site occupancies and the disappearance of the ordering (as well as of the birefringence).

Let us consider a crystal containing two types of atoms occupying two structural sites in an ordered way. Let us denote the sites with a subscript $i = 1, 2$; the mole fractions of one of the components in the first and second sites are x_1 and x_2 , respectively. In overall, any type 1 site has n_{1-1} and n_{1-2} closest neighbours of the types 1 and 2, respectively. By considering the diffusion as a random walk of an atom and assuming only jumps between the adjacent sites, one can write the kinetic equation, which statistically characterises the time changes in the concentration of this component in the site 1 (the result will not change if the site 2 is considered), as follows

$$\begin{aligned} \frac{dx_1}{dt} &= \frac{n_{1-1}P_E x_1 + n_{1-2}P_E x_2}{n_{1-1} + n_{1-2}} - P_E x_1 = \\ &= \frac{n_{1-2}}{n_{1-1} + n_{1-2}} P_E (x_2 - x_1) = n^* P_E (x_2 - x_1). \end{aligned} \quad (1)$$

Here, t is time, P_E is the probability of an atomic jump to a neighbouring (vacant) site, $n^* = n_{1-2}/(n_{1-1} + n_{1-2})$. The solution of this equation is given by

$$\frac{x_2 - x_1}{x_{20} - x_{10}} = \exp(-2n^* P_E t) = \exp\left(-\frac{2n^* D t}{h^2}\right), \quad (2)$$

where $(x_2 - x_1)$ and $(x_{20} - x_{10})$ are the differences in the site occupancies for the crystal before and after the annealing for a duration t , h is the distance between the neighbouring sites i , D is the self-diffusion coefficient, $D = h^2 P_E$ [strictly speaking, the self-diffusion coefficients should be different for each type of atoms, therefore, an effective mean value is placed in Eqn (2)]. Let us assume that the birefringence Δn (or another appropriate quantitative criterion for the distortion of the optical indicatrix) is directly proportional to the differences in the concentrations of one type of atoms in different sites. This assumption is reasonable, which is supported by simulations of the optical indicatrix based on the crystal structure data¹⁵ (Fig. 14). The transition of the crystal from the birefringent to the isotropic state can be regarded as a quasichemical reaction. The conversion level (ξ) can then be written as

$$\xi = \frac{\Delta n}{\Delta n_0} = \exp\left(-\frac{2n^* D t}{h^2}\right) = \exp(-kt). \quad (3)$$

This implies that the relief of optical anomalies should obey the first-order reaction kinetics and thus the birefringence should exponentially attenuate with the annealing time. The reaction rate constant k includes the self-diffusion coefficient of atoms, which in turn exponentially depends on temperature

$$D = D_0 \exp\left(-\frac{E_d}{RT}\right). \quad (4)$$

(E_d is the activation energy of self-diffusion).

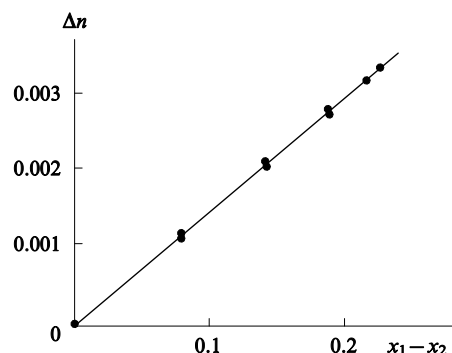


Figure 14. Anomalous birefringence as a function of the difference in the iron occupancies between the two octahedral cationic sites Y_1 and Y_2 for garnets of the grossularite–andradite isomorphous series (calculated in the orthorhombic space group $Fddd$), adapted from Ref. 15.

This implies that the rate of the relief of optical anomalies exponentially increases with an increase in the annealing temperature.

These theoretical conclusions agree well with the available experimental data. The relaxation kinetics upon annealing for crystals manifesting the growth ordering of atoms was elucidated for quartz,^{78, 79} two isomorphous alum series, viz., $(K, NH_4)Al_2(SO_4)_2 \cdot 12 H_2O$ and $K(Al, Cr)(SO_4)_2 \cdot 12 H_2O$,¹⁵⁶ garnets of the grossularite–andradite series $Ca_3(Al_{0.9-0.5}Fe_{0.1-0.5})_2(SiO_4)_3$ (Ref. 15) and lead strontium nitrate solid solutions.³⁶

The case of garnets is considered in more detail below. The kinetics of the attenuation of the birefringence upon annealing was elucidated for two crystals from the Mali deposit. It was found that different parts of the same crystal were characterised by different birefringence attenuation rate constants k . In particular, for one of the crystals, the transformation rate was 3.3 times higher for its outer part, which is characterised by an increased content of water, titanium and defects (dislocations), than in a more perfect central part. And this is logical since the self-diffusion accelerates in areas with a higher defect concentration, since its mechanism involves vacancies. The experimental kinetic points form straight lines in the Arrhenius plot (Fig. 15). The lines are characterised by identical slopes within the experimental accuracy, and the differences between them are exclusively due to the preexponential factors. Similar trends are characteristic of different growth sectors in alum crystals. According to a set of experimental data on two garnet crystals (Fig. 16), the activation energy of transition from the birefringent to the isotropic state is $249 \pm 12 \text{ kJ mol}^{-1}$ in a temperature range from 950 °C to

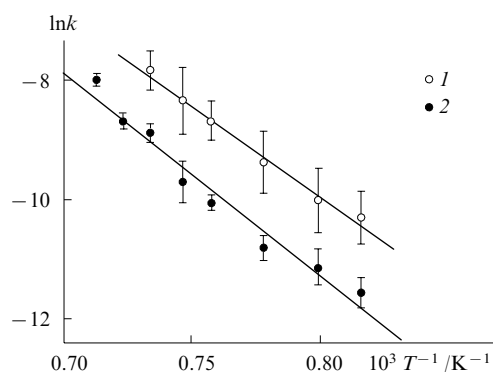


Figure 15. Temperature dependences of the rates of anomalous birefringence attenuation for the central part (1) and periphery (2) of a garnet $Ca_3(Al_{0.5-0.7}Fe_{0.5-0.3})_2(SiO_4)_3$ crystal.¹⁵

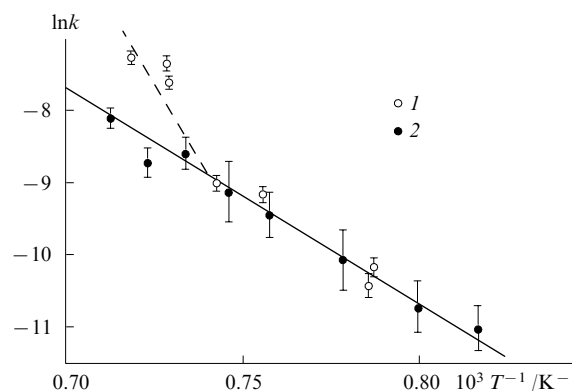


Figure 16. Temperature dependences of the rates of anomalous birefringence attenuation for two garnet crystals (the data points 1 and 2).¹⁵

1090 °C. Data points measured above 1090 °C for one of the crystals deviate strongly from the common trend giving rise to a kink in the plot, which is manifested in the experiment as an abrupt acceleration of the birefringence attenuation at a temperature about 1090 °C (see Fig. 16). This can be rationalised assuming an alteration of the diffusion mechanism, which results in a strong acceleration of the anomalous birefringence attenuation. Presumably, the diffusion mechanism is controlled by the concentration of preexisting vacancies (due to admixtures or linear defects) at a sufficiently low temperature, whereas thermally generated vacancies start to play a key role at high temperature.^{157, 158} In addition to the observed trends in the activation energy of thermal curing of optical anomalies in garnets as a function of temperature, this suggestion explains why it is constant in different crystals or in different zones and sectors of one crystal despite strong variations in the preexponential factors that depend on the vacancy concentration. Similar observations were made for alum crystals¹⁵⁶ and lead strontium nitrate solid solutions.³⁶

Unfortunately, accurate values of the self-diffusion coefficients of trivalent cations in grandites are unknown. On the other hand, extensive information on the diffusion coefficients of bivalent cations in pyrralspites^{159–162} (see also references cited in Ref. 162) is available. The activation energies of diffusion for bivalent cations range from 155 to 290 kJ mol^{-1} . These values agree well with the experimental activation energies of birefringence attenuation upon annealing, which strongly supports the diffusion nature of the process.

VI. The kinetic ordering and the atomic structures of growing faces

The close relation of the dissymmetrisation ordering to the surface atomic structure of a growing crystal (neglecting possible surface reconstruction or relaxation) can be considered as an argument in favour of its growth origin. A careful analysis of sites equivalent in the bulk of a crystal reveals their geometrical differences with respect to faces and growth steps on faces, which is the main driving force for the atomic ordering in the course of the crystal growth. Such an approach has been demonstrated above as applied to the analysis of site symmetries. In that case, only the possibility of the manifestation of differences was stressed, although a direct analysis of the surface structures makes it possible to elucidate these differences in more detail. The surface structures were determined for a number of compounds, including quartz SiO_2 ,^{75, 79} cordierite $Mg_2Al_3(AlSi_5O_{18})$,⁴³ chabazite $Ca_2Al_4 \cdot Si_8O_{24} \cdot 13 H_2O$,¹⁰⁸ topaz $Al_2SiO_4(OH, F)_2$,⁶⁹ stilbite $Na_2Ca_4Al_{10}Si_{26}O_{72} \cdot 34 H_2O$,¹¹⁶ adularia $KAlSi_3O_8$,⁶³ yugawaralite $CaAl_2Si_6O_{16} \cdot 4 H_2O$,⁷³ garnets $Ca_3(Al, Fe)_2(SiO_4)_3$,^{7, 14} brew-

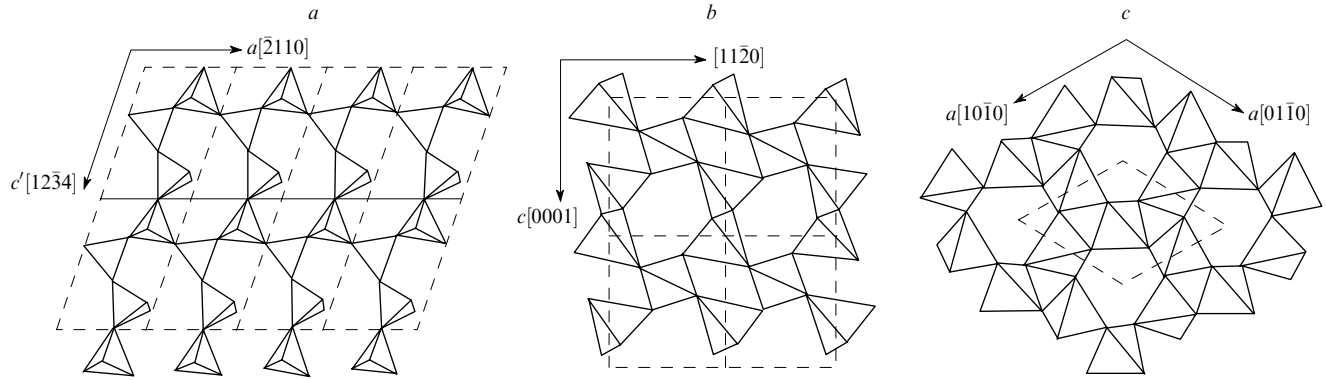


Figure 17. Projections of the crystal structure of α -quartz onto the $\{01\bar{1}1\}$ (a), $\{1\bar{1}20\}$ (b) and $\{0001\}$ (c) crystallographic planes.⁷⁹

sterite $(\text{Sr,Ba})_2\text{Al}_2\text{Si}_{12}\text{O}_{32} \cdot 10 \text{H}_2\text{O}$ (Ref. 67), *etc.* Below, the correlation between ordering in quartz and the structure of its faces is considered in more detail (*cf.* Ref. 79). Geometrical differences in the arrangement of the SiO_4 tetrahedra with respect to the crystal growth front can be analysed using projections of the crystal structure of quartz onto planes corresponding to faces belonging to possible regular forms of the crystal, *i.e.*, rhombohedron, prism and pinacoid (Fig. 17). There are three possible arrangements of the silica tetrahedra relative to the rhombohedral faces (in the respective growth sectors, the hole concentrations are different for all three possible oxygen sites). Relative to the prismatic faces, there are two non-equivalent orientations of the silica tetrahedra (two out of three oxygen sites are characterised by identical hole occupancies). Finally, all tetrahedra are oriented identically with respect to the pinacoidal faces (*i.e.*, all three oxygen sites are equally occupied by holes). Therefore, the ratios between the site occupancies correlate with the geometrical orientation of different SiO_4 tetrahedra with respect to the growth front, which explains how the crystal face symmetry determines the crystal symmetry resulted from the growth ordering. The atomic structure of a face provides the geometrical non-equivalence of the sites according to the face symmetry, which gives rise to the dissymmetrisation.

In a similar way, tight interrelation between the atomic structure of faces and resultant distribution of site occupancies with isomorphous atoms was established for garnets of the grossularite–andradite isomorphous series¹⁴ and sodium chlorate bromate.²⁸

VII. The diffusion relaxation

The ordering of isomorphous components emerging in the course of the crystal growth in steps or on a surface layer tends to relax directly during the growth via the diffusion-driven intersite exchange. The mechanism of the diffusion relaxation was considered by Chernov *et al.*,¹²² as applied to the non-equilibrium incorporation of isomorphous admixtures. We modified this mechanism to extend it to the kinetic ordering of atoms in the crystal structure.

Let us consider the growth of a mixed crystal, where isomorphous atoms can be ordered in several sites that are equivalent in the bulk but different with respect to steps and faces. In such a case, the occupancy of the sites by isomorphous atoms can be described with the equilibrium distribution coefficients (see Section VIII.1), which are different for steps, faces and the bulk of the crystal due to different geometrical environments. When atoms are incorporated in steps, the non-equivalent sites get differently occupied by isomorphous atoms in agreement with the actual growth medium composition and growth conditions, *i.e.*, an atomic distribution corresponding to the tangential selectivity is realised. As soon as the step appears completed thus transforming into a surface layer, the preformed atomic distribution becomes non-equilibrium, since the geometrical environment

of the sites has changed. Thus this state tends to transform into the state that is equilibrium for a surface layer, *i.e.*, the one corresponding to the normal selectivity, by means of the diffusion redistribution of atoms. Such a diffusion redistribution proceeds until the layer is completely covered with the next one thus entering the bulk of the crystal. All the sites appear equivalent in the bulk of the crystal and thus the diffusion redistribution will tend to equilibrate the site occupancies completely. However, this process can proceed efficiently only at a high temperature (*i.e.*, upon annealing, see Section V).

Let us consider a crystal surface layer formed by the movement of a growth step, which is non-equilibrium with respect to the solution. The rate of atomic exchange between any site on the crystal surface and the solution is determined by the probability of the detachment of an atom from the surface layer (P_d). This process is accompanied by a change in the concentration x_i of an element in the site i from a value x_{si} corresponding to the equilibrium between the step and the solution to a value x_{fi} required by the equilibrium between the face and the solution. The rate of this change can be written as

$$\frac{dx_i}{dt} = (x_{fi} - x_{si})P_d. \quad (5)$$

The probability of the detachment of an atom from the surface layer is given by

$$P_d = \frac{D_s}{h^2},$$

where D_s is the diffusion coefficient for the transition of an atom from the surface layer to the growth medium, h is the height of an elementary step. By solving this equation with a boundary condition $x_i(0) = x_{si}$, one gets

$$\frac{x_{fi} - x_i}{x_{fi} - x_{si}} = \exp(-\tau_{ml}P_d). \quad (6)$$

Here, $\tau_{ml} = h/V$ is the time period required to cover the surface layer with a new one, *i.e.*, the monolayer formation time; V is the normal crystal growth rate. The resultant occupancies are then as follows

$$x_i = x_{fi} + (x_{si} - x_{fi}) \exp\left(-\frac{D_s}{Vh}\right). \quad (7)$$

To a first approximation, the diffusion coefficient is given by the following equation

$$D_s = \nu h^2 \exp\left(-\frac{E_s}{RT}\right), \quad (8)$$

where $\nu = 10^{12} \text{ s}^{-1}$ is the frequency of atomic vibrations, E_s is the activation energy of diffusion of atoms from the crystal surface to the mother liquor.

For a transition from a lower-symmetry to a higher-symmetry phase, the left-hand side of Eqn (6) represents the degree of completion of the transition [*i.e.*, the order parameter defined by the exponential term in the expression (7)]

$$\eta = \exp\left(-\frac{D_s}{Vh}\right).$$

If this exponential term is close to unity (*i.e.*, the diffusion rate is low as compared to the crystal growth rate), $x_i = x_{si}$ and no diffusion redistribution of occupancies occurs, then a state corresponding to the initial ordering in the step (the tangential selectivity case) is preserved in the bulk of the crystal. To the contrary, if the exponential term is close to zero (the diffusion rate is high as compared to the crystal growth rate), then $x_i = x_{fi}$. In this case, the diffusion redistribution effectively proceeds until completion such that a new state corresponding to the surface layer ordering (the normal selectivity case) enters the bulk of the crystal.

Unfortunately, no information on E_s is available, which hinders quantitative estimates based on this mechanism. Nevertheless, let us assume that the activation energy of detachment of an atom from the crystal surface layer E_s is higher than the activation energy of crystal dissolution E_{ds} and lower than the activation energy of bulk self-diffusion E_d . This assumption is based on the following arguments. The detachment of an atom from step kinks (which is the main process responsible for the crystal dissolution) requires several bonds to be broken. But this number is certainly less than that required to remove an atom from the surface layer and, especially, from the bulk. Due to the fact that E_{ds} and E_d can be realistically estimated, at least upper and lower estimates of E_s can be obtained to a good approximation. Two examples are given below.

The dissymmetrisation in garnets of the grossularite–andradite isomorphous series gives rise to the decrease in the initial cubic symmetry to either orthorhombic space group $Fddd$ (due to the ordering of cations in two sites, which corresponds to the normal selectivity case) or to triclinic space group $\bar{1}$ (due to the ordering of cations in eight sites, which corresponds to the tangential selectivity case). Naturally occurring garnet crystals differ drastically in the normal growth rates: from one cm per 10 million years to one cm per year; a detailed analysis of these data can be found elsewhere.¹⁶³ For further calculations, let us take the maximum value (10^{-9} m s^{-1} or 3.1 cm per year), which is most reasonable, in our opinion. The detachment of a cation from an octahedral site (Al, Fe) of the surface layer in a garnet crystal requires the breakage of three to four bonds, depending on the orientation of the respective octahedron. Meanwhile, only two bonds have to be broken for the detachment of an atom from a step kink. Thus, to a first approximation, one may assume that $E_s \approx 1.75 E_{ds}$. To our knowledge, no experimental measurements of E_{ds} for grandites have been reported. However, this value can be estimated based on the activation energies of growth and dissolution for other crystals grown under comparable conditions (in particular, hydrothermal ones). According to Dem'yanets (personal communication) and Kuznetsov,¹⁶⁴ the activation energies of crystal growth E_g lie within a range of $33\text{--}92 \text{ kJ mol}^{-1}$ for a number of oxides and silicates [*e.g.*, quartz, cancrinite $\text{Na}_6\text{Ca}_2(\text{AlSiO}_4)_6(\text{CO}_3)_2$, sodalite $\text{Na}_4\text{Al}_3\text{Si}_3\text{O}_{12}(\text{Cl})$, Al_2O_3 , ZnO , TeO_2] except for corundum (for which it amounts to 130 kJ mol^{-1} for some of the regular forms). Typically, the specific heat of crystallisation ΔH does not exceed 20 kJ mol^{-1} , therefore

$$E_{ds} = E_g + \Delta H = 53\text{--}112 \text{ kJ mol}^{-1}.$$

According to results by Lasaga,¹⁵⁷ the activation energy of dissolution E_{ds} is $37\text{--}75 \text{ kJ mol}^{-1}$ for diopside $\text{CaMgSi}_2\text{O}_6$, enstatite $\text{Mg}_2\text{Si}_2\text{O}_6$, augite $(\text{Ca},\text{Na})(\text{Mg},\text{Fe},\text{Al})(\text{Si},\text{Al})_2\text{O}_6$, forsterite Mg_2SiO_4 and quartz (150 kJ mol^{-1} was given as the upper estimate for diopside). The published data on the activation energy of dissolution for almandine crystals $\text{Fe}_3\text{Al}_2(\text{SiO}_4)_3$ ($E_{ds} = 46\text{--}54 \text{ kJ mol}^{-1}$, see Ref. 165) and on the crystallisation kinetics of pyralspites $(\text{Fe},\text{Mg},\text{Mn},\text{Ca})_3\text{Al}_2(\text{SiO}_4)_3$ ($E_g = 50 \text{ kJ mol}^{-1}$, see Ref. 163) also fall into the above ranges. Therefore, the upper estimate of the activation energy of dissolution for grandite $\text{Ca}_3(\text{Al},\text{Fe})_2(\text{SiO}_4)_3$ crystals is 110 kJ mol^{-1} , whereas that of E_s is 192 kJ mol^{-1} . The most probable mean values are $E_{ds} = 60 \text{ kJ mol}^{-1}$ and $E_s = 105 \text{ kJ mol}^{-1}$.

According to experimental data on the annealing of grandites, the activation energy of cation self-diffusion is 249 kJ mol^{-1} (see Section V). A jump of a cation from one octahedral site into another one requires six bonds to be broken, therefore

$$E_s \approx 0.58 E_d = 145 \text{ kJ mol}^{-1},$$

which agrees well with the previous estimate.

Calculations according to the Eqn (7) indicate that either triclinic or orthorhombic phase enters the bulk of the crystals, depending on the crystallisation temperature and the activation energy of detachment of a cation from an octahedral site (Fig. 18*a*). For a constant E_s , the choice of the resultant modification depends on the crystallisation temperature. Typically, the crystallisation temperature lies in a range of $200\text{--}700^\circ\text{C}$, thus the orthorhombic phase should form exclusively if the activation energy is equal or lower than 100 kJ mol^{-1} (which is of low probability). On the other hand, the exclusive formation of the

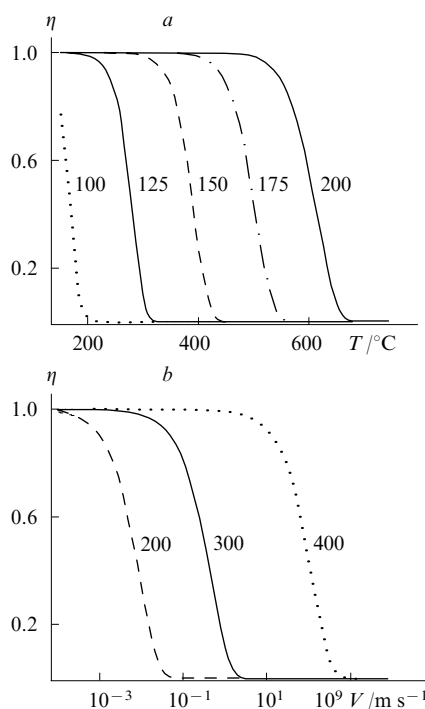


Figure 18. Ordering parameter as a function of the crystallisation temperature and activation energy of the detachment of an atom (*a*) and on the growth rate (*b*) in a garnet crystal (the values $\eta = 1$ and $\eta = 0$ correspond to the most ordered triclinic and orthorhombic structures, respectively). Adapted from Ref. 16.

(*a*): Numbers at the curves correspond to the activation energies in kJ mol^{-1} , the growth rate is 10^{-9} m s^{-1} ; (*b*): numbers at the curves correspond to the crystallisation temperature in $^\circ\text{C}$, the activation energy is 125 kJ mol^{-1} .

triclinic phase is expected for $E_s > 230 \text{ kJ mol}^{-1}$ (which is of very low probability). For intermediate values of E_s (which is apparently the most realistic estimate), the preferable crystal structure (symmetry) is governed by the crystallisation temperature. This explains the fact that both orthorhombic and triclinic garnets occur in nature. The value of the order parameter η is also affected by the crystallisation rate (Fig. 18b), which acts in this case as the control parameter of the kinetic phase transition.

The dissymmetrisation of sodium chlorate bromate crystals for the growth sector of the cubic faces gives rise to a symmetry decrease from cubic to monoclinic or triclinic (which correspond to the cases of the normal and tangential selectivity in the incorporation of isomorphous cations, respectively). The crystals are usually grown at a low temperature from aqueous solutions. Thus typical growth rates, the specific heat of crystallisation and the activation energy of crystal growth are reliably established.^{166–169} According to calculations, the activation energy of dissolution varies from 35 to 40 kJ mol^{-1} . Three to four bonds have to be broken to remove a HalO_3^- anion from a step kink. Meanwhile, the detachment of an anion from the surface layer requires the breakage of five bonds. Taking this into account, one gets

$$E_s \approx 1.43 E_{ds} = 50 - 57 \text{ kJ mol}^{-1}.$$

A calculation based on this estimate together with typical growth rates (*viz.*, $0.1 - 5 \times 10^{-8} \text{ m s}^{-1}$) predicts either monoclinic modification or an intermediate structure transient to the most ordered triclinic modification, *i.e.*, indicates a border zone between the two structures, which completely agrees with the experimental observations.

VIII. Control factors of the kinetic ordering

1. Solid solution composition

Let us consider the degree of the kinetic ordering of atoms along isomorphous series as a function of the ratio of well miscible components (*e.g.*, ideal isomorphism in garnets, alum, *etc.*). We assume that two components, A and B, of a completely miscible solid solution undergo ordering in two non-equivalent subsystems of sites, which initially belonged to the same regular system of points. Let us denote the subsystems with a subscript $i = 1, 2$. Presumably, each of the subsystems behaves independently as regards the crystal growth and is characterised by its own distribution coefficient K_i with respect to the solution (crystallisation medium). The distribution coefficient K_i is used in the following equation (for a definition of K_i , see, for instance, Ref. 170)

$$\frac{x_i}{1 - x_i} = K_i \frac{y}{1 - y}. \quad (9)$$

Here, x_i is the mole fraction of one of the components (*viz.*, B) in the site i of the crystal and y is the respective mole fraction of the same component in the solute. The distribution coefficients defined in this way are independent of the ratio of the components A and B both in the crystal and the solution assuming that the solid solution insignificantly deviates from the ideal solution. The ratio of the left-hand sides of Eqn (9) for different subsystems i yield the so-called intersite distribution coefficient

$$K = \frac{K_2}{K_1} = \frac{1 - x_1}{x_1} \frac{x_2}{1 - x_2}. \quad (10)$$

In order to determine the difference between the incorporation of the component B in the different subsystems, one should express the site occupancy by the component B through its average content in the crystal

$$x = \frac{n_1 x_1 + n_2 x_2}{n_1 + n_2}$$

and the difference in the occupancies is then equal to

$$\delta = \frac{x_1 - x_2}{n_1 + n_2} > 0,$$

where n_i is the total number of sites in the subsystem,

$$\begin{aligned} x_1 &= x + n_2 \delta, \\ x_2 &= x - n_1 \delta. \end{aligned} \quad (11)$$

The sum

$$n_1 + n_2 = n$$

is referred to as the multiplicity of this regular system of points in the parent high-symmetry space group. Within the notation scheme used, $x_1 > x_2$ and $0 < K < 1$. After substitution of expression (11) into Eqn (10), an equation quadratic on δ is yielded. This equation has two solutions, only one of which has physical meaning

$$\begin{aligned} x_1 - x_2 &= \frac{n_1 + n_2}{2n_1 n_2} \left\{ x(n_2 - n_1) + \frac{Kn_2 + n_1}{1 - K} - \right. \\ &\quad \left. - \sqrt{\left[x(n_2 - n_1) + \frac{Kn_2 + n_1}{1 - K} \right]^2 - 4x(1 - x)n_1 n_2} \right\}. \end{aligned} \quad (12)$$

If $n_1 = n_2$, the resultant function is symmetric with respect to $x = 0.5$. If K deviates significantly from 1, the function can be represented as two virtually linear segments intersecting at $x = 0.5$. If K is close to 1 (the degree of ordering is low), the resultant expression is reduced to

$$x_1 - x_2 \approx \frac{2(1 - K)}{1 + K} x(1 - x), \quad (13)$$

which implies that the difference of site occupancies depends parabolically on the crystal composition. The deviation of the approximate expression (13) from the accurate one (12) reaches the maximum for the middle of the isomorphous series and depends on the distribution coefficient: the difference rapidly decreases as K approaches unity (which means that the difference between the site occupancies becomes small). In particular, the difference is 40% for $K = 0.01$, it decreases to 21% for $K = 0.1$ and further to 13% for $K = 0.2$ becoming negligibly small ($< 5\%$) already for $K = 0.4$. If $n_1 \neq n_2$, the maximum of $(x_1 - x_2)$ shifts towards the component B, provided that $n_1 > n_2$ and $x_1 - x_2 > 0$. The closer K to unity, the less significantly the maximum deviates from the middle of the isomorphous series.

Eqns (12) and (13) are valid only for ideal solid solutions, *i.e.*, provided that $K = \text{const}$. For non-ideal solid solutions, the distribution coefficient depends on the solution composition, which gives rise to a small shift in the maximum of the $x_1 - x_2$ difference.

The dependence of optical indicatrix characteristics on the composition of the crystal is a useful criterion of the ordering degree. The experimental determination of this dependence does not require complicated X-ray diffraction studies. It is reasonable to assume that the birefringence (or another appropriate characteristics of the optical indicatrix distortion) is directly proportional to the deviation of the structure from the disordered one, *i.e.*, to a first approximation,

$$\Delta n \sim x_1 - x_2.$$

In such a case, the functional correlation between the anomalous birefringence and the crystal composition is given by expres-

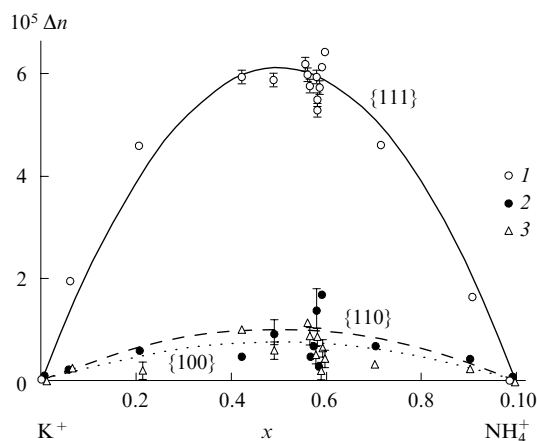


Figure 19. Anomalous birefringence as a function of stoichiometry for alum $[K_{1-x}(NH_4)_x]Al(SO_4)_2 \cdot 12 H_2O$ crystals in the octahedral {111} (1), rhombododecahedral {110} (2) and cubic {100} (3) growth sectors.³²

sions (12) and (13). When the ordering occurs over several sites, there will be no such a simple correlation, although a general trend of an increase in the ordering degree towards the middle of the isomorphous series will still be valid.

We surveyed the correlation between the anomalous birefringence and ordering degree from the one side and the crystal composition from the other side based on our own and literature data on three isomorphous alum series, viz., $(NH_4,K)Al(SO_4)_2 \cdot 12 H_2O$, $K(Al,Cr)(SO_4)_2 \cdot 12 H_2O$ and $NH_4(Al,Fe)(SO_4)_2 \cdot 12 H_2O$,^{29, 32} sodium chlorate bromate crystals^{27, 28} and garnets of the grossularite–andradite isomorphous series.^{13, 15} A quasiparabolic function similar to that predicted theoretically is observed in all cases. As an example, the function anomalous birefringence vs. crystal composition for an alum isomorphous series with a common stoichiometry $(NH_4,K)Al(SO_4)_2 \cdot 12 H_2O$ is plotted in Fig. 19. Additionally, it was demonstrated for a $[(NH_4)_{0.47}K_{0.53}](Al_{0.885}Cr_{0.115})(SO_4)_2 \cdot 12 H_2O$ crystal that the value of birefringence changes additively upon isomorphous substitutions in different sites.¹⁵⁶

The naturally occurring garnets $Ca_3(Al,Fe,Cr)_2(SiO_4)_3$ represent a most striking example of the dissymmetrisation in crystals. However, a correlation between the birefringence and the aluminium to iron ratio for a series of crystals (according to data from several independent sources) looks like an array of data points

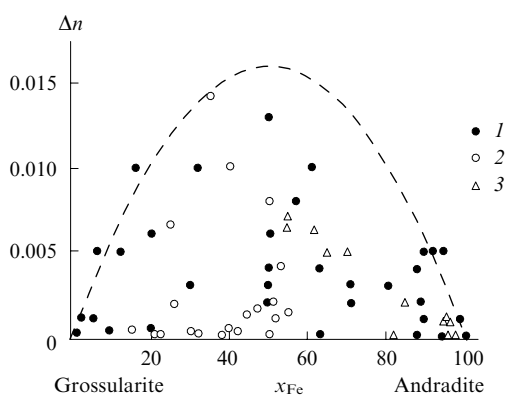


Figure 20. Birefringence as a function of the mean fraction of iron in the octahedral sites x_{Fe} for garnets of the grossularite–andradite isomorphous series.³² (1) Literature data by various authors, (2) our data, (3) data on a one-zoned crystal. For a better comparison with the theoretical prediction, a parabola is drawn with the dashed line.

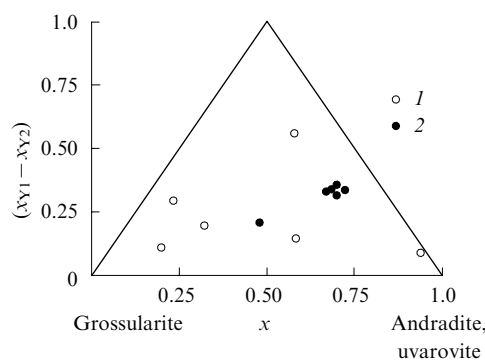


Figure 21. Difference in occupancy between two octahedral cationic sites as a function of the mean content of iron or chromium (x) for garnets of the grossularite–andradite (1) and grossularite–uvarovite (2) isomorphous series (assuming the orthorhombic space group $Fddd$). The lines limit the region of possible crystal structures (corresponding to the maximum ordering degree); (1) from Refs 6, 9, 14–16, (2) from Ref. 17.

limited from bottom with a straight line of zero birefringence and from top with a parabola-like curve with a maximum in the middle of the isomorphous series (Fig. 20) rather than a mere parabola. The ordering degrees of Al/Fe and Al/Cr cations in two octahedral sites of birefringent garnets reveal the same trend, according to all available (although rather scarce) crystal structure refinements (Fig. 21). Such a complex pattern is explained by the presence of crystals grown under very different conditions (primarily, at different temperatures) among the samples studied, which strongly affects the extent of optical anomalies (see Section VIII.5). If the correlation between the birefringence and the crystal composition is plotted for one crystal with compositional zoning, the theoretical parabola-like function is reproduced much better.

The ordering in the growth sectors of the tetrahedral faces in sodium chlorate bromate solid solutions occurs in two groups of sites containing one and three sites, respectively.²⁷ In such a case, the dependence of the ordering degree on the crystal composition should be asymmetric, according to expression (12). The experimental data nicely confirm the expected behaviour pattern (Fig. 22).

For the case of microisomorphism (*e.g.*, minor admixtures of Al^{3+} and Fe^{3+} in quartz or of Cu^{2+} in $ZnSeO_4 \cdot 6 H_2O$), Eqn (12) is substantially simplified. The degree of kinetic ordering becomes

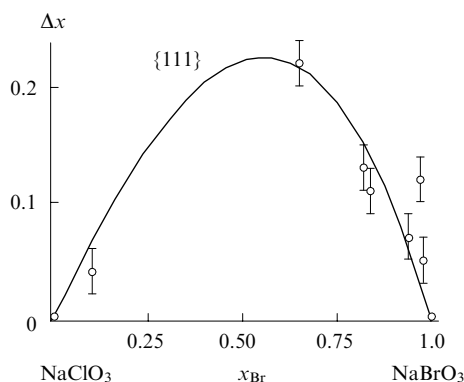


Figure 22. Difference in site occupancies as a function of the mean bromine content for the tetrahedral growth sectors of sodium chlorate bromate crystals (adapted from Ref. 27). The line represents the result of calculations according to the formula (12) for $K = 0.4$.

Table 11. A comparison of parameters of different alum isomorphous series and the anomalous birefringence values for the octahedral growth sectors of the respective crystals.

Isomorphous series	Substitution site	Sign of Δn	$10^7 \Delta n_{\max} $	$\delta a / \text{\AA}$	$\delta r / \text{\AA}$	δn
(NH ₄ ,K)Al(SO ₄) ₂ · 12 H ₂ O	A ⁺	—	600 ± 30	0.082	0.10	0.0029
(Rb,K)Al(SO ₄) ₂ · 12 H ₂ O	A ⁺	—	540	0.085	0.14	0.0001
(Rb,NH ₄)Al(SO ₄) ₂ · 12 H ₂ O	A ⁺	?	~ 0	0.003	0.04	0.0028
(NH ₄ ,K)Cr(SO ₄) ₂ · 12 H ₂ O	A ⁺	—	> 70	0.078	0.10	0.0028
(K,Rb)Cr(SO ₄) ₂ · 12 H ₂ O	A ⁺	?	~ 0	0.083	0.14	0.0001
K(Al,Cr)(SO ₄) ₂ · 12 H ₂ O	M ³⁺	+	820 ± 30	0.038	0.09	0.0249
NH ₄ (Al,Fe)(SO ₄) ₂ · 12 H ₂ O	M ³⁺	+	550 ± 70	0.078	0.02	0.0254
NH ₄ (Al,Cr)(SO ₄) ₂ · 12 H ₂ O	M ³⁺	+	> 430	0.034	0.09	0.0248
NH ₄ (Fe,Cr)(SO ₄) ₂ · 12 H ₂ O	M ³⁺	?	~ 0	0.044	0.07	0.0006
NH ₄ (Al,Ga)(SO ₄) ₂ · 12 H ₂ O	M ³⁺	+	> 130	0.027	0.09	0.0090

Notes. The following notations are adopted: δa is the difference in the unit cell parameters between the end members of the isomorphous series; δr is the difference in the ionic radii (after Shannon¹⁷¹) of the isomorphous ions substituting each other; δn is the difference in the refraction indices between the end members of the isomorphous series.

directly proportional to the impurity concentration. Unfortunately, we are unaware of any experimental results supporting or disproving this conclusion.

According to a comparative analysis of characteristics of optical anomalies for ten isomorphous series of the same structural type (*viz.*, alum, Table 11), the optical sign is unambiguously defined by the site subject to substitution.³² The maximum birefringence strongly varies between the series showing no apparent correlation with the difference in substituting cation radii, unit cell parameters or refraction indices of the end members of the series.

The degree of ordering of atoms or vacancies in a specific crystallographic site can also be affected by admixtures occupying other sites in the crystal. Experimental data on this phenomenon are rather scarce and its origin is unclear. This can be illustrated with the experimentally observed influence exerted by some impurities on the ordering of Si and Al in synthetic cordierites. Various admixtures occupying different structural sites were tested, such as Be, Cs, Ca, Mn, Ti, Li, Cu, B, Sc, V, Cr and Fe.^{45,46} Cordierites Mg₂Al₂Si(Al₂Si₄O₁₈) can undergo a phase transition from the hexagonal (space group *P6/mcc*) into the orthorhombic (space group *Cccm*) modifications. This transformation can occur both as a usual thermodynamic phase transition under specific *P–T* conditions and as a kinetic phase transition under other conditions. The latter transition relates to the ordering of aluminium and silicon in three groups of the SiO₄ tetrahedra.⁴³ It turned out that the ordering degree is a function of the crystal composition. In particular, an increase in the concentration of such admixtures as Be, Al, Sc or B in the crystal gives rise to a decrease in the ordering degree and to the formation of hexagonal crystals. Indeed, no dissymmetrisation occurs or it is manifested to an insignificant extent in beryllium indialite Mg₂(Al,Be)₃Si₆O₁₈, indialite Mg₂Al₄Si₅O₁₈ and beryl Al₂Be₃.(Si₆O₁₈) crystals, which are isostructured to cordierite.^{48,50–52} To the contrary, the introduction of Cs, Rb, Li and Cr admixtures enhances the ordering degree. However, it has to be noted that the exact composition of admixtures affects not only the kinetic Al/Si ordering, but the thermodynamic parameters of the equilibrium phase transition as well, which complicates the interpretation of the above data.

The heavy water substitution for a substantial fraction (~70%) of normal water in alum K(Al,Cr)(SO₄)₂ · 12 H₂O crystals results in a substantial (severalfold) attenuation of the anomalous birefringence. The mechanism of this process remains unexplored.

2. Crystallisation medium composition

Atoms and admixtures present in the crystallisation medium but not incorporated in the crystal also affect the kinetic ordering.

This influence can be illustrated with garnets of the grossularite – andradite isomorphous series as an example. As has been established in experiments devoted to the hydrothermal synthesis of garnets,¹⁷² the birefringence shows an evident correlation with the crystallisation medium composition. In particular, the use of CaO or Ca(OH)₂ instead of CaCO₃ as a calcium source attenuates the birefringence. Furthermore, Na₂CO₃ aqueous solution as a solvent provides a higher birefringence than Na₂SiO₃ or Na₂B₄O₇ solutions. The amount of CO₂ and H₂O in the load for the hydrothermal synthesis of garnets also affects the emergence of optical anomalies.¹⁵⁵ For instance, if the synthesis is accomplished at a temperature of 650 °C and a pressure of 800 bar, the presence of 10% of water in the load gives rise to optical anomalies, whereas no anomalies were observed for the water content at a 5% level. Crystals with optical anomalies can also be grown from CO₂- and H₂O-free media. The mechanism of this correlation between the anomalous birefringence and medium composition has not been elucidated in sufficient detail so far.

3. Temperature and pressure

The dependence of the difference of site occupancies ($x_1 - x_2$) and, consequently, of the degree of distortion of the optical indicatrix on the crystal growth temperature can be deduced theoretically. The distribution coefficient is characterised by the Arrhenius-type exponential temperature dependence¹²²

$$K_i = K_i^{\#} \exp\left(-\frac{U_i}{RT}\right), \quad (14)$$

where $K_i^{\#}$ is the preexponential factor, U_i includes the energy of elastic deformations and the mixing energy due to the substitution in the crystal, $i = 1, 2$. After substitution of (14) into Eqn (12), one gets a rather complicated expression, which is not given here. However, it can be demonstrated that the difference in site occupancies decreases with an increase in temperature. A more prominent asymptotic dependence comes into effect when the distribution coefficient approaches unity, *i.e.*, the difference of site occupancies becomes small. In such a case, an inversed correlation of the difference of site occupancies on temperature is afforded³²

$$x_1 - x_2 \approx x(1 - x) \left(\frac{U_1 - U_2}{RT} \right). \quad (15)$$

Thus according to theoretical predictions, the ordering degree should decrease with an increase in the crystal growth temperature. Physically, this correlation means that the energy of atomic vibrations becomes comparable with the energy difference between non-equivalent sites at elevated temperatures. Respectively, the selectivity of the incorporation of isomorphous atoms is

weakened, which gives rise to a lower degree of the ordering. In addition to this effect, the diffusion relaxation processes and the annealing of the ordered distribution of atoms directly in the course of the growth and in the post-growth period are accelerated at elevated temperatures (see Sections V and VII).

The attenuation of the kinetic ordering and optical anomalies with an increase in the growth temperature were observed and elucidated experimentally for alum^{32, 156} (Fig. 23) and quartz crystals.^{77, 79} Furthermore, the absence of optical anomalies for crystals grown at a sufficiently high temperature was registered for garnets of the grossularite–andradite isomorphous series^{155, 173} (Fig. 24) and cordierites.⁴³

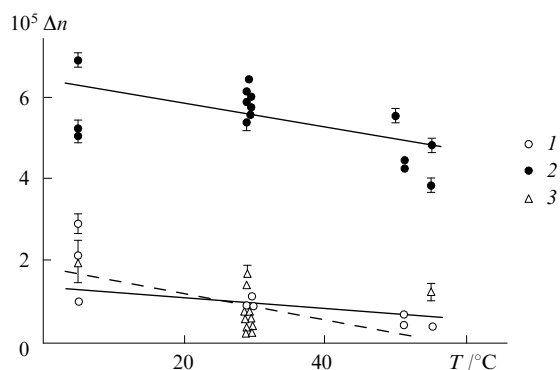


Figure 23. Anomalous birefringence as a function of the growth temperature for three growth sectors of alum $[K_{0.51-0.40}(NH_4)_{0.49-0.60}]Al_2(SO_4)_2 \cdot 12H_2O$ crystals.¹⁵⁵ The measurements were accomplished for cuts along the (110) plane. The growth sectors: (1) {100}, (2) {111}, (3) {110}.

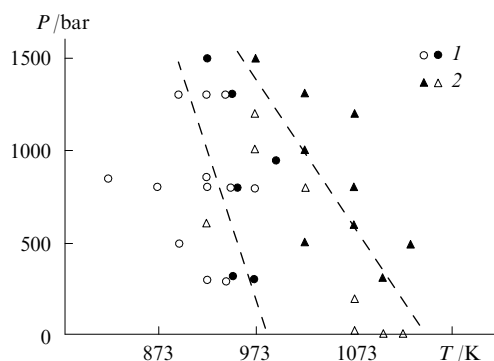


Figure 24. The regions of formation of isotropic (shaded symbols) and anisotropic (plain symbols) crystals of garnets of the grossularite–andradite isomorphous series in the P , T coordinates (tentatively divided by dashed lines).¹⁵⁶ (1) Artificial crystals, (2) naturally occurring crystals.

Experimental data on the influence of pressure on optical anomalies are very scarce. We are aware of only one such example concerning garnets of the grossularite–andradite series (see Fig. 24). In that study, a trend to an increase in the optical anomalies with an increase in pressure was revealed.¹⁵⁵

Apparently, it is variations in the P – T conditions of the crystal growth that are responsible for the lack of a strict correlation between the anomalous birefringence of grandite crystals and their composition as regards the Al/Fe ratio (see Section VIII.1 and Fig. 20), which explains the fact that all experimental points fall into the area limited from the top by the theoretical parabola.

4. Growth rate

The kinetic ordering of atoms and resultant optical anomalies should attenuate with an increase in the crystal growth rate. This reflects the fact that the conditions for the statistical selection of atoms on the surface of a growing face get worse at higher crystallisation rates. Since the incorporation of atoms into the crystal obeys to a large extent the trial-and-error statistics,¹²² the components do not have enough time to settle in ordered positions before the surface layer gets buried in the bulk of the crystal. This means that a state that is not equilibrium with respect to the growing crystal surface gets buried (however, this state can appear much closer to the equilibrium state with respect to the bulk). This effect was observed experimentally for a number of natural minerals⁴⁷ prone to ordinary thermodynamic order–disorder phase transitions [feldspars $KAlSi_3O_8$, omphacite $(Ca,Na)(Mg,Fe,Al)Si_2O_6$, dolomite $CaMg(CO_3)_2$].

The attenuation of dissymmetrisation-induced optical anomalies with an increase in the crystal growth rate was also reported for analcime $NaAlSi_2O_6 \cdot 2H_2O$.²³ A detailed analysis devoted to the dependence of the birefringence on the growth rate in alum $(K,NH_4)Al(SO_4)_2 \cdot 12H_2O$ crystals³² revealed no correlation (Fig. 25a) over a wide range of growth rates. On the other hand, an evident trend towards a decrease in the birefringence with an increase in the growth rate was confirmed for crystals of another isomorphous alum series, viz., $K(Al,Cr)(SO_4)_2 \cdot 12H_2O$ (Fig. 25b). Therefore, the effect of the growth rate on optical anomalies can indeed be detected but it is insignificant in some cases.

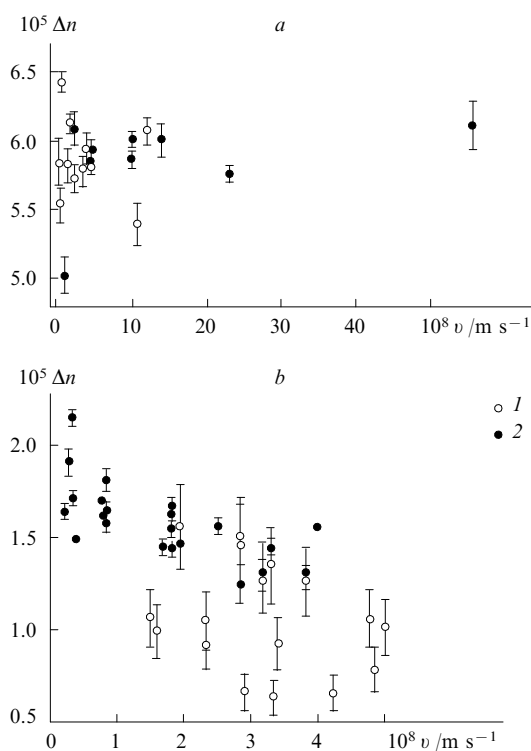


Figure 25. Anomalous birefringence as a function of the growth rate for alum crystals.³²

(a) The isomorphous series of solid solutions $[K_{1-x}(NH_4)_x]Al_2(SO_4)_2 \cdot 12H_2O$: (1) $x = 0.55-0.60$ ($T = 28-30^\circ C$); (2) $x = 0.36-0.42$ ($T = 29.5-32^\circ C$); (b) $K(Al_{1-x}Cr_x)(SO_4)_2 \cdot 12H_2O$: (1) $x = 0.03-0.05$ ($T = 24-37^\circ C$); (2) $x = 0.04-0.05$ ($T = 34-36^\circ C$). The crystals were grown under conditions of free convection (plain symbols) or stirring (shaded symbols) at a Reynolds number of 1400–3200.²⁹

The kinetic disordering (which is the inverse process with respect to the growth dissymmetrisation) occurring within the stability range of ordered solid solutions, was treated theoretically for the cases of crystallisation from both vapour^{1,2,174} and melt.¹⁷⁵ In these studies, the growth of a binary Kossel crystal composed of equal proportions of particles A and B was simulated for the case of the following pairwise interaction energies: $\varepsilon_{AA} = \varepsilon_{BB}$ and $\varepsilon_{AB} = \varepsilon_{BA} = \psi \varepsilon_{AA}$. This effect should attenuate the growth ordering with an increase in the crystal growth rate. According to our calculations³² performed within the model proposed by Chernov,¹ the deviation of the ordering degree from the equilibrium value becomes negligibly small when a crystal grows in a nearly equilibrium mode (although the solution supersaturation can be as high as 0.3) and $\psi = 2$. It has to be noted that this model is rather rough, since it assumes strong collective interactions between neighbouring atoms together with a significant positive non-ideality of the solid solution. Although in the majority of real cases, crystals prone to the growth dissymmetrisation are nearly ideal solid solutions, for which $\psi \rightarrow 1$ and the Chernov's equations do not hold. As an alternative to this approach, the problem can be treated within the theory of absolute reaction rates. This approach is based on the dependence of the distribution coefficient on the crystal growth rate (*i.e.*, the solution supersaturation).^{1,122,176} According to the theoretical analysis, the dissymmetrisation-induced ordering degree should be inversely proportional to the solution supersaturation; however, no experimental result on this subject is available.

5. Hydrodynamics and mass transfer in the solution

Experimental data on the influence of hydrodynamics and mass transfer in the mother liquor on the dissymmetrisation-induced optical anomalies are available only for alum crystals.³² No correlation between the value of anomalous birefringence and mass transfer coefficient against the background of a large scatter among the experimental points was revealed for an extended set of crystals from two isomorphous series, $(K, NH_4)Al(SO_4)_2 \cdot 12H_2O$ and $K(Al, Cr)(SO_4)_2 \cdot 12H_2O$, grown under different hydrodynamic conditions. A dramatic change in the mixing regime of the mother liquor (from the natural convection to an intense stirring) produced no effect on the anomalous birefringence in one crystal grown from the solution. This lack of significant influence indicates that it is the processes on the surface of the crystal that play the key role in the emergence of optical anomalies in alum crystals, which is in accord with the hypothesis of the kinetic ordering of atoms.

Meanwhile, the mass transfer conditions can strongly affect the inhomogeneity of the distribution of optical anomalies over the crystal. This influence is manifested in the formation of a more complex vicinal topology upon specific hydrodynamic conditions of the mother liquor (which results in a complicated pattern of the subsectorial structure of the crystal). Additionally, the mixing conditions affect the character of the birefringence trend.^{33,149}

IX. Conclusion

The comprehensive analysis of kinetic ordering phase transitions that give rise to the dissymmetrisation of crystalline solid solutions demonstrates their obvious difference from the classical polymorphous transformations. The symmetry and the structure of a growing crystal face are clearly distinguished from those of the bulk crystal, which enables the emergence of ordering of structural units on the growing surface, which can be transferred to the bulk under certain conditions. Therefore, it is the selective adsorption of solid solution components by a growing crystal that acts as the control parameter of this phase transition. This fact determines major specific features of the kinetic ordering phase transitions.

The state of the surface and the kinetics of adsorption of components in the course of the crystal growth cannot be characterised by a single parameter, since they are affected by both usual thermodynamic parameters (temperature, pressure,

chemical potentials of the components) and specific kinetic parameters (growth rate, peculiarities of the surface microtopography). As a result, one compound under similar crystallisation conditions can yield a variety of structures characterised by different symmetries and ordering degrees. Therefore, the classical question concerning the symmetry and structure of analcime crystals: 'Is each analcime different?'[‡] can be answered positively. And this is valid not only for analcime but for the majority of inorganic crystalline solid solutions.

In addition to the aspects mentioned above, it has to be noted that the kinetic ordering of atoms is always metastable and can be converted into the equilibrium disordered state by means of high-temperature annealing. Furthermore, the annealing can be actuated directly during the growth process or just after it, which additionally increases the complexity of possible transient crystal structures.

Since the mechanism of the kinetic ordering differs strongly from that of the ordinary equilibrium ordering, both these phenomena can be manifested in a crystal simultaneously. Thus the kinetic ordering can occur in crystals with negative (the components tend to order), zero or even positive (the components tend to segregate up to the emergence of a miscibility gap) energies of mixing of components constituting a solid solution. As an example of this apparent contradiction, sodium chlorate bromate crystals can be mentioned, which are characterised by a significant positive energy of mixing of components (with a possible emergence of a miscibility gap¹⁷⁷) but simultaneously manifest distinct kinetic ordering of the $HalO_3^-$ anions.²⁸

Kinetic phase transitions are very common, they are typical of virtually any crystalline solid solutions. However, this phenomenon remains largely unexplored, despite the long history of its studies. Over the last decade, the structural origins of the dissymmetrisation have been elucidated and methods for the analysis of symmetry in crystals with anomalous optical properties based on X-ray diffraction data have been developed, with the active involvement of the authors of the present review. A large body of information on the actually occurring ordering patterns, effects of the crystal composition, the role of high-temperature annealing, reasons for the inhomogeneity of the spatial distribution of regions with different degrees of ordering over a crystal have been analysed quite thoroughly (although not comprehensively). Still, the issues related to the influence exerted by the chemical composition of dopant structural units and the growth conditions, primarily, temperature and the growth rate, on the growth ordering have not been addressed adequately. Furthermore, the validity of the suggested mechanism of the growth dissymmetrisation has been supported only by indirect data, whereas no direct confirmations have been obtained so far. This is mainly due to the insufficient power of presently available experimental techniques for the real-time structural monitoring of surface layers of growing crystals. Therefore, the story concerning the growth dissymmetrisation mechanism should be continued.

This work was performed with a partial financial support from the Russian Foundation for Basic Research (Project No. 05-05-64 289) and INTAS YS Fellowship Program (Grant 2004-83-2826).

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